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Immunotherapy with BCG-VPM1002BC in patients with recurrent non-muscle invasive bladder cancer after conventional BCG therapy (trial SAKK 06/14)

Information on the results of the trial

We report below on the key results of the trial «Immunotherapy with BCG-VPM1002BC in patients with recurrent non-muscle invasive bladder cancer after conventional BCG therapy».

Trials are very important in enabling progress to be made in medicine and science. If you agree to be treated in the context of a clinical trial, you make a significant contribution to this end. By doing so, you help to answer health-related questions of other patients, to develop new treatments, or to improve existing ones. The Swiss Group for Clinical Cancer Research (SAKK) would like to express its sincere thanks for your participation and commitment.

1. Name of the trial

The original title of the trial is:

A phase I/II open label clinical trial assessing safety and efficacy of intravesical instillation of VPM1002BC in patients with recurrent non-muscle invasive bladder cancer after standard BCG therapy

Explanation of terms:

- "*Phase I/II trial*": These are the first clinical trials and are designed to investigate the efficacy and tolerability of a new active substance in a relatively small number of people.
- "*BCG*" is the abbreviation for Bacillus Calmette-Guérin. These are weakened bacteria (incapable of causing an infection) used in the treatment of bladder cancer. The bacteria are inserted via a catheter into the bladder, where they help stimulate an immune response to the cancer cells in the bladder mucosa.
- "*VPM1002BC*" is a BCG bacterial strain in which a gene has been replaced by another bacterial gene. In comparative investigations with conventional BCG, the BCG strain VPM1002BC triggers a modified immune response that may be more effective for treating bladder cancer.
- "*Non-muscle invasive bladder cancer*" means that the cancer cells are located only in the bladder mucosa and have not penetrated into the muscle layer. It is an early stage of bladder cancer.

Further explanations of technical terms can be found in the glossary at the end of this document.

2. Organization of the trial

The Swiss Group for Clinical Cancer Research (SAKK) planned and executed this trial. For more information about SAKK visit the website: www.sakk.ch.

3. General information about the trial

An early form of bladder cancer is termed non-muscle invasive bladder cancer. This term means that the cancer cells are limited to the bladder mucosa and have not yet penetrated into the muscle layer of the bladder. Non-muscle invasive bladder cancer is usually removed by surgery, which is followed by what is known as BCG therapy, with the aim of preventing recurrence of the cancer. In this treatment, special bacteria (Bacillus Calmette-Guérin, BCG) are instilled into the bladder, triggering an immune response in the bladder mucosa and thereby helping to combat the cancer.

Various bacterial strains of BCG exist, and it is assumed that the efficacy of each strain differs. In comparative investigations with conventional BCG, a promising new, genetically modified BCG strain termed "VPM1002BC" triggers a modified immune response that may be more effective for treating bladder cancer.
In trial SAKK 06/14 we wanted to find out how safe, well tolerated, and effective a treatment with BCG-VPM1002BC is in bladder cancer. People who suffered a recurrence of non-muscle invasive bladder cancer after an initial treatment (tumor recurrence) took part in the trial.

4. Participants

Between September 2015 and April 2018, 36 male and 4 female patients with non-muscle invasive bladder cancer participated in the trial (40 subjects in all). After diagnosis, their cancer had been removed and they had then received treatment with a standard BCG. Despite this treatment, the bladder cancer had recurred. In all trial participants there was a relatively high risk that the cancer would progress.

5. Course of trial treatment

All trial participants received treatment with BCG-VPM1002BC once a week for six weeks. These first six treatments constituted the *induction therapy.*. The treatments proceeded as follows:

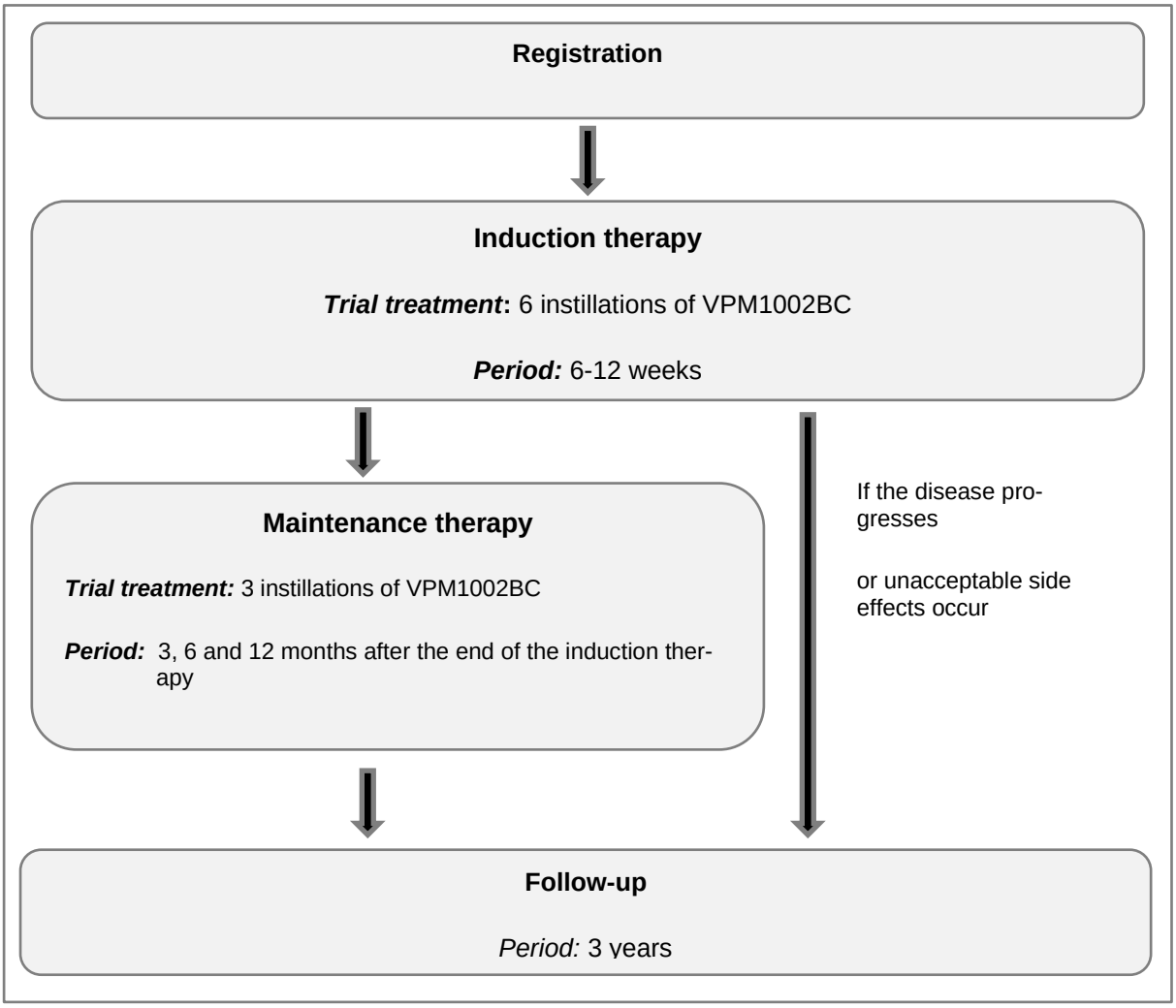
- A liquid solution with BCG-VPM1002BC was introduced into the bladder (instillation).
- The solution remained in the bladder for about two hours,
- after which the solution was flushed out of the bladder during urination.

The induction therapy phase was followed by the *maintenance therapy*. As maintenance therapy, BCG-VPM1002BC was again instilled into the bladder at months 3, 6 and 12 after the completion of the induction therapy. The maintenance therapy was not administered to all trial participants, either due to recurrence of the cancer or the decision, by two patients, to decline any further treatments.

The numbers of trial participants who received maintenance treatments were as follows:

- Instillation after 3 months: 33 participants
- Instillation after 6 months: 25 participants
- Instillation after 12 months: 15 participants

On completion of the trial treatment, all participants were followed up at regular intervals for a maximum of three years.



6. Factors examined

Various parameters were investigated in connection with the trial, including:

- *Recurrence-free rate (RFR):* In what percentage (rate) of trial participants is **no cancer detectable** in the bladder 60 weeks after the start of the treatment with BCG-VPM1002BC?
- *Time to recurrence*: How long does it take for a tumor to recur in the bladder after the start of the treatment with BCG-VBM1002BC?
- *Safety and tolerability* of the treatment: What side effects does the treatment have and how intense are they?
- *Quality of life*: What is the quality of life of the trial participants like during and after the treatment?

7. Results of the trial

Recurrence-free rate (RFR): 60 weeks after the start of treatment, the bladder cancer had not recurred (no tumor recurrence) in 49.3% of the trial participants. The recurrence-free rates two and three years after the start of treatment were 47.4% and 43.7% respectively.

Time to recurrence: The median time from the start of treatment to the diagnosis of a tumor recurrence in the bladder was 1.3 years.

Safety and tolerability of the treatment: The most common side effects of the treatment were bacterial infections of the urinary tract and reproductive system. Such infections occurred in 16 subjects, two of whom had to be treated in hospital as a result. Other common side effects were increased or frequent urge to urinate (12 subjects), pain in the urinary tract (7 subjects) and skin reactions (5 subjects). These and other less common side effects were mild and did not adversely affect the individuals concerned to any great extent.

Quality of life: The quality of life of the trial participants remained stable throughout the treatment period. Roughly one third of the patients reported a decline in quality of life during the induction therapy, for example due to physical limitations or tiredness.

8. Significance of the trial results

In almost half of those who were treated with BCG-VPM1002BC, the cancer had not recurred one year after the start of treatment. Three years after the start of treatment, the rate of participants without tumor recurrence in the bladder was still as high as 43.7% – this percentage indicates that the treatment with BCG-VPM1002BC has a long-term effect. The treatment with BCG-VPM1002BC was also safe, well tolerated (hardly any serious side effects) and did not adversely affect the participants' quality of life after the end of the trial.

The authors of the trial consider the treatment with BCG-VPM1002BC to be promising. Since, as the authors point out, the number of trial participants was low, generally valid conclusions cannot yet be drawn from these trial results. Trials with more participants are now needed to enable a better assessment of the effect of this treatment.

If future trials were to confirm that the treatment of non-muscle invasive bladder cancer with BCG-VPM1002BC is effective and well tolerated, then that would be an important advance in the treatment of this type of cancer. Many patients with bladder cancer could profit from this new therapeutic option.

Moreover, for 10 years there has been a global shortage of BCG for treating patients. This has led to an increase in tumor recurrences, more cystectomies and higher costs.

VPM1002BC could help solve this worldwide shortage of BCG.

Annex: Glossar

- **Bacterial strain:** Although different bacterial strains of the same bacterial species exist, they each differ slightly from each other, for example as a result of different genes. Various bacterial strains are grown in bacterial cultures**.**
- **BCG:** Abbreviation for Bacillus Calmette-Guérin; special bacteria instilled into the bladder for treating bladder cancer.
- **BCG therapy:** Treatment of bladder cancer with BCG**.**
- **Bladder catheter:** Thin plastic tube inserted into the bladder via the urethra. A catheter is used to empty the bladder of urine or – as in this trial – to introduce fluids into the bladder.
- **Single-arm trial:** Trial in which all participants receive the same treatment**.**
- **Open-label trial:** Trial in which the researchers and the participants know what treatment is being used.
- **Immunotherapy:** Treatment in which the body's own defenses (immune system) are stimulated to fight the cancer cells.
- **Instillation:** Administration of a drug into a hollow organ, in this trial the bladder**.**
- **Median:** In a set of data, the median is in the middle: half of the numbers are below and half above the median.
- **Non-muscle invasive:** Cancer cells have not penetrated into the muscle layer, in this trial the muscle layer of the bladder.
- **Phase I trial:** Trial in which an active substance that has never been previously tested in humans is administered to a small number of cancer patients with the aim of finding a safe dose.
- **Phase II trial:** Trial in which the efficacy of a treatment is investigated in a fairly large number of patients.
- **Recurrence:** Renewed occurrence of a disease**.**
- **Tumor recurrence:** Recurrence of a cancer after a successful treatment.
- **VPM1002BC:** A specific BCG bacterial strain in which a gene has been replaced by another**.**