

OPAXIO™ (paclitaxel poliglumex, CT-2103) is our novel chemotherapeutic agent that links paclitaxel to a biodegradable polymer. OPAXIO was designed to improve the delivery of paclitaxel to tumor tissue while protecting normal tissue from toxic side effects. Because the polymer is water-soluble, OPAXIO can be administered without solvents and infused over an average of ten to twenty minutes. OPAXIO remains stable in the bloodstream for several days after administration; this prolonged circulation allows the passive accumulation of OPAXIO in tumor tissue.³

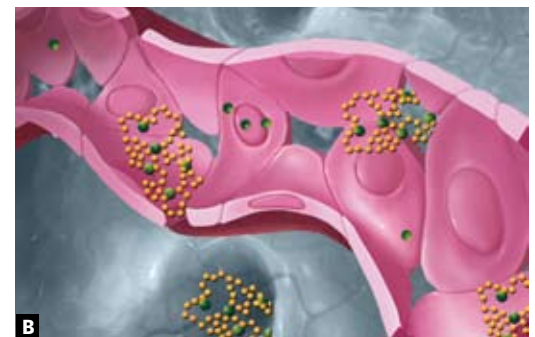
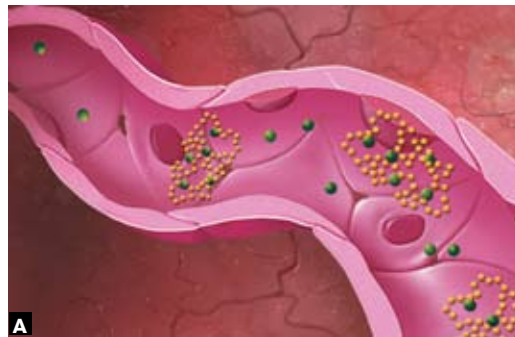
Limited Potential of Current Taxanes

Because taxanes are small, hydrophobic agents, their therapeutic potential is limited by unfavorable pharmacokinetic properties:^{1,2}

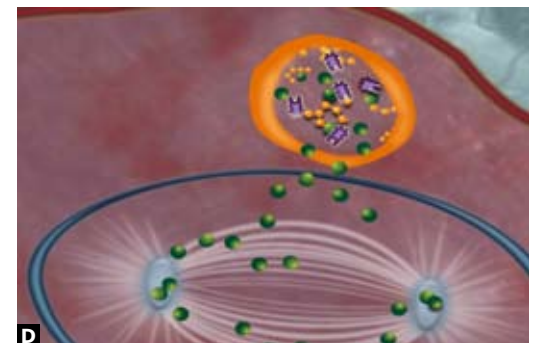
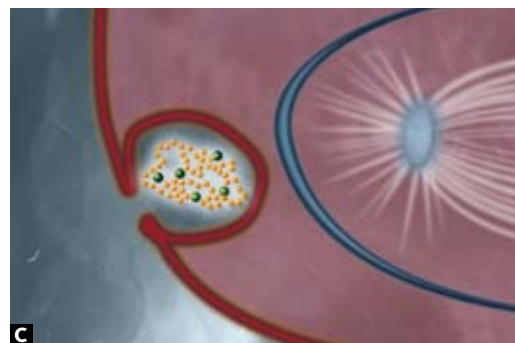
- Solvents are needed for administration, and these solvents are linked to clinically important adverse events.
- High peak levels of drug immediately following administration expose normal tissues to toxic effects.
- Rapid elimination of the drug from blood limits tumor exposure.

Taxanes, including paclitaxel (Taxol®) and docetaxel (Taxotere®), are widely used for the treatment of various solid tumors, including non-small cell lung, ovarian, breast, and prostate cancers. According to the Tandem Cancer Audit 2006, more than half of the taxane use in taxane-sensitive advanced cancers is in lung and ovarian cancers.

WHAT SCIENTISTS HAVE FOUND



Unlike vessels in healthy tissue (A), those in tumor tissue (B) have openings that make them porous. Due to the larger size of OPAXIO compared to standard paclitaxel, the OPAXIO leaks through the pores in tumor blood vessels and is preferentially trapped and distributed to the tumor tissue.



Once in the tumor tissue (C), the OPAXIO is taken up by the tumor cells through a cellular process called endocytosis. Because the biopolymer OPAXIO is made up of biodegradable amino acids, it is slowly metabolized by lysosomal enzymes (principally cathepsin B) inside the lysosome of the tumor cell.⁴ This metabolism releases the active chemotherapy agent, paclitaxel (D). The activity of this enzyme and thus the rate of release of OPAXIO is increased in the presence of estrogen.

CLINICAL RESEARCH

Currently, we are studying OPAXIO™ in pivotal trials for non-small cell lung and ovarian cancers.

(OPAXIO™ was formerly branded as XYOTAX™.)

Gender Differences in Lung Cancer

Differences in lung tumor biology between men and women affect the relative risk for lung cancer, the relationship between smoking and lung cancer, and response to therapy.⁶⁻⁹

- Female non-smokers are more likely to develop lung cancer than male non-smokers.
- Compared to men, women who smoke are more likely to develop lung cancer at a younger age and at lower levels of exposure to cigarette smoke.
- Younger, presumably premenopausal, women with NSCLC have shorter survival than older women.
- Women on hormone replacement therapy developed NSCLC at a younger age.
- Estrogen enhances the effects of carcinogens in the environment and in smoke, possibly leading to a higher risk for NSCLC, and once it occurs, appears to enhance its development.

Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death worldwide. Among females, the incidence of lung cancer continues to increase, killing more women than breast, ovarian, and cervical cancers combined. The American Cancer Society estimates that in 2008 there will be about 215,020 new cases of lung cancer in the United States: 114,690 among men; 100,330 among women. More than 85 percent of lung cancers are diagnosed as non-small cell. Nearly 60 percent of people with lung cancer die within one year of their diagnosis. The five-year survival rate is only 15%, a figure that has changed little in more than 30 years.

Two randomized phase III trials, STELLAR 3 and STELLAR 4, compared OPAXIO alone or in combination with carboplatin to standard therapy in PS2 patients with advanced NSCLC. STELLAR 2, also phase III, compared OPAXIO to docetaxel in patients with relapsed disease. Another phase III trial, PIONEER (PGT305), compared OPAXIO to paclitaxel in first-line treatment of PS2 women with advanced NSCLC. These studies treated more than 1,900 patients.

The STELLAR trials did not meet their endpoints of superior survival. Instead single-agent OPAXIO resulted in similar efficacy, and with the exception of neuropathy, improved tolerability in both first-line and second-line treatment of advanced NSCLC. Hypersensitivity reactions were rare on the OPAXIO arms of the studies despite the lack of required premedications.

In December 2006, in agreement with the Data Safety Monitoring Board, we closed the PIONEER trial and took patients off both treatment arms. Our decision was due in part to the diminishing utility of the PIONEER trial given our plans to submit a new protocol to the U.S. Food and Drug Administration (FDA).

Women and Lung Cancer

The efficacy of OPAXIO as a first-line treatment in advanced NSCLC was evaluated in our STELLAR 3 and 4 trials. The composite analysis showed a statistically significant survival benefit for women receiving OPAXIO (198 patients) compared to the control arms, where men treated with OPAXIO did similarly to men treated with comparator agents. The largest improvement in survival

with OPAXIO was seen in women under age 55 and in women with premenopausal estrogen levels, regardless of age (51 patients).

Studies show that premenopausal women and women receiving hormone replacement therapy have a poor outcome compared to post-menopausal women.⁵ Elevated estrogen levels have an adverse effect on prognosis in advanced NSCLC even with standard chemotherapy. Retrospective analysis of clinical data from STELLAR 3 and STELLAR 4 suggest that OPAXIO's anti-tumor activity may be modulated by estrogen levels. Recent *in vivo* studies indicate that OPAXIO metabolism by some cancer cells is enhanced in the presence of estrogen, which leads to increased levels of paclitaxel in tumor tissue and greater anti-tumor effects.

Clinical Trials for Women with NSCLC PGT307 (Enrolling)

A phase III clinical trial, known as PGT307, is currently recruiting women with advanced NSCLC who have premenopausal estrogen levels (> 25 pg/mL) – a group whose survival is significantly shorter than post-menopausal women. We received Special Protocol Assessment (SPA) approval from the FDA on the design of the trial.

This phase III trial is expected to enroll 450 patients. Each study arm of approximately 225 patients will be randomized to receive either OPAXIO 175mg/m² plus carboplatin, or paclitaxel 225mg/m² plus carboplatin once every three weeks. Patients will be treated for up to six cycles. The primary endpoint is superior overall survival with several secondary endpoints including progression-free survival, disease control, clinical benefit, response rate, quality of life, and the safety and tolerability of the treatment arms.

STELLAR 3 and STELLAR 4

STELLAR 3 and STELLAR 4 were randomized, open-label, multinational phase III studies in patients with advanced NSCLC who were chemotherapy-naïve and had poor performance status (PS2). STELLAR 3 compared the effect of standard paclitaxel/carboplatin to OPAXIO/carboplatin. STELLAR 4 compared OPAXIO to standard single-agent therapy with either gemcitabine or vinorelbine. These studies were conducted simultaneously.

Pre-specified analysis by stratification factors shows a trend for improved survival in women receiving OPAXIO in each of the two randomized studies. Because women made up only about 25 percent of patients on STELLAR 3 and 4, each individual study had limited statistical power for gender-specific analysis. A composite analysis of the studies shows a statistically significant survival benefit (HR: 0.70; P=.03) for women receiving OPAXIO compared to the control arms (paclitaxel in STELLAR 3 or gemcitabine or vinorelbine in STELLAR 4). Males had similar survival in both arms.

OPAXIO™ in Lung Cancer Trials

Enrolling

PGT307 - Phase III, First-line PS0-2 (450 patients)
Women with advanced NCSLC and premenopausal estrogen levels (> 30pg/mL) comparing OPAXIO plus carboplatin to paclitaxel and carboplatin

Completed

STELLAR 2 - Phase III, Second-line PS0-2 (849 patients)

	OPAXIO	Docetaxel
Median OS (mo)	6.9	6.9
1-year survival	25%	29%
2-year survival	9%	12%
Avg. infusion time	19 minutes	68 minutes

STELLAR 3 - Phase III, First-line PS2 (400 patients)

	OPAXIO/ carboplatin	Paclitaxel/ carboplatin
Median OS (mo)	7.8	7.9
1-year survival	31%	31%
2-year survival	13%	11%
Avg. infusion time	48 minutes	224 minutes

STELLAR 4 - Phase III, First-line PS2 (381 patients)

	OPAXIO	Gemcitabine or Vinorelbine
Median OS (mo)	7.2	6.5
1-year survival	26%	26%
2-year survival	15%	10%
Avg. infusion time	12 minutes	30 minutes

In the STELLAR 3 trial, the OPAXIO/ carboplatin arm provided comparable survival to standard paclitaxel/carboplatin without required pre-medications. There was a lower incidence of alopecia, musculoskeletal symptoms (arthralgia/myalgia), cardiac symptoms, and neuropathy. However, more grade 3/4 neuropathy was seen on the OPAXIO arm (17 percent vs. 10 percent), as well as more grade 3/4 thrombocytopenia (23 percent vs. 8 percent), and grade 3/4 neutropenia (27 percent vs. 16 percent).

In the STELLAR 4 trial, OPAXIO had similar efficacy when compared to two control agents, either vinorelbine or gemcitabine, and the median survival of OPAXIO as a single agent was similar to doublet therapy in PS2 patients. Patients who received single-agent OPAXIO experienced a 40 percent improvement in overall survival, which was statistically significant when compared to patients who received vinorelbine (32 patients), one of the control agents. The OPAXIO arm had a significant reduction of all toxicities except neuropathy which was higher (grade 3, 4 percent vs. 0 percent), and infection. The trial demonstrated a significant reduction in severe (grade 3/4) neutropenia and anemia.

Patients on OPAXIO in the STELLAR 4 trial required less supportive care, including decreased use of red blood cell transfusions, erythropoietin, growth factors, and narcotic pain relievers, as well as fewer clinic visits, than patients on the control arm.

STELLAR 2

OPAXIO was compared to docetaxel for second-line treatment of NSCLC patients in STELLAR 2. OPAXIO was administered without required premedications. While OPAXIO had comparable efficacy, it resulted in a significant reduction in many side effects including infections, neutropenia, febrile neutropenia, fatigue, and breathing problems. The OPAXIO arm had more neuropathy (50 percent vs. 30 percent), and more grade 3/4 neuropathy (19 percent vs. 3 percent).

Ovarian Cancer

Ovarian cancer ranks fifth in cancer deaths among women in the United States. The American Cancer Society estimates that there will be about 21,650 new cases of ovarian cancer and 15,520 deaths in the United States during 2008.

Phase II Induction Trial (PGT201)

At the 41st American Society of Clinical Oncology Annual Meeting (ASCO 2005), preliminary data were reported from a phase II study of OPAXIO in combination with carboplatin for first-line induction and single-agent maintenance therapy of advanced stage III/IV ovarian cancer. Of the 82 patients studied,

Exploratory Analysis: Effect of Sex

Overall Survival (OS; Months) by Sex

	OPAXIO			Control		
	N	OS	1-yr	N	OS	1-yr
STELLAR 3	199	7.8	31%	201	7.9	31%
Male	151	7.8	29%	156	7.9	33%
Female	48	7.8	37%	45	8.2	25%
STELLAR 4	191*	7.2	26%	190	6.5	26%
Male	142	6.8	20%	134	6.3	25%
Female	49	10.3	43%	56	6.9	26%

*Patients receiving OPAXIO at 175 mg/m²

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98 percent (80 patients) achieved a major tumor response based on CA125 levels, including 85 percent complete response (CR) and 12 percent partial response (PR). Grade 3/4 side effects at the 175 mg/m² dose in combination with carboplatin (AUC=6) included neuropathy (23 percent), nausea (15 percent), vomiting (7 percent), febrile neutropenia (19 percent), anemia (11 percent), thrombocytopenia (55 percent), and neutropenia (92 percent). Only three patients (5 percent) at the 175 mg/m² dose required dose delay due to neutropenia. No grade 4 neuropathy was observed.

OPAXIO™ in Ovarian Cancer Trials

GOG0212 Phase III	Maintenance therapy compared to no therapy Enrolling	Dose 135 mg/m ²	~ 1,100 patients
PGT201 Phase II	Induction therapy in combination with carboplatin Completed	Dose 175 mg/m ²	N=82

Phase III Maintenance Trial (GOG0212)

CTI and the Gynecologic Oncology Group (GOG) are presently evaluating OPAXIO (135 mg/m²) as monthly maintenance in a phase III clinical trial in ovarian cancer patients who have achieved a complete response following standard first-line chemotherapy. Target enrollment for the trial, which includes a third paclitaxel arm to determine safety, is approximately 1,100 patients. The GOG has established the standards for treatment of ovarian and other gynecologic cancers in the United States and has a track record of conducting high quality clinical trials upon which product registration has been based.



Making cancer more treatable®

Additional Information

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Radiation Research

Data from a phase I study of weekly OPAXIO given in combination with radiation for patients with esophageal or gastric cancer was published in the August 2006 issue of the *American Journal of Clinical Oncology*. Twenty-one patients were treated to evaluate the safety of the regimen and to determine the maximum tolerated dose of OPAXIO in combination with 50.4 Gy concurrent radiation.

Of the 12 patients with loco-regional disease in whom tumor responses were evaluated, four patients (33 percent) achieved a complete response and seven patients (58 percent) achieved a partial response (50 percent or greater shrinkage of their tumor), for an overall objective response rate of 91 percent. At the maximum tolerated dose of 70 mg/m²/week given for six weeks, one patient had

grade 3 esophagitis. There were no grade 3/4 toxicities at dose levels below 70 mg/m²/week. At the 80 mg/m² dose level, three of four patients had dose limiting toxicities including grade 3 esophagitis/gastritis (2 patients), grade 3 dehydration (1 patient), and grade 4 neutropenia (1 patient). Except for the four patients who experienced dose limiting toxicity, all patients completed the full six weeks of concurrent chemoradiation.