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Developing a unique NK cell-based approach to CAR-T Cell Therapy, Celyad SA is focused on triggering the Patient's own Immune System to Kill Cancer Cells

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CEOCFO: ***Dr. Homsy, according to the Celyad website, you are bringing breakthrough pioneering technologies to patients with life threatening diseases. How so? What are you working on?***
Dr. Homsy: We are trying to address cancer. Our approach is using the immune system of patients, basically the natural defenses that patients have. We do that by using a technology that is called CAR-T, which, in very broad strokes, means that we take the white blood cells from the patients and we equip them with something that recognizes cancer cells. After that, once they are injected back to patients they go and kill cancer cells. That is the CAR-T field, in general.

CEOCFO: ***What are you putting into the cells? Would you give us a little bit of what the science is, how it works and why it works?***
Dr. Homsy: We have a number of products, but our lead clinical candidate, CYAD-01, expresses a cell membrane receptor called NKG2D in T-cells. That receptor is usually present on another type of white blood cell called NK cells (Natural Killer cells). However, on NK cells, the NKG2D receptor is regulated by inhibitory signals. Therefore, we transduce, in other words, put the code of that receptor in a T-cell to express the receptor, which allows it to recognize cancer cells. That is what we do in a nut shell. Other companies in the field are transducing other types of receptors or antibodies in their CAR-Ts, such as CD19 or BCMA. We can point at Novartis, Gilead Sciences, Juno Therapeutics or bluebird bio. All those companies have specific CAR-Ts that have achieved great successes in certain types of blood cancers, and we are on our path to getting there as well.

CEOCFO: ***What type of cancer is your focus? What is it about the receptor that you are working with that makes it effective or perhaps more effective than others?***
Dr. Homsy: The great advantage of that receptor is that instead of targeting a particular type of cancer it targets stress cells. All cancer cells are stressed. Our CAR-T approach can't target all cancers, but a broad range including both solid tumors and blood cancers. About 80% of the cancers that we have studied express the counterpart of the NKG2D receptor, called ligands, and therefore positions our lead candidate as a very universal type of CAR-T cell therapy making it unique compared to other approaches in the field. The first clinical data that we have generated is in a blood cancer called AML (Acute Myeloid Leukemia), which is a very aggressive cancer. It is called acute because it progresses very quickly and usually there is not a very effective treatment for that type of cancer, so patients succumb very quickly. That is our lead indication for our cell therapy and we have seen some pretty convincing data to date from the ongoing Phase I trial.

CEOCFO: ***What is different about it that allows you to target stress cells? Have people looked at that before? What have you figured out?***
Dr. Homsy: The inventor of the technology is Professor Charles Sentman from Dartmouth College. He is specialized in what is called innate immunity. Basically, we are all born with a certain level of immunity that is provided by the innate system. The cornerstone of that innate immunity is the NK cells which are very good at scanning the body to recognize cells that are sick and then destroy them. That is what the innate system does. NK cells are initially designed to fight against mostly viral infections. You get a virus and that virus infects a cell. The infected cell becomes stressed and in turn uses stress ligands as a flag to basically call the innate system and say: "Come and kill me, I am a disease." There are eight of those ligands; MIC-A, MIC-B and a family of six ULBP ligands. These ligands are very strongly repressed in normal cells, because it's a flag for suicide, in a sense. In general, the immune system recognizes a cell that has been infected previously. Much like a vaccine, if you get the measles your immune system is going to recognize that protein on the surface of the cells and as soon as you get infected again your T-cells will come and kill them. However, T-cells on their own are not very good at the initial recognition. Therefore, the great invention of Professor Sentman was to combine those two immune systems; the innate immune system and the acquired immune system, and then make them work together.

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CEOCFO: ***What did you learn during the recent trials that may have surprised you?***
Dr. Homsy: The dogma in CAR-T cell therapy with the other companies is that in order for CAR-T cells to work, you have to pre-condition the patient. It means that you firstly treat the patient with a couple of chemotherapy agents that reduces the tumor and will prepare the bone marrow to receive the CAR-T cells and allow the CAR-T cells to expand. Our first surprise was that in our first trials (without any pre-conditioning and chemotherapy agents), we started seeing some responses which were never seen before in CAR-T therapies. The second thing that surprised us is how well tolerated the therapy looks to date. In other words, we have seen very few severe adverse events as compared, again to other CAR-T therapies and traditional cancer treatments. Those are the two things that surprised us the most. As in any drug development scenario, you start putting things in a funnel and the first things that came out of that funnel were clear indications that for acute myeloid leukemia, we have a product candidate that holds great promise! That is basically how we got to where we are today.

CEOCFO: ***What are your next steps?***
Dr. Homsy: Our next step is to make this treatment more effective, more durable and expand into other types of cancers. Up to now, at least, we have a treatment that does not seem to be causing serious adverse events. Now we are looking into the next stage of the development, which is, "Okay, are the initial signals that we are seeing now going to translate as well in larger patient populations or other cancer types?" That's what we hope, but we'll get a better sense as we treat additional patients with the candidate.

CEOCFO: ***What has been the response of the medical community that is aware of Celyad's approach?***
Dr. Homsy: The physicians that are in our trials and we have a number of them in the US and in Europe, are encouraged with the initial data and want us to rapidly move to further evaluate the candidate in the treatment of AML. That is because they say that patients have no other options, so if we can provide something that could help those patients, they would really value that. We agree and are balancing our efforts by remaining cautious as well because we obviously want to take forward a proper development plan and make sure we do it the right way. In addition, they are also advising us to expand into other cancer types as well.

CEOCFO: ***What has been the response from the investment community?***
Dr. Homsy: Since we began to provide initial clinical data readouts, we have seen a number of high-profile investors come into the story. Before that it was really early, and we didn't know what the safety profile was going to look like. The risk was the potential to target stress ligands on healthy tissue that could perhaps lead to some adverse events. We have not seen that, so now investors feel more comfortable with the approach. We have had a few investors who are very knowledgeable that came into the stock and the response has been quite positive. The flip side to the story is that our history dates back for about ten years, when we were in a different type of cell therapy company with a treatment targeting heart failure. Therefore, many of the legacy shareholders that we have are from that period. We see some progressively crossing over and changing to the investors that are more knowledgeable about cancer.

CEOCFO: ***Are you looking at partnerships with other organizations as you continue? Will you be going it on your own for a while? What is the strategy?***
Dr. Homsy: I think in terms of partnership, what matters is how much value we can bring to our shareholders. That is one side of the equation. The other side of the equation is how long can we be better than other partners in developing that product. As long as we are in Phase I and II trials and going pre-commercial, we think we can do it ourselves. We have the resources, the knowledge, the cash and we must do it at least as well, if not better, than large corporations. As we approach commercial stage, more than likely, a partner would be the right way forward.

CEOCFO: ***How do you deal with some of the frustration on a personal level of getting a product developed, the length of time it takes and the process that can be arduous at times?***
Dr. Homsy: What is the most frustrating Lynn, is when we get, and we do get, at least three or four calls from patients or family per week: "Can I get your product, because my son or my dad is passing away and we have no other options and I really want to get your product." That is what is the most frustrating. The desire is to be able to go as quickly as you can and win the race against time for those patients! The fact that it takes time is normal. We have to pass every step, making sure that the product is safe and effective in a proper way and drug development takes time. Would we like to do it quicker? Yes! However, unfortunate those things do take time.

CEOCFO: ***What is in the pipeline at Celyad?***
Dr. Homsy: We have generation two of that NKG2D CAR that is currently completing the animal and the pre-clinical work that should roll into the clinic towards year end. That should be an even more potent and probably a more durable type of response that we get. Then we are addressing the whole field of what is called solid tumors, such as colon cancer or pancreatic cancer. The challenge with those tumors is that if you want to portray them or to picture them as a mass, as a ball, the cells have to get into that ball, which is what is called tumor infiltration, and getting yourself into that ball is another type of challenge. We are working on that as well. That is, for us, on the multi-year horizon. Then, over the next twelve to twenty-four months, we are going to be making important strides into what is called allogeneic treatment. That means that instead of taking cells from the patient and returning them to the patient, we take cells from healthy donors and institute large banks of cells. Those cells are then available and it's possible to be able to treat patients "off-the-shelf", instead of having a complex process of taking cells from a patient, getting them to a lab, getting them back to the patient. That's the future. Right now, we are working up to getting CYAD-01, our first-generation product into a pivotal trial for the treatment of AML. Therefore, we have a "today" strategy, which is getting our lead candidate to registration, a "tomorrow" target which is mostly focusing on our "off-the-shelf" cell therapy platforms, and we already have some patients enrolled in such a trial, and lastly our plan for "beyond", which is a little bit further away yet focused on tackling solid tumors.

CEOCFO: ***How do you spend your time as CEO? What are you working on day to day?***
Dr. Homsy: I have the chance to have an incredibly gifted CFO that therefore takes care of investor meetings, of financing and of getting the resources that we need. I have a very talented and gifted head of research and development as well, that takes care of research and basically invents all of the new ideas that we are working on. We also have a very good COO, so the team is exceptional. My role as a CEO is to make that team work together, to make sure that everyone has the resources to do what they need to do and that they work within the frame that I or we define together, which are the values, that vision and the mission of the company and providing an environment in which people can express their full potential. That is mostly what I do. On the side of more practical things, I am basically heading the strategy part of the company; where do we go, how do we allocate resources between projects and what is further down the horizon for the company.