

(NASDAQ market code: NVGN)

Novogen (NRT) Buy

POSITIVE RESULTS FROM ASCO

Shareprice:	\$4.18	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	\$400m	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

The American Society of Clinical Oncology (ASCO) meeting commenced last week in Chicago. Novogen had a presentation at ASCO relating to phenoxodiol's efficacy in ovarian cancer cells. Phenoxodiol induces apoptosis in ovarian cancer cells by specifically removing the blockers of apoptosis. In the present studies, Yale University demonstrated phenoxodiol induces sensitivity to chemoresistant ovarian cancer cells to low levels of chemotherapy.

Results: Phenoxodiol treatment for 48 hours induces 60-80% decrease in ovarian tumour cell viability in chemotherapeutic (carboplatin & paclitaxel – two standard chemotherapies) resistant cells. Thus emphasising that phenoxodiol is a very promising monotherapy for ovarian cancer.

In addition, these studies indicate that Phenoxodiol can be effectively used as a combination therapy. Pre-treatment for 2 hours with phenoxodiol in chemoresistant tumour cells followed by chemotherapy (carboplatin or paclitaxel) for 48 hours resulted in 30% and 50% significant decrease in tumour cell viability, respectively. *In vivo* studies showed cisplatin had no effect on tumour size while the combination of phenoxodiol and cisplatin reduced tumour mass by 75%.

Conclusion: Phenoxodiol is both an effective monotherapy and combination therapy for the treatment of ovarian cancer by restoring the sensitivity to standard chemotherapies in resistant ovarian cancer cells.

Recommendation. Given Novogen's progress in its Phenoxodiol trials, we have upgraded our recommendation from Spec Buy to Buy.

The Science

Ovarian cancer is the fourth leading cause of cancer death and the most lethal of the gynaecologic malignancies. New therapies have led to improvements in the five-year survival, yet there has been no improvement in the overall survival. The limitations of therapy in ovarian cancer patients are chemoresistance and side-effects. Phenoxodiol induces apoptosis in ovarian cancer cells by specifically removing the blockers of apoptosis. In the *in vivo* and *in vitro* studies, Yale University demonstrated phenoxodiol induces sensitivity to chemoresistant ovarian cancer cells to low levels of chemotherapy.

The *in vivo* effect was tested by injecting an established ovarian cancer cell line subcutaneously into nude mice (mice that possess no immune system). Animals received daily oral administration of phenoxodiol, 10-20 mg/kg for 8 days alone or in combination with cisplatin 0.5 mg/kg. After 8 days the animals were sacrificed and the tumour volume was measured.

With respect to the data, one of the key endpoints is the IC50, which is a measure of the number of tumour cells eliminated. The lower the IC50, the more tumour cells are being eliminated. It is a commonly used measure in clinical trials for cancer treatment. Typically, IC50 is calculated using various concentrations of the drug to determine the optimal dose for therapy.

Phenoxodiol treatment for 48 hours induced 60-80% decrease in cell viability in carboplatin and paclitaxel resistant cells.

Pre-treatment with phenoxodiol alone for 2 hours decreased cell viability by 20%. Furthermore, pre-treatment with phenoxodiol for 2 hours in chemoresistant cells followed by carboplatin or paclitaxel for 48 hours resulted in a 30% and 50% significant decrease in cell viability, respectively. The IC50 was significantly reduced by a factor of 100 for carboplatin and paclitaxel. This means that after cells were pre-treated with phenoxodiol, standard chemotherapy eliminated tumour cells in very low concentration – concentration so low that they would cause minimal adverse side-effects to the patient.

In vivo, cisplatin (0.5mg/kg) had no effect on tumour size while the combination of phenoxodiol (10mg/kg) and cisplatin (0.5mg/kg) reduced human ovarian tumour mass by 75%. This data indicates that phenoxodiol retains its potent anti-cancer effect *in vivo*, in this case, in rat models.

This data suggests that phenoxodiol is an effective monotherapy and it restores the sensitivity to standard chemotherapies in resistant ovarian cancer cells by interacting with apoptotic blockers. Thus the strategy to developing phenoxodiol is two fold.

- 1) Phenoxodiol will be developed as a monotherapy because the results indicate potent anti-cancer properties.
- 2) Phenoxodiol will be developed in combination with standard chemotherapeutic agents because as the results show, there is a synergistic therapeutic effect at doses that are not associated with adverse side-effects.

Clinical Trials

The clinical trials for ovarian cancer at Yale University and the Royal Prince Alfred are using phenoxodiol as a monotherapy. Novogen's strategy is to register phenoxodiol as a monotherapy with the FDA as soon as possible, then extend the label indication by running further clinical trials using phenoxodiol as combination therapy.

To date, 30 patients suffering from late stage IV ovarian cancer have been enrolled and trials are progressing well. Patients with stage IV ovarian cancer have tried every other therapy available and have failed. Some patients have been on as many as 6 different regimens of different chemotherapy cocktails. Patients on phenoxodiol have experienced tumour regression and/or stabilisation. The trial was designed to be multi-centered, having trial sites both in the USA and Australia. However, there has been such a demand in the USA that the trial will predominantly be run in the USA, and a small sample size to be trialled in Australia. These phase II trials are expected to be completed by September 2003 and results are expected to be presented at the Society of Gynaecology meeting in February 2004.

A Revolutionary Discovery

One of the most exciting properties of phenoxodiol is its ability to kill a number of different types of cancers. Phenoxodiol has shown clinical efficacy in ovarian cancer, prostate cancer, renal cancer, leukaemia and squamous cell cancer (one of the forms of skin cancer). For years this has perplexed Novogen scientists as to the ubiquitous nature of phenoxodiol's anti-cancer action.

Scientists at Purdue University in Indiana believe they have discovered the reasons as to why phenoxodiol is effective against various types of cancer. Phenoxodiol induces apoptosis. Apoptosis (programmed cell death) is essential for tissue homeostasis, which is the balance between cell proliferation and apoptosis. An imbalance in tissue homeostasis such as unwanted tissue atrophy (i.e. cells dying via apoptosis too rapidly resulting in ageing) or excessive cell proliferation (i.e. tissue becomes immortal resulting in cancer) causes a disease state.

The main difference between normal cells and cancer cells is its sensitivity to apoptosis. In cancer cells, the ability for those cells to die via apoptosis is inactivated by a series of enzymes such as protein tyrosine kinase, sphingosine kinase and cyclin-dependant kinases. These kinases all require a common molecule to function, that is, they all require a phosphate molecule in which the enzyme undergoes a process known as phosphorylation. Phenoxodiol interrupts the phosphorylating ability of kinases by targeting an enzyme known as NOX, making phenoxodiol the first phosphorylating inhibitor to be tested in the clinic. This is effectively the master switch, which is upregulated in cancer cells. Phenoxodiol is specific to this master switch only in cancer cells, and leaves normal cells unaffected.

In comparison, all other anti-cancer drugs tend to target only one kinase or enzyme. This is true for new cancer drugs like IRESSA, which was recently approved for the treatment of lung cancer. IRESSA only targets one protein kinase and provides only a slight improvement to the quality of life of the patient.

Conclusion

- Yale researchers have discovered that phenoxodiol is an effective monotherapy for ovarian cancer.
- Furthermore phenoxodiol combined with small doses of chemotherapy significantly reduces tumour mass and tumour cell viability in chemoresistant tumour cells.
- A revolutionary discovery at Purdue University which explains why phenoxodiol works on multiple enzyme pathways to induce apoptosis in cancer cells while showing no toxicity in normal cells.

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