samyang
Biopharmaceuticals

Genexol-PM
(Paclitaxel)

- **Metastatic or Recurrent Breast Cancer**
- **Advanced or Metastatic Non-small Cell Lung Cancer**
- **Advanced Pancreatic Cancer (clinical stage)**
- **Ovarian Cancer (clinical stage)**

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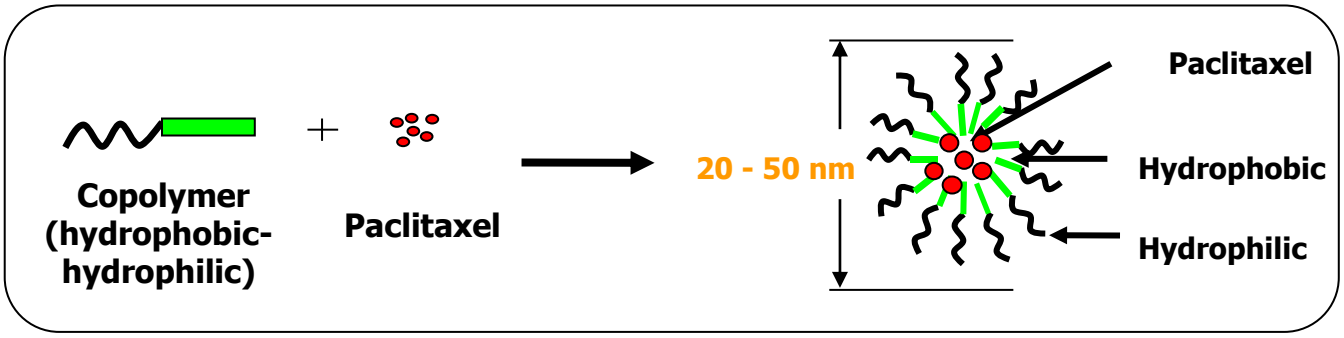
Rev. January/11/2013

Genexol-PM

1. Composition

- Package : 30 mg paclitaxel/vial and 100 mg paclitaxel/vial
- Composition: Paclitaxel + proprietary biopolymer

2. Formulation (Lyophilisate)



* **Samyang's Polymeric Micelle (PM) platform is a non-toxic, biodegradable polymer based system for solubilization of poorly soluble drugs**

- **Cremophor free formulation of paclitaxel (Less Toxicity)**
- **Higher MTD value compared to chremophore based paclitaxel formulation (Higher Efficacy)**

3. Indications

- **Metastatic or Recurrent Breast Cancer (1st line)**
- **Locally Advanced or Metastatic NSCLC (in combination with Cisplatin)**

- **Advanced Pancreatic Cancer (phase II in US)**

4. Market

- **Breast & NSCLC cancers**
- **Launched in Korea (2007)**
- **Launched in India, Vietnam, Philippines, & Indonesia (2009)**

5. Dosage and Administration

- Metastatic or recurrent breast cancer :

✓ 300 mg/m^2 i.v. over 3 hours every 3 weeks. No Premedication required.

- Locally advanced or metastatic non-small cell lung cancer :

✓230 mg/m^2 i.v. over 3 hours every 3 weeks. Premedication required.

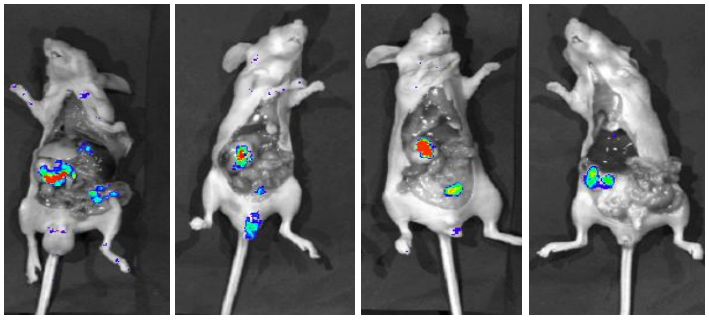
Preclinical Studies

1. Toxicity studies

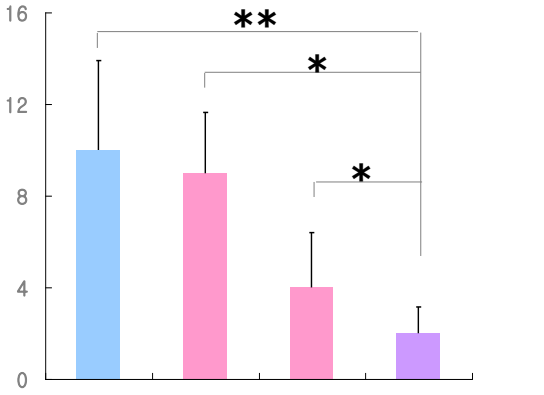
Species/model	Dosing regimen	MTD (mg/kg)	
		Genexol-PM	Taxol ®
Mice bearing B16F10	Once/day x 3	**50**	20
Nude mice bearing SKOV3	4 times/day x 3	**50**	20
CD-1 mice	Single	**420**	9
	5 cycles (3weekly)	**120**	9
SD rats	Single	**200**	8
Beagle dogs	Single (infusion)	4.5/3 hr inf.	2.5/30 min inf.
	5 cycles (infusion, 3wks.)	4.5/3 hr inf.	2.5/30 min inf.

2. Efficacy study in orthotopic pancreatic tumor model

- GFP- ASPC-1 tumor fragment was surgically implanted onto pancreas
- Animal : (BALB/C, nu/nu, female) athymic nude mice
- Drug administration & group : 20 days after implantation, i.v.(3 times/dx3) , 6 mice/group
- Evaluation: 50 days after implantation, primary tumor weight & metastasis
- RESULT: Higher MTD, Higher tumor concentration & Reduction in tumor volume



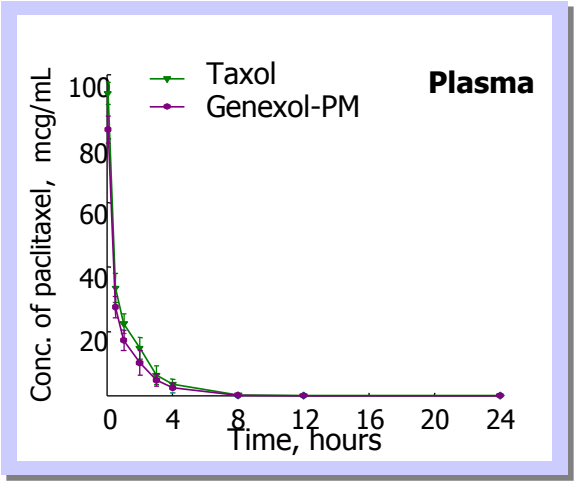
Control **Taxol 20mg/kg** **Taxotere 13 mg/kg** **Genexol-PM 50 mg/kg**

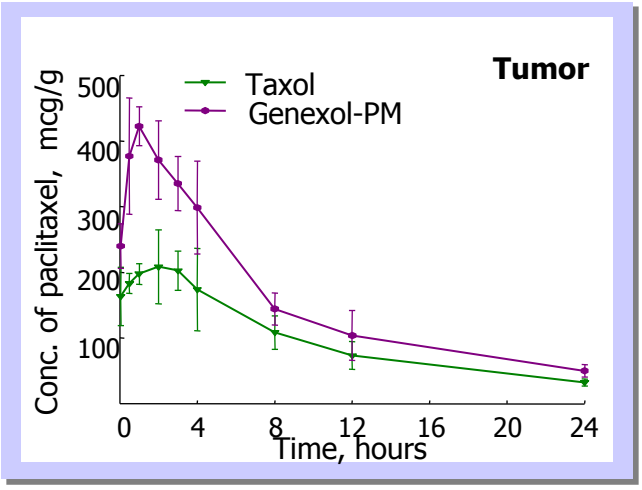


**, p<0.01; *, p<0.05

3. Pharmacokinetic studies

- Animal: Female C57BL/6 mice ; s.c. inoculation of murine B16F10 melanoma
- Treatment initiated after tumors grew to 50~400 mm^3
- Group and Dose: Genexol-PM (50 mg/kg, n=4), Taxol (20 mg/kg, n=4)
- RESULT: Substitution of Cremophor by patented bioabsorbable polymer results in changes in Pharmacokinetic behavior of paclitaxel: higher MTD and lower toxicity.





Clinical Studies (Completed)

1. Phase I studies

	Korea	US
Number of patients	21	23
MTD	390 mg/m^2	> 435 mg/m^2
DLT	Neutropenia, myalgia, neuropathy	Diarrhea, fatigue, neutropenia

2. Phase II studies

1) Metastatic or recurrent breast cancer (in Korea)

- Dose : 300 mg/m^2 administered over 3 hours every 3 weeks
- Primary endpoint : response rate

- Response

Tumor Response	ITT (N=41*)
Complete Response	12.2%
Partial Response	46.3%
Stable Disease	31.7%
Progressive Disease	4.9%
Not evaluable	4.9%

- Adverse events (Grade III & IV)

Major adverse events (N=41)	
Neotropenia (Grade IV)	17.1%
Febrile Neutropenia	0.0%
Neuropathy[1)]	17.1%
Hypersensitivity[2)]	4.9%

[1)] :Analyzed for the treatments prior to 6 cycle
[2)] :Premedication was not applied

2) Locally advanced or metastatic NSCLC (in Korea)

- Dose : 230 mg/m^2 administered over 3 hours every 3 weeks in combination with 60 mg/m^2 of cisplatin
- Primary endpoint : response rate

- Response

Tumor Response	ITT (N=69)
Complete Response	0.0%
Partial Response	37.7%
Stable Disease	29.0%
Progressive Disease	23.2%
Not evaluable	10.1%

- Adverse events (Grade III & IV)

Major adverse events (N=69)	
Neutropenia (Grade IV)	17.4%
Febrile Neutropenia	2.9%
Neuropathy	13.0%
Myalgia/Arthralgia	7.3%
Hypersensitivity	5.8%

3) Advanced pancreatic cancer (in US)

- Dose : 300 mg/m^2 or 350m/m2 administered over 3 hours every 3 weeks
- Primary endpoint : time to tumor progression (TTP)

- Efficacy

Number of Pts	N=45
Response (CR+PR)	7.7 %
TTP	2.7 Mon
Overall Survival	6.5 Mon

- Adverse events (Grade III & IV)

Major adverse events (N=69)	
Neutropenia (Grade IV)	15.6%
Neuropathy	13.3%
Nausea/Vomiting	4.4%

Clinical Studies (Recent & Ongoing)

1. Phase I combination therapy (completed)

- Genexol-PM and Gemcitabine in advanced pancreatic cancer (under US FDA IND) ; Preliminary Results

- Dose finding :
  Genexol-PM administered over 3 hours every 3 weeks in combination with 1250 mg/m^2 of Gemzar

	Genexol PM		Tarceva
Dose	1,250 mg/m^2 of Gemzar with 220, 260, 300 mg/m^2 of Genexol-PM	1,250 mg/m^2 of Gemzar with 300 mg/m^2 of Genexol-PM	1,000 mg/m^2 of Gemzar with 100 or 150 mg/d of Tarceva
RR (%)	28	**50**	**8.6**
Patients #	18	6	285

2. Post Marketing Surveillance (completed)

1) PMS in Breast cancer (safety)

- Dose : 300 mg/m^2 administered over 3 hours every 3 weeks
- Enrollment: 132 patients
- Safety evaluation results
  - ✓ Adverse Events : Occur in 97 patients(73.5%), 496 case ➔ Grade IV & V (7.86%)
  - ✓ Unexpected Adverse Events : 3 case

2) PMS in Lung cancer (safety & efficacy)

- Dose : 230 mg/m^2 administered over 3 hours every 3 weeks in combination with 60 mg/m^2 of cisplatin
- Enrollment: 191 patients (safety), 181 patients (efficacy)
- Safety evaluation results
  - ✓ Adverse Events : Occur in 168 patients(88%), 1,306 case ➔ Grade IV & V (2.84%)
  - ✓ Unexpected Adverse Events :Occur in 93 patients(49%), 191 case
    - Tingling sensation 8.3% , Hiccup 6.8%, Rash 6.3%
- Efficacy evaluation results
  - ✓ Objective Response Rate: 50%

3. Phase II study

1) Ovarian cancer (in Korea: completed)

- Dose : 260 mg/m^2 administered over 1 hours every 3 weeks in combination with Carboplatin 5 AUC
- No. of patients: 100

4. Phase III study

1) Breast cancer (in Korea, ongoing)