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Working with "reovirus" or Respiratory Enteric Orphan Virus, Oncolytics Biotech® Inc has developed a revolutionary Cancer Therapy that allows the Immune System to Visualize and Learn what the Tumor Looks Like and send Natural Killer Cells

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CEOCFO: ***Dr. Coffey, would you give us a brief background on how you came to be a part of the founding of Oncolytics Biotech® Inc?***
Dr. Coffey: This was part of my doctoral thesis. I worked on this project with another individual called Jim Strong when we were working in an infectious disease lab at the University of Calgary. The intention here was not to develop an immunotherapy, but rather to understand how the virus was able to grow and replicate. We were working with "reovirus," which is an acronym for Respiratory Enteric Orphan Virus, which is very safe, so you can work with it in the university setting without handling precautions, without fear that you are going to make a student sick. We were working with it to understand how this particular family of viruses grow and replicate. We thought we could use a non-pathogenic form, understand what its requirements for replications were and apply those lessons to pathogenic, or deadly forms, of disease. What we quickly came to understand is that we can only replicate the virus in transformed or tumorigenic cells. As I said, reovirus, or pelareorep as the drug is known, is a non-pathogen and does not pose a risk because we do not normally have a reservoir of cells or a population of cells that allows it to replicate. When we have cancer cells, the normal checks and balances that prevent pelareorep from making copies of itself are defunct. What we find is these infected cells act as a wonderful beacon and danger symptom to your immune system, and the infection process allows us to visualize the tumor. These were our initial findings in the university setting, and we were able to file some patents and incorporate around those findings.

CEOCFO: ***The efforts in using immunotherapies in cancer have been around for a while, such as with checkpoint inhibitors. Make the case for oncolytic viruses and why that is a different approach?***
Dr. Coffey: You are right, it is a different approach, but it is an old approach. Going into this project we thought - as others thought - that pelareorep was going to go into a cancer cell, replicate, kill the cancer cell, and that would be the end of it. What we are finding is these viruses are not that adept at killing. What they are good at is generating a danger signal to your immune system. Our immune systems are very adept at dealing with our environment, as we're exposed to bacteria, fungi, parasites, and viruses on a daily—and almost hourly—basis. Therefore, our immune system is able to act appropriately and prevent the spread of the disease. I think the novelty of our approach is that we are riding on the coattails of checkpoint inhibition. People did not appreciate how the immune system could actually be reengaged to target disease. When we started this project some time ago, there was thinking that a cancer patient's immune system was so deranged that it could never extend the life of a cancer patient. It was through the work with checkpoint inhibition, where

we found out that twenty to twenty-five percent of patients could reengage their immune systems, and it was capable of educating the immune system to target disease.

In the last couple of years, the thinking has been that pelareorep allows your immune system to visualize the tumor tissue because of its infection at the tumor site itself. Therefore, it is something like a checkpoint blockade, which requires T cells to be present and requires checkpoint moieties to be expressed on tumor cells. By that, I mean receptors like PD-L1, CTLA-4 or PD-L2, which are what the checkpoint inhibitors target through antibodies. If they do not express these receptors, the checkpoint will not work. If they do not have the immune system mobilized into the tumor there, it will not work. We can now take something like a natural infection and use it to engage your immune system.

Our thinking now is pelareorep is able to infect these tumors specifically, and not replicate in normal tissue. These infected cells are then able to send distress beacons to the immune system that they are infected, and this causes our innate response which is our natural killer cells that deal with the usual suspects such as bacteria, viruses, parasites, fungi. They then begin killing off the tumor cells only because the viral infection lets the immune system know that there is something going on and that it should be engaged. This is the first time that your immune system gets to visualize and learn what the tumor looks like.

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CEOCFO: ***Is this something you have seen in the lab?***
Dr. Coffey: We have seen this in both human studies and in the lab, and we know that it is the immune system causing the effect. For example, if we give a mouse a tumor, then treat it with pelareorep and cure it of its tumor, we can then actually try to re-implant that same tumor and the mouse will reject it. Pelareorep causes tumors to look for something foreign and it makes our immune systems reject it. It is so profound that we can actually take cured animals and put their immune cells in animals who have never been exposed to a tumor, never been exposed to pelareorep, and they will reject the tumors. Therefore, we know pelareorep is causing a learned immune effect.

CEOCFO: ***Would you tell us about Pelareorep, which is your intravenously delivered non-pathogenic, proprietary isolate of the unmodified reovirus and why is intravenous delivery important?***
Dr. Coffey: There are a few advantages that we have. One is that RNA viruses, which pelareorep is, are very good at engaging the immune system through multiple pathways. RNA, especially double-stranded RNA in our cells, looks very foreign and it is one of the best ways of stimulating the immune response. The second thing is, because we are not modified, there is no change to hospital practice. We can actually treat patients as an outpatient where they can go home with their families after treatment. Modified viruses require special handling and significant changes to clinical practice, including bleaching of rooms following treatment. If there is anything physicians and hospital staff don't want, it's change. Especially change requiring additional work.

IV administration is key. Cancer therapies for the most part try to treat systemic diseases and by that I mean metastatic disease spread everywhere in the body. If you are doing intratumoral injection, you are treating a localized lesion, so generally something you can administer into, such as a melanoma expressed on the skin or head and neck where it is expressed superficially. It is very difficult to treat someone with lung cancer and go in and inject the lesion because it is very dangerous and requires imaging guidance. Importantly, it is also not a positive experience for the patient. IV administration allows us to treat systemic diseases or metastatic disease very efficiently because we basically infuse the patient with a trillion viral particles so we are able to get pelareorep to the sites and it is able to replicate there, and that is really key. We have been able to demonstrate in patients, successful delivery of pelareorep and delivery after multiple rounds of therapy when the immune system is aware of the virus, and propagation and replication of the virus in these

patients, through these windows of opportunities. We have been able to demonstrate that pelareorep is engaging the immune system the way we want it to.

CEOCFO: ***In traditional chemotherapies people are always worried about toxins. Where do you stand with side-effects?***
Dr. Coffey: We are very fortunate. The side-effect profile is very favorable. We have trialed it with chemotherapy, with radiation therapy, and with checkpoint inhibitors. The tell-tale side-effect is a flu-like malaise. This is more pronounced in the patients who do well, as there are significant chemical signals that the tumor is letting go of or releasing in response to the viral infection, including interferon, chemokines and cytokines. Therefore, the patients have the sensation like they are coming down with the flu; they will get the sensation 24-48 hours after administration. There will be things like fever, aches, pains and the chills. However, we can treat a lot of it with just Tylenol, and if you get a cancer therapy where you can block some of the side-effects with Tylenol, I think that speaks to the safety. As a class of agents, oncolytic viruses have proven themselves time and again to be remarkably safe and something you can efficiently tack onto existing therapies without worsening the underlying side-effects, especially an unmodified virus like pelareorep. I think that speaks to how broadly used these agents are. If we can add this to checkpoint blockade and convert the percent of patients that respond to those drugs from approximately 20%, to 30%, 40% or more, that can be extremely meaningful to hundreds of thousands of patients. Checkpoints are expected to sell more than $25 billion in 2022, so it can be extremely meaningful from a commercial standpoint as well.

CEOCFO: ***Why will your technology have success in solid tumors, when so many others have failed?***
Dr. Coffey: We have been able to demonstrate that pelareorep is very effective when delivered to both hematological malignancies and solid lesions and a lot of this has to do with the fact that it is a very small particle, only sixty nanometers. So it can escape the vasculature and get into the tumor and distribute there. In addition, it is able to avoid the impact that you would normally expect with neutralization, and it is able to avoid the immune system until it finds tumor tissue and begins to replicate. We have co-evolved with viruses for thousands of years – it's a cat and mouse game where they are always trying to avoid the immune system and replicate without detection. Pelareorep is good at avoiding the neutralizing aspect of antibodies, but what it is not very good at is avoiding the effects of natural killer cells, which is the innate immune response, and eventually T cells, which is an adaptive immune response. Therefore, it is able to be delivered systemically, and able to replicate, but its replication ultimately leads to its demise and the demise of its host cells, which in this case are cancer cells, which for a patient is exactly the result we are aiming for.

CEOCFO: ***Would you tell us about your 3 combination programs and where you are with them today?***
Dr. Coffey: The sharp end of the spear really is the work we are doing in metastatic breast cancer and breast cancer in general. We announced in 2017 that we have been able to demonstrate a seven-month improvement in median overall survival in patients with second, third, and fourth line metastatic disease. This is huge, as metastatic breast cancer has never demonstrated a meaningful survival benefit in any patient group. In hormone receptor positive disease, which is about 70% of metastatic breast cancer, we saw a near doubling of overall survival, so these patients got an extra Christmas with their family, an extra anniversary or extra birthday. This is meaningful time. The difficulty we originally had for the breast cancer program we are running with Roche is that we could not identify who was responding from those who were not. In collaboration with Roche, we identified what we believe is a biomarker that allows us to assess whether a patient has adequate immune response at baseline to derive benefit. Importantly, we can confirm that we engaged the immune system as early as eight days. The Roche study will now validate a biomarker that can predict response at baseline, as well as verify it by the beginning of cycle two – approximately three weeks. That program is ongoing right now and that is likely to be the lead-in to our phase 3 registration study in breast cancer because it should identify the biomarker and also tell us whether or not we should be adding a checkpoint inhibitor to the phase 3 program. We think the addition of a checkpoint inhibitor is likely because our pre-clinical studies suggest that pelareorep primes the tumor to respond to the checkpoint blockade by doing two things. One, it causes the over expression of PD-L1 on tumor targets, which in hormone receptor positive disease is not commonly expressed. And two, it remodels the solid tumor to allow inflammatory cells to come to the site of infection and it promotes the accumulation of these inflammatory cells, especially T cells which are required for the opportunity of checkpoint blockade. That is our breast cancer program.

With multiple myeloma, we had run two studies, looking at pelareorep plus proteasome inhibitors. We had 100% response rate at the top dose, but importantly when we looked at the immunological changes, it was very clear that it was priming the tumor to respond to checkpoint blockade. Multiple myeloma has failed to respond to checkpoint blockade because it is a very immunosuppressive tumor. It actively prevents inflammatory cells from participating in the biological processes and it does not commonly overly express PD-L1. What we were able to demonstrate in these two studies is that pelareorep primes the immune system by causing over expression of checkpoint moieties like PD-L1 on tumor cells, but also CTLA-4.

The second thing it does is it causes the immunosuppressive environment to be replaced by pro-inflammatory environments. We removed the cells, the T regs that suppress the immune system, and we replace these with natural killer cells and with pro-inflammatory CD8-positive cells into the bone marrow. There are two investigator sponsored studies going on now: one with Merck which will hopefully begin in Q2 and the other one with Emory University in collaboration with Bristol-Myers Squibb, which is currently enrolling patients.

Our last program is an investigator sponsored trial with Merck, in pancreatic cancer. The background to this is we ran a small study, with 12 patients in second-line pancreatic cancer with Merck's Keytruda® and what was important there is those patients have a very short life expectancy of four to five months, with half of the patients passing away during the four to five months. However, in the other patients receiving pelareorep with Keytruda®, we saw patients on treatment for up to thirty-six months. We were able to demonstrate a pro-inflammatory cytokine response and importantly that is the work where we have identified a biomarker. What we are able to do is use TCR (T Cell Repertoire) sequencing, which is basically getting a snapshot of your T cell repertoire or adaptive arm of the immune system at baseline, and patients who had adequate reserve had very good outcomes. The hazard ratio was measured at .05, and non-responders had very little immunological reserves, so they just could not mount a response. Importantly we could identify those patients at the beginning of cycle-2, or basically three weeks later, who had seen an immune change. By this I mean, we were able to cycle through about 50% of your T cell repertoires and re-educate those to recognize new targets, whether they be viral targets or tumor targets themselves. Being able to detect this change, we can identify with a very high rate of accuracy who is responding and who has failed to respond.

This may be the most important thing we have done in the last twelve months for a number of reasons. From a patient perspective we were able to tailor their treatments to their immune system. If they have immune reserve we can say you have adequate T cell function to mount a response to it. The second thing is we can confirm in these patients that they are responding very early. The problem with immune therapy is that sometimes it takes months for the patient to realize they are mounting a response against their disease. We can give the patients the peace of mind that they are mounting an immune response, and that they can learn to recognize new challenges to the immune system both viral and tumor. That is important because for patients who failed to respond, we can quickly tell them that they are not having the desired outcome and we can get them on something that is hopefully more efficacious for them. For those patients who are responding, we can keep them on study, we can monitor their immune system and we can tell them whether or not this response is long lived. For payors this is very important because checkpoint blockade is very expensive, at an average of $150,000, and only approximately 20% of patients are responding to these types of treatments. However, we can identify those patients that are likely to respond and this saves payor an appreciable amount of money.

CEOCFO: ***Would you tell us about the manufacturing of Pelareorep? Who is doing this for you?***
Dr. Coffey: Vaccine production, it is very simple, it is something that people have been doing since vaccines were introduced. We are producing in Carlsbad, California with Merck Millipore. It is a wonderful facility that Kite Pharma uses to manufacture their CAR-T technology, so this is a state-of-the-art facility that is more than adequate for launch. We are actually at a launch ready scale at this point. We produce at a 100-liter bioreactor in a stir tank reactor in approved cell lines that we infect, grow the virus up in and then we purify it. That production run will actually produce around 75 to 85 thousand dosages of the recommended dose. The product, because it is an environmental virus, is very stable, so we can store it at -20 degrees for six or seven years. Think vaccine production. It is a cheap cost of goods and it allows us a lot of flexibility in final pricing. This is especially important if we want to be a standardized backbone for checkpoint blockade, which is currently an expensive treatment option for patients. However, if we couple this with a prognostic and predictive biomarker, then it would be something that payors would be very excited about.

CEOCFO: ***Where are you today with funding? Are you reaching out to investors or for partnerships, and if so, what has been their response?***
Dr. Coffey: It is very positive. We were listed on the Nasdaq last June. We did a small raise before we had any of our checkpoint collaborations in place. Since then, we have been able to announce two investigator sponsored studies with Merck – in multiple myeloma and pancreatic cancer – one investigator sponsored study with Bristol-Myers Squibb, also in multiple myeloma and our clinical supply agreement with Roche which is initially being used in our AWARE-1 breast cancer study. The one study that Oncolytics sponsors and is responsible for. So we'll see data from multiple checkpoint inhibitor combinations in both solid and hematological tumors. The President of Oncolytics Biotech U.S. and Head of Global Business Development, Andrew de Guttadauro, has seen a lot of interest in pre-clinical collaborations as well, and we will see results from those labors later this year. We have also seen a lot of interest from large pharma. These are parties that we have not previously announced, who are engaging because we can now not only extend or enhance their checkpoint franchise, but we can also identify patients who are likely to respond to it. The checkpoint aspect as well as the

biomarker has also resonated with investors who have seen the value. We have seen a bit of erosion in the share prices because we delayed the phase 3 breast cancer study to validate our biomarker, but I think at the end of the day, this does not delay the company's entry into the marketplace. If anything, it expedites by running studies that require far too fewer patients and as a result far less capital.

CEOCFO: ***Final thoughts. Why is Oncolytics an important company in the future of cancer therapies?***
Dr. Coffey: I believe that cancer will be a manageable disease like diabetes. We are able to engage a patient's immune system and I think that is the most promising aspect for the patient. It allows them to use their own reservoir, their own body, to actually combat disease. I think that is going to be over the next ten years where oncology moves. I would very much like to be to the forefront of that movement.