

(NASDAQ market code: NVGN)

Novogen (NRT) Buy

APPROVAL TO TREAT CERVICAL CANCER

Shareprice:	\$5.35	Y/end June	2002a	2003e	2004e	2005e
Shares now	95.6m	Revenue \$m	23.1	29.1	32.5	32.4
Market Cap A\$m	\$511.5m	NPAT \$m	-14.7	-12.2	-10.8	-12.7
Risk	High	EPS c	-0.15	-0.13	-0.11	-0.13
		PER x	N/a	N/a	N/a	N/a
		DPS c	0.0	0.0	0.0	0.0
		Yield %	0.0	0.0	0.0	0.0

Shareprice \$

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Key Points

Novogen's subsidiary, Marshall Edwards, has announced that an Investigational New Drug application (IND) has been approved by the FDA for the commencement of a phase II clinical trial of phenoxodiol, administered orally as a monotherapy to women with squamous cell carcinoma (SCC) of the cervix, vagina and vulva. The women registered for the trial have been scheduled for surgery, but will initially try phenoxodiol.

Marshall Edwards has commissioned Yale University to conduct the clinical trial, the same team which is currently involved in a phase II clinical trial using phenoxodiol to treat ovarian cancer.

Each year, about 20,000 women in the United States learn that they have cancer of the cervix. Most cervical cancers are squamous cell carcinomas (SCC). Squamous cells are thin, flat cells that form the surface of the cervix. SCC is a common type of cancer found in the skin (which Novogen is currently running another phase II trial in Sydney) and mucous membranes of the body such as the mouth and lungs.

The potential for phenoxodiol in the treatment of SCC arose from an observation that patients being treated with phenoxodiol for other forms of cancer, who coincidentally had SCC of the skin had experienced SCC tumour regression. Hence the treatment of SCC is now being further developed.

We maintain our Buy recommendation as this exemplifies the multitude of potential treatments phenoxodiol offers in the battle against cancer.

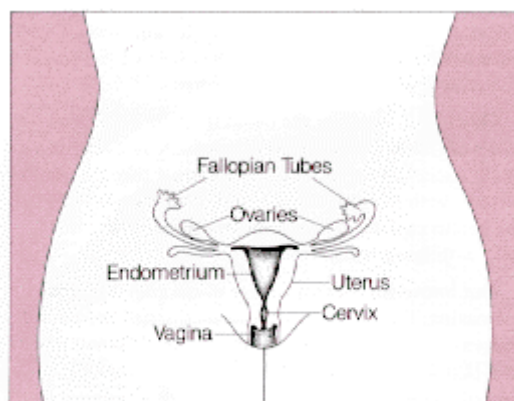
Clinical Trials

Cancer Type	Clinical trials commences	Expected completion
Leukemia	Q4 CY2002	Q2 CY2004
Ovarian	Q4 CY2002	Q1 CY2004
Skin	Q3 CY2003	Q4 CY2004
Cervical	Q3 CY2003	Q1 CY2005
Prostate	Q1 CY2003	Q1 CY2004

As opposed to the ovarian trial, which is intravenous, both the skin cancer and the cervical cancer trials are orally administered. Usually an oral formulation is very difficult to develop because the digestive tract destroys the drug, or the drug does not pass through the gut wall or, the stomach conjugates sugar molecules onto the drug rendering it inactive. However, phenoxodiol is of a similar chemical structure to steroids, and acts very similar to the oral contraceptive pill in the stomach. Developing an effective oral formulation would be of a similar challenge to developing the oral contraceptive pill.

The Cervix

The cervix is the lower, narrow part of the uterus (womb). The uterus, a hollow, pear-shaped organ, is located in a woman's lower abdomen, between the bladder and the rectum. The cervix forms a canal that opens into the vagina, which leads to the outside of the body.



This picture shows the uterus, cervix, and other parts of a woman's reproductive system.

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What is Cervical Cancer?

Cancer is a group of more than 100 different diseases. They all affect the body's basic unit, the cell. Cancer occurs when cells become abnormal and divide without control or order.

Like all other organs of the body, the cervix is made up of many types of cells. Normally, cells divide to produce more cells only when the body needs them. This orderly process helps keep us healthy.

If cells keep dividing when new cells are not needed, a mass of tissue forms. This mass of extra tissue, called a growth or tumor, can be benign or malignant.

- **Benign tumors** are not cancer. They can usually be removed and, in most cases, they do not come back. Most important, cells from benign tumors do not spread to other parts of the body. Benign tumors are not a threat to life. Polyps, cysts, and genital warts are types of benign growths of the cervix.
- **Malignant tumors** are cancer. Cancer cells can invade and damage tissues and organs near the tumor. Cancer cells also can break away from a malignant tumor and enter the lymphatic system or the bloodstream. This is how cancer of the cervix can spread to other parts of the body, such as nearby lymph nodes, the rectum, the bladder, the bones of the spine, and the lungs. The spread of cancer is called metastasis.

Cancer of the cervix also may be called cervical cancer. Like most cancers, it is named for the part of the body in which it begins. Cancers of the cervix also are named for the type of cell in which they begin. Most cervical cancers are squamous cell carcinomas. Squamous cells are thin, flat cells that form the surface of the cervix.

When cancer spreads to another part of the body, the new tumor has the same kind of abnormal cells and the same name as the original (primary) cancer. For example, if cervical cancer spreads to the bones, the cancer cells in the bones are cervical cancer cells. The disease is called metastatic cervical cancer (it is not bone cancer).

Cancer of the cervix is different from cancer that begins in other parts of the uterus and requires different treatment. The most common type of cancer of the uterus begins in the endometrium, the lining of this organ.

Precancerous Conditions

Cells on the surface of the cervix sometimes appear abnormal but not cancerous. Scientists believe that some abnormal changes in cells on the cervix are the first step in a series of slow changes that can lead to cancer years later. That is, some abnormal changes are precancerous; they may become cancerous with time.

Detection

If all women had pelvic exams and Pap tests regularly, most precancerous conditions would be detected and treated before cancer develops. That way, most invasive cancers could be prevented. Any invasive cancer that does occur would likely be found at an early, curable stage.

In a pelvic exam, the doctor checks the uterus, vagina, ovaries, fallopian tubes, bladder, and rectum. The doctor feels these organs for any abnormality in their shape or size. A speculum is used to widen the vagina so that the doctor can see the upper part of the vagina and the cervix.

The Pap test is a simple, painless test to detect abnormal cells in and around the cervix.

A Pap test can be done in a doctor's office or a health clinic. A wooden scraper (spatula) and/or a small brush is used to collect a sample of cells from the cervix and upper vagina. The cells are placed on a glass slide and sent to a medical laboratory to be checked for abnormal changes.

Symptoms

Precancerous changes of the cervix usually do not cause pain. In fact, they generally do not cause any symptoms and are not detected unless a woman has a pelvic exam and a Pap test.

Symptoms usually do not appear until abnormal cervical cells become cancerous and invade nearby tissue. When this happens, the most common symptom is abnormal bleeding. Bleeding may start and stop between regular menstrual periods, or it may occur after sexual intercourse, douching, or a pelvic exam. Menstrual bleeding may last longer and be heavier than usual. Bleeding after menopause also may be a symptom of cervical cancer. Increased vaginal discharge is another symptom of cervical cancer.

Treatments

The choice of treatment for cervical cancer depends on the location and size of the tumor, the stage (extent) of the disease, the woman's age and general health, and other factors.

Most often, treatment for cervical cancer involves surgery and radiation therapy. Sometimes, chemotherapy or biological therapy is used. Patients are often treated by a team of specialists. The team may include gynecologic oncologists and radiation oncologists. The doctors may decide to use one treatment method or a combination of methods.

Surgery is local therapy to remove abnormal tissue in or near the cervix. If the cancer is only on the surface of the cervix, the doctor may destroy the cancerous cells in ways similar to the methods used to treat precancerous lesions. If the disease has invaded deeper layers of the cervix but has not spread beyond the cervix, the doctor may perform an operation to remove the tumor but leave the uterus and the ovaries. In other cases, however, a woman may need to have a hysterectomy or may choose to have this surgery, especially if she is not planning to have children in the future. In this procedure, the doctor removes the entire uterus, including the cervix; sometimes the ovaries and fallopian tubes also are removed. In addition, the doctor may remove lymph nodes near the uterus to learn whether the cancer has spread to these organs.

Radiation therapy (also called radiotherapy) uses high-energy rays to damage cancer cells and stop them from growing. Like surgery, radiation therapy is local therapy; the radiation can affect cancer cells only in the treated area. The radiation may come from a large machine (external radiation) or from radioactive materials placed directly into the cervix (implant radiation). Some patients receive both types of radiation therapy.

A woman receiving external radiation therapy goes to the hospital or clinic each day for treatment. Usually treatments are given 5 days a week for 5 to 6 weeks. At the end of that time, the tumor site very often gets an extra "boost" of radiation.

For internal or implant radiation, a capsule containing radioactive material is placed directly in the cervix. The implant puts cancer-killing rays close to the tumor while sparing most of the healthy tissue around it. It is usually left in place for 1 to 3 days, and the treatment may be

repeated several times over the course of 1 to 2 weeks. The patient stays in the hospital while the implants are in place.

Chemotherapy is the use of drugs to kill cancer cells. It is most often used when cervical cancer has spread to other parts of the body. The doctor may use just one drug or a combination of drugs.

Anticancer drugs used to treat cervical cancer may be given by injection into a vein or by mouth. Either way, chemotherapy is systemic treatment, meaning that the drugs flow through the body in the bloodstream.

Chemotherapy is given in cycles: a treatment period followed by a recovery period, then another treatment period, and so on. Most patients have chemotherapy as an outpatient (at the hospital, at the doctor's office, or at home). Depending on which drugs are given and the woman's general health, however, she may need to stay in the hospital during her treatment.

A common chemotherapeutic drug used for the treatment of cervical cancer is cisplatin. Recently, Novogen have discovered that using cisplatin in combination with phenoxodiol has an enhanced therapeutic effect and renders chemoresistant cancer cells sensitive to chemotherapy.

Biological therapy is treatment using substances to improve the way the body's immune system fights disease. It may be used to treat cancer that has spread from the cervix to other parts of the body. Interferon is the most common form of biological therapy for this disease; it may be used in combination with chemotherapy. Most patients who receive interferon are treated as outpatients.

Side-effects

It is hard to limit the effects of therapy so that only cancer cells are removed or destroyed. Because treatment also damages healthy cells and tissues, it often causes unpleasant side effects.

The side effects of cancer treatment depend mainly on the type and extent of the treatment. Also, each patient reacts differently.

Surgery

Methods for removing or destroying small cancers on the surface of the cervix are similar to those used to treat precancerous lesions. Treatment may cause cramping or other pain, bleeding, or a watery discharge.

Hysterectomy is major surgery. For a few days after the operation, the woman may have pain in her lower abdomen. The doctor can order medicine to control the pain. A woman may have difficulty emptying her bladder and may need to have a catheter inserted into the bladder to drain the urine for a few days after surgery. She also may have trouble having normal bowel movements. For a period of time after the surgery, the woman's activities should be limited to allow healing to take place. Normal activities, including sexual intercourse, usually can be resumed in 4 to 8 weeks.

Many women have an emotionally difficult time after this surgery. A woman's view of her own sexuality may change, and she may feel an emotional loss because she is no longer able to have children.

Radiation Therapy

Patients are likely to become very tired during radiation therapy, especially in the later weeks of treatment. Resting is important, but doctors usually advise patients to try to stay as active as they can.

With external radiation, it is common to lose hair in the treated area and for the skin to become red, dry, tender, and itchy. There may be permanent darkening or "bronzing" of the skin in the treated area. This area should be exposed to the air when possible but protected from the sun, and patients should avoid wearing clothes that rub the treated area. Patients who receive external or internal radiation therapy also may have diarrhea and frequent, uncomfortable urination.

Chemotherapy

The side effects of chemotherapy depend mainly on the drugs and the doses the patient receives. In addition, as with other types of treatment, side effects vary from person to person. Generally, anticancer drugs affect cells that divide rapidly. These include blood cells, which fight infection, help the blood to clot, or carry oxygen to all parts of the body. When blood cells are affected by anticancer drugs, patients are more likely to get infections, may bruise or bleed easily, and may have less energy. Cells in hair roots and cells that line the digestive tract also divide rapidly. When chemotherapy affects these cells, patients may lose their hair and may have other side effects, such as poor appetite, nausea, vomiting, or mouth sores.

Biologicals

The side effects caused by biological therapies vary with the type of treatment the patient receives. These treatments may cause flu-like symptoms such as chills, fever, muscle aches, weakness, loss of appetite, nausea, vomiting, and diarrhea. Sometimes patients get a rash, and they may bleed or bruise easily. These problems can be severe, but they gradually go away after the treatment stops.

Causes

By studying large numbers of women all over the world, researchers have identified certain risk factors that increase the chance that cells in the cervix will become abnormal or cancerous. They believe that, in many cases, cervical cancer develops when two or more risk factors act together.

Research has shown that women who began having sexual intercourse before age 18 and women who have had many sexual partners have an increased risk of developing cervical cancer. Women also are at increased risk if their partners began having sexual intercourse at a young age, have had many sexual partners, or were previously married to women who had cervical cancer.

Scientists do not know exactly why the sexual practices of women and their partners affect the risk of developing cervical cancer. However, research suggests that some sexually transmitted viruses can cause cells in the cervix to begin the series of changes that can lead to cancer. Women who have had many sexual partners or whose partners have had many sexual partners may have an increased risk for cervical cancer at least in part because they are more likely to get a sexually transmitted virus.

Scientists are studying the effects of sexually transmitted human papillomaviruses (HPVs). Some sexually transmitted HPVs cause genital warts (*condylomata acuminata*). In addition, scientists believe that some of these viruses may cause the growth of abnormal cells in the cervix and may play a role in cancer development. They have found that women who have HPV or whose partners have HPV have a higher-than-average risk of developing cervical cancer.

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