

Targeted therapy of bone metastasis

# Fighting tumors with **alpha radiation**

*Many types of cancer form daughter tumors in the skeleton. These metastases cause severe pain and can lead to bone fractures. Scientists at Bayer HealthCare are now testing a promising new drug product that could specifically target bone metastases. The active ingredient is currently undergoing an initial clinical Phase III trial in prostate cancer.*

The disease's main effect on men is physical, but it also has an enormous impact on their self-esteem. Prostate cancer not only attacks the tissue of the male reproductive system but frequently also causes severe psychological damage to the patient's sexuality, which can have an extremely negative impact on his relationship with his partner. If doctors diagnose the tumor at an early stage while it is still confined to the prostate, it can often be successfully treated by surgery. Patients who are given optimum treatment can look forward to a normal life expectancy. If the disease is not diagnosed until it is in the late stage, however, it can be life-threatening.

Many of the elderly men who regularly visit Dr. Chris Parker, an oncologist at the Royal Marsden Hospital and Institute of Cancer Research to the south of London, are active and certainly do not

make the impression of being seriously ill. Nonetheless, they all have a dramatic problem: they are suffering from late-stage prostate cancer. In this phase of the disease, daughter tumors have already spread to the rest of the body. They come from cancer cells that the primary tumor distributes throughout the body via the lymphatic system and the bloodstream. Via the blood they attack the skeleton, in particular the spinal column, ribs, femur and pelvis.

### **Prostate cancer: resistance to standard active ingredients**

This leads to devastating pain, muscle weakness and weight loss. There is little prospect of a cure in this phase. Prostate cancer occurs primarily in elderly men and is as good as unknown in men aged below 40. Above this age, however, it is markedly more prevalent. Autop-

sies of U.S. men aged above 70 show that more than 80 percent of them had a latent prostate carcinoma which was not the cause of death. The standard treatment for advanced prostate cancer is chemotherapy, which extends life expectancy by 14 months on average. Doctors also rely on radiation and hormonal therapy, as the body's own testosterone promotes tumor growth. However, most carcinomas gradually develop a resistance to the active ingredients that reduce the body's levels of the sex hormone.

In the context of a controlled Phase III clinical trial, Parker is supplying these men suffering from late-stage prostate cancer with the novel substance Alpharadin, a radiopharmaceutical whose active ingredient is based on radium-223. This drug product is deposited into areas of new bone formation where it releases alpha

Deadly internal danger: prostate carcinoma is one of the forms of cancer that spread the most bone metastases (left) throughout the body. If the tumor is detected at an early stage – while it is still confined to the prostate gland – surgery can provide a cure. In screening tests, Dr. Martin Pelster (right in photo, right) checks certain indicators that may show that the disease is present.





Oncology expert Dr. Dimitris Voliotis, Vice President of Bayer HealthCare Global Clinical Development Oncology, is convinced that Alpharadin can improve the therapeutic prospects for prostate cancer sufferers.

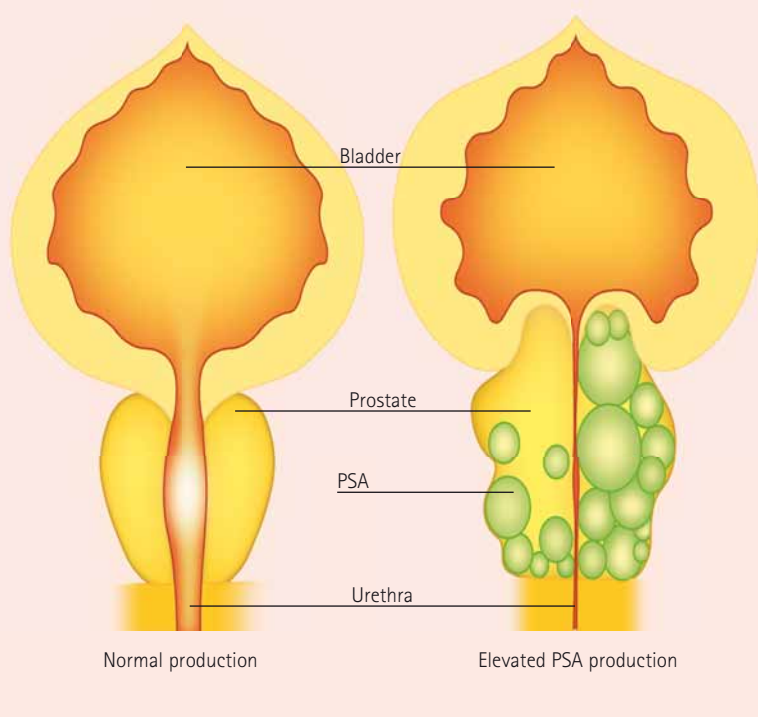
radiation, thereby attacking the bone metastases. "There are currently next to no options for late-stage prostate cancer. Participating in a clinical trial with the new active ingredient Alpharadin gives these patients another chance to fight their cancers," explains Parker. The ALSYMPCA study – short for Alpharadin in Symptomatic Prostate Cancer – is the last clinical testing stage before potential registration. "If this trial confirms what smaller studies have already demonstrated, we can further extend the life expectancy of patients by several months on average and markedly improve their quality of life," says Parker. But that is not the only success he is hoping for. "There is also the prospect that it may be possible to use Alpharadin for bone metastases resulting from other types of cancer in the near future," he adds. Prostate carcinoma is one of the types of cancer that spread the most bone metastases, and is therefore an ideal proving ground for testing the general efficacy of the new substance.

### New radiation therapy for bone metastasis

Research with the new radiation agent was initially started by radiochemist Roy Larsen and cancer researcher Øyvind S. Bruland, founders of the Norwegian company Algeta. Once the first stud-

## The value of early recognition

*The prostate surrounds the male urethra, which transports urine from the bladder through the penis to the glans. The prostate also produces prostate-specific antigen (PSA for short), which liquefies semen. In an early diagnosis method known as PSA screening, the patient's PSA level is determined. The higher the PSA level, the greater the risk that the patient suffers from prostate cancer. The gland tissue then proliferates and constricts the urethra – urine can no longer flow unimpeded from the bladder. The medical world is however still in debate about whether the PSA test leads to overtherapy; some doctors believe that not every tumor diagnosed at an early stage would automatically lead to the death of the patient without early recognition or treatment.*



ies for prostate cancer had been successfully concluded, they looked for a partner with international experience in oncology to further develop the substance and prepare it for registration by the authorities. Their inquiry was received with great interest by the scientists at Bayer HealthCare: "Alpharadin is a highly targeted radiation therapy to specifically treat bone metastases, and fits perfectly into our oncology portfolio," says Mark Gelder, Head of Oncol-

ogy in Global Medical Affairs at Bayer HealthCare. In addition to Nexavar®, a drug product to treat liver and kidney cancer, the portfolio also includes several new compounds, some of which are likewise already undergoing clinical testing.

Alpharadin has several special characteristics that make this alpha radiation agent a hopeful candidate in the battle against bone metastasis. For example, it can be administered intra-



Cells in focus: a biopsy – a tissue sample taken from the patient – can help to identify a dangerous prostate tumor. Wafer-thin cell layers are examined under a microscope to determine whether the tissue changes are benign or malignant.

venously without problems. In addition, its half-life – the length of time after which half of the radionuclides have decayed – is only 11.4 days. The most important advantage of Alpharadin, however, is its selective effect: the radium-223 makes its way to the skeleton within ten minutes, limiting the exposure to other healthy tissues and organs. This is because the substance is very similar to the bone mineral calcium. As a result, the body is easily able to integrate Alpharadin into the bone structure during the rebuilding process. Metastases in the skeleton are particularly active: some form new bone substance, while others destroy the structure. In any case, however, they absorb the active ingredient directly while doing so.

### Minimal scatter allows even more targeted treatment

The same principle applies to the radiopharmaceutical active ingredient strontium-89. However, this beta radiation agent also damages the surrounding tissue due to its greater range. Radium-223 by contrast is an alpha radiation agent whose concentrated dose of radiation does not cause an effect further than two to ten cells away. Another advantage of Alpharadin is that it moves quickly to the gut from where it is rapidly excreted. No notice-

able traces of it appear elsewhere in the body.

Initial successes have already been achieved in a Phase II trial with 64 subjects: the Alpharadin patients with late-stage prostate cancer lived for four months longer than the control group on average. They also suffered less pain. The Phase III trial in which the Royal Marsden Hospital and Parker's Institute of Cancer Research and other leading cancer research centers in Europe and North America are involved has been running since 2008. 900 patients with hormone-refractory, late-stage prostate cancer are taking part in it to gather statistically meaningful data on the positive effects of the new substance.

Preparations have also been made for the time after regulatory approval has been hopefully granted. "A trial to test Alpharadin in combination with the chemotherapy docetaxel recently got underway," says Dr. Dimitris Voliotis from Global Clinical Development at Bayer HealthCare. The scientists from Bayer and Algeta plan to test the drug product in extended patient groups with prostate carcinomas, bone metastases in breast cancer and potentially also in primary bone tumors (osteosarcomas). A Phase II trial for patients with hormone-refractory breast cancer and bone metastasis has already been launched.

# Interview



## Patients lead their normal lives

Dr. Chris Parker from the Royal Marsden Hospital and Institute of Cancer Research to the south of London is in charge of the Phase III trial with Alpharadin. *research* talked to him about his experiences.

### What have been your experiences with treatment with Alpharadin?

It was only a small-scale trial, but the results impressed me. It was also very gratifying to see how well tolerated the drug product was. In the second phase, we injected four doses at four-week intervals. Now it's six doses in the current Phase III trial.

### Why is more now being administered?

Because the substance had such a good effect and its toxicity was surprisingly low, it seemed like a good idea to use it for longer.

### How many people are taking part in the current Phase III trial (ALSYMPCA)?

So far, 20 patients have taken part at our hospital. One patient even comes from abroad. And that shows how well tolerated the drug product is. The patients carry on living their normal lives while they are in treatment.

### What therapeutic options are available for late-stage, hormone-refractory prostate cancer besides Alpharadin?

Chemotherapy is currently the standard. However, many of the patients taking part in this Phase III trial have already been through chemotherapy. These patients would therefore normally receive only what is known as palliative care – measures for pain management such as "spot" radiation therapy.

