CEO's Corners

Ultimovacs

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Q4-19 Report

UV1 – a Universal cancer vaccine

Being Universal

The goal for any cancer vaccine is to make the immune system produce T-cells able to recognize and kill cancer cells. The crucial question for researchers is: exactly what should the T-cells recognize? There are two basic requirements to be fulfilled: 1. It must be present on the cancer cells you are trying to kill. 2. It must not be present on the surface of the cells you do not want to kill. All cancer vaccines in development fulfil these two criteria, but beyond this they differ.

We (Ultimovacs) state that our vaccine (UV1) is universal. We use the word 'universal' for two reasons. First, the 'marker' (hTERT) we make t-cells recognize is present in 85-90% of all cancers. Please note that we say 90% of all types of cancer, not 90% of all cancer patients. Very few cancer patients have tumors not expressing telomerase.

Second, we also know that the cancer cells always must have hTERT since their lives literally depends on it. If they stop having hTERT (the UV1 'marker'), they die. Almost all cancers have it and they can not live without it.

Universal: Easy to combine with other immunotherapies

With basic knowledge about immunotherapy and checkpoint inhibitors, you will recognize a similarity between UV1 and checkpoint inhibitors: Both blocking checkpoints and producing T-cells recognizing hTERT are universal principles of cancer treatment. This is not 'personalized' cancer treatment. In his talk at Oslo Cancer Cluster a few weeks ago, James P (Jim) Allison used the word 'impersonalized' cancer treatment about the checkpoint inhibitor that won him the Nobel Prize.

Since both checkpoint inhibitors and UV1 are universal and that they will facilitate each other in supporting the killing of cancer cells, there is a good reason to combine them. This is exactly what we are doing in two large, randomized trials. We will find out if the combination of UV1 from Ultimovacs with two checkpoint inhibitors from Bristol-Myers Squibb is superior to the two checkpoint inhibitors alone. This will be tested in two different cancer types, malignant melanoma (the INITIUM trial) and mesothelioma (the NIPU trial) as described elsewhere in this report. When these trials are reporting their results, we will have tested UV1 in four different cancer types: prostate cancer, non-small cell lung cancer, malignant melanoma and mesothelioma. We might also include other types of cancer to further document that UV1 is truly universal.

Universal: Simple to manufacture and use

Since we know that hTERT is expressed in the cancer, we do not need biopsies or complex testing of patient and tumor to decide if the patient can benefit. All patients use the same vaccine, and the use does not require complex infrastructure. The production is not very complex and Ultimovacs has

already established and tested the process for mass production. The shelf life of the vaccine is long and the same as for other, chemically stable medicines.

Universal: Can be developed to prevent cancer

A cancer vaccine used to prevent a cancer from growing must produce T-cells recognizing a marker on the cancer cells we beforehand know will be there. If you need to analyze a biopsy to decide what your T-cells will recognize, such a vaccine can not be used to prevent cancer.

In the Ultimovacs development plan you will find the pre-clinical development of UV2. Here we will explore the possibilities for developing UV2 in stages of cancer where there is no real tumor or tumors so small that they are very difficult or impossible to detect. In the future we might also be able to explore the effect of our vaccines in preventing cancers from occurring in people with very high risk, identified in a screening program.

Q3-19 Report

How does immunotherapy and a cancer vaccine work?

When I present Ultimovacs and our vaccine, UV1, to investors and business development in pharma companies, I sometimes find a misunderstanding of how UV1 works. The misunderstanding is a belief that UV1 is an attempt to block or destroy telomerase, but there is a fundamental difference between conventional cancer therapy and immunotherapy of cancer.

The principle for conventional therapy is to apply an agent that directly kills or makes the cancer cells unable to divide. Immunotherapy of cancer does not kill cancer cells; it gets cancer cells killed – by the immune system.

The killing of cancer cells by the immune system is mostly done by T-cells. The body spontaneously makes T-cells as a response to having a growing tumor. How many T-cells the body makes differs between cancer types and patients. When the tumor is growing and is a serious threat to the patients, these T-cells are unable to control the cancer. Immunotherapy today mostly uses so called check point inhibitors. Their mode of action is to facilitate the killing of cancer cells by the T-cells the body made as a response to the growing tumor. The effect of checkpoint inhibitor totally relies on the spontaneous immune response to the tumor.

Checkpoint inhibitors can cure cancer in a subset of the patients receiving them. However, if the patient does not have enough relevant T-cells, the immune system will not be able to reduce the tumor, even with the support of one or more checkpoint inhibitors. These patients might benefit from new T-cells induced by a vaccine.

When receiving our vaccine, the body responds with making T-cells able to recognize, kill and facilitate killing of cells having telomerase. A large majority of cancer cells have telomerase. What telomerase does in the cancer cell is not the point in this context. The point is that telomerase serves as a marker for the T-cells to recognize the cancer cells. It is a good marker because we find it in most cancer types and the cancer cells will have telomerase as long as the tumor is in the patient.

We are now starting a randomized trial where we test if patients not responding to a combination of checkpoint inhibitors will benefit from receiving new T-cells induced by UV1 vaccination. From our earlier trials we know that 80-90% of the patients get T-cells recognizing telomerase after vaccination with UV1. We also know that patients that spontaneously (without vaccination) have made T-cells recognizing telomerase survive longer than patients that do not have these cells. We have a good rationale for our vaccine and trial, and the process for starting the trial is progressing according to our plan. It is exciting times!

Annual report 2018

Immunotherapy is a paradigm shift in treatment of cancer

Immunotherapy represents a true revolution in cancer treatment where the key is to boost the patient's immune system to fight cancer. Ultimovacs has developed a universal cancer vaccine that has the potential to give patients clinical benefits across most cancer types.

1. Immunotherapy represents a new paradigm in cancer treatment

During the last decades, immunotherapy has been a central area of cancer research and is now an established treatment option in many types of cancer. As compared with conventional treatments, immunotherapy utilizes a different approach to killing cancer cells. Instead of treating with toxic substances, strategies applied in immunotherapy are aimed at boosting the patient's immune system to fight cancer.

Recent successes in this field have provided significant impact on survival for cancer patients, most notably with the introduction of checkpoint inhibition.

Researchers found that even though some immune cells could recognize and potentially kill malignant cells, they were left inactivated through what is called immune checkpoint molecules. Immune checkpoints are defence mechanisms exploited by the tumor to avoid the immune system which are otherwise utilized by the body's tissue to prevent auto-immunity. Checkpoint inhibitor monoclonal antibodies were developed to block this defence mechanism, allowing the otherwise inactivated immune cells to kill cancer cells expressing their cognate antigen. Though many patients experience extraordinary response to checkpoint inhibition, unfortunately the majority of patients do not. Fundamental for a clinical benefit of this therapy is a pre-existing immune response against the tumor. It is believed that a lack of effect can be attributed to a non-existing recognition of cancer cells by the immune system.

2. Ultimovacs has developed a universal cancer vaccine that may play a major role in treatment and possibly prevention of cancer across most types of cancer

Ultimovacs aims to increase the pool of immune cells able to recognize and engage the cancer cells, thereby creating an inflammatory response ultimately leading to death of the tumor. To achieve this goal, we have developed a vaccine consisting of a known tumor-associated antigen, found to be almost universal to all cancer types. By combining our vaccine with a checkpoint inhibitor, we aim to mount a strong immune response against the tumor while simultaneously eliminating the tumors ability to diminish this response, opening for a possible synergistic relationship between these two treatment modalities.

We believe that our vaccine is well positioned to play a major role in future cancer treatment and possibly prevention. Manipulating the immune system to kill cancer cells and clear tumors will save many lives that earlier cancer treatments could not. It is important to remember that no matter how you manipulate the immune system, the effect of the treatment comes from cells in the immune system that are able to recognize and kill the cancer cells. The vast majority of immunotherapy treatments used today rely on these cells being made spontaneously by the immune system. These treatments make it possible for immune cells to do their job by removing some of the obstacles

preventing them from attacking the tumor. If patients do not have enough cells with the capability to kill the cancer cells, the present therapies simply cannot work. Our vaccine can supply these patients with activated cells able to fire up the immune system against the tumor. How do we know this? We know this because we have documented it in the trials we already have done. This, and the changes we see in some patients, is the very reason why we think it is right to take the next step and document the effect of the vaccine in one of more randomized trials.

If we can document a clinical benefit in one cancer type, we will over time seek to document the effect of the universal cancer vaccine in many different types of cancer and in different stages of disease, right up to where we possibly can prevent cancer from occurring in persons with very high risk. This will also be the future for cancer treatments in general. New technology will make it possible to diagnose cancer much earlier than we do now. The biology will be very different in a small, newly established tumor as compared to an older tumor with metastasis (i.e disease spread to other organs). What they will have in common is the possibility to be killed by an activated immune system. It is likely that a small "inexperienced" tumor is easier to eliminate than the tumors we are treating today. The best might be to make the immune system fit and ready to attack if the cancer appears. We believe that our vaccine can do that.

In 2018 we have taken one more step on this way, where a phase I trial study in malignant melanoma in which UV1 is given in combination with the PD-1 checkpoint inhibitor pembrolizumab was commenced. The acquisition of Tet Pharma AB (renamed to Ultimovacs AB) also strengthens our team as well as adding new technology to our R&D pipeline. I would like to convey sincere appreciation to our hard-working team and our gratitude for the continued support of our shareholders and board. We all are looking forward to a new exciting year in 2019.

Q4-18 Report

The objective of Ultimovacs

The main purpose of Ultimovacs at the present stage is to document the possible clinical usefulness of our cancer vaccine UV1. The company has now generated the knowledge needed to reach a decision on attempting to register UV1.

The main reason for starting on the final step towards possible filing for registration in 2023 is that we believe our vaccine is well positioned to play a major role in future cancer treatment and possibly prevention. Manipulating the immune system to kill cancer cells and clear tumors will save many lives that earlier cancer treatments could not. It is important to remember that no matter how you manipulate the immune system, the effect of the treatment comes from cells in the immune system that are able to recognize and kill the cancer cells.

The vast majority of immunotherapy treatments used today rely on these cells being made spontaneously by the immune system. These treatments make it possible for immune cells to do their job by removing some of the obstacles preventing them from attacking the tumor. If patients do not have enough cells with the capability to kill the cancer cells, the present therapies simply cannot work. Our vaccine can supply these patients with activated cells able to fire up the immune system against the tumor. How do we know this? We know this because we have documented it in the trials we already have done. This, and the changes we see in some patients, is the very reason why we think it is right to take the big leap and document the effect of the vaccine in a large, randomized trial.

If we succeed and are allowed to use the vaccine as a regular cancer treatment, we will continue to document the effect of the universal cancer vaccine in many different types of cancer and in different stages of disease, right up to where we possibly can prevent cancer from occurring in persons with very high risk. This will also be the future for cancer treatments in general. New technology will make it possible to diagnose cancer much earlier than we do now. The biology will be very different in a small, newly established tumor as compared to an older tumor with metastasis (i.e disease spread to other organs). What they will have in common is the possibility to be killed by an activated immune system. It is likely that a small "inexperienced" tumor is easier to eliminate than the tumors we are treating today. The best might be to make the immune system fit and ready to attack if the cancer appears. We will try to make our vaccine do that.