samyang
Biopharmaceuticals

Docetaxel-PNP
(Docetaxel, anhydrous)

- **Resistant Cancers (clinical stage)**

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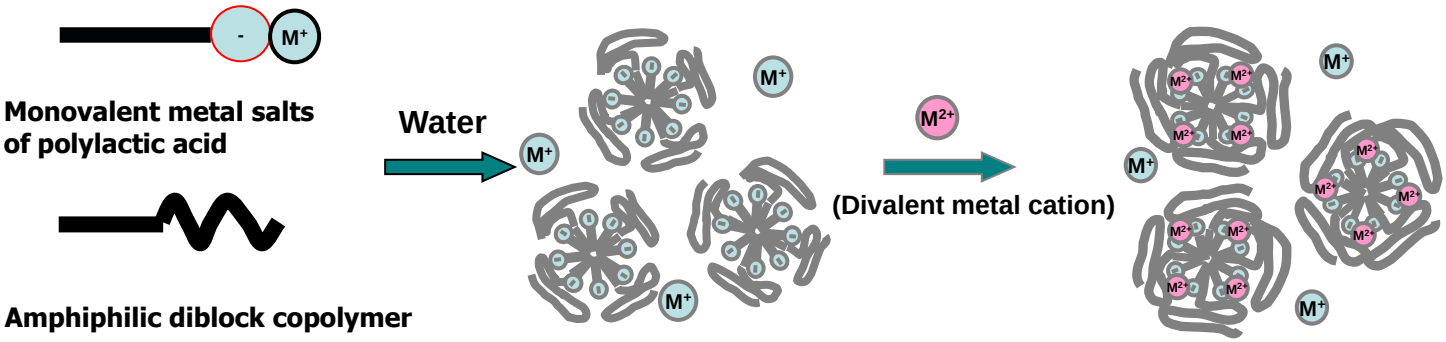
Docetaxel-PNP (Polymeric Nano-Particle)

1. Unmet Needs of existing chemotherapy

- Shortcoming of conventional Docetaxel formulation
  - Tween-80 originated hypersensitivity, requires premedication
  - Short period of blood circulation, limited efficacy

- Opportunities to improve therapy
  - Prolonged exposure of docetaxel to tumor
  - Minimizing the systemic toxicity related to vehicle

2. PNP (Polymeric Nano-Particle)



- Feature of PNP (Polymeric Nano-Particle)
  - Nanometer size particle (10 ~ 1,000 nm)
  - Sustained release of Docetaxel
  - Biocompatible & biodegradable polymer

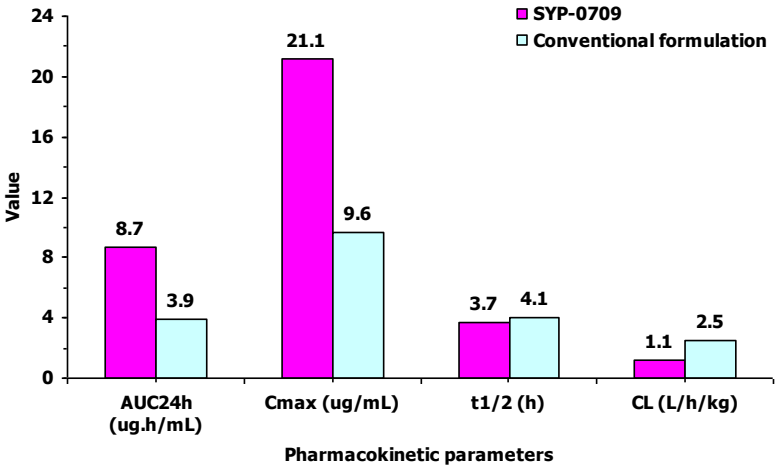
3. Expected Dosage and Administration

- No premedication required
- Indicated for the treatment of various advanced/resistant cancers
- Dosage information & treatment cycle (undecided)

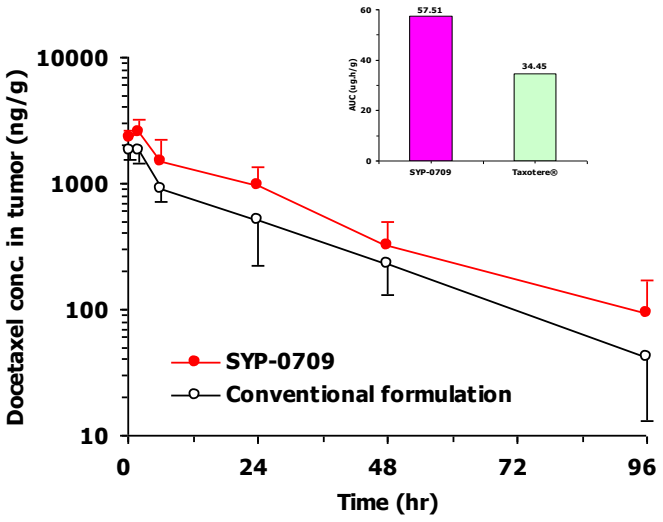
Pre-Clinical Study of Docetaxel-PNP (SYP-0709)

1. Pharmacokinetic studies

- Animal : ICR mice (8 weeks, ca. 28 g), n=5
- Group and Dose: Docetaxel-PNP (10 mg/kg)
  Docetaxel conventional formulation (10 mg/kg)
  via tail vein
- RESULT: Longer blood circulation
  higher AUC & slower clearance

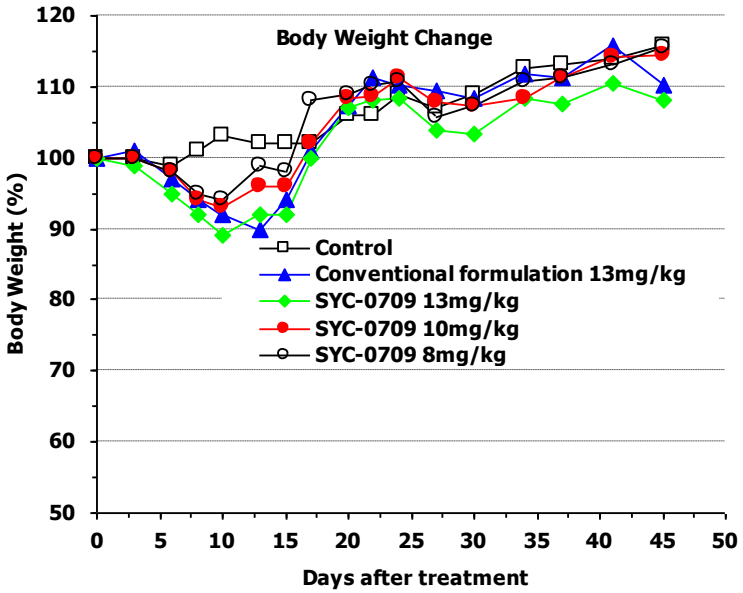


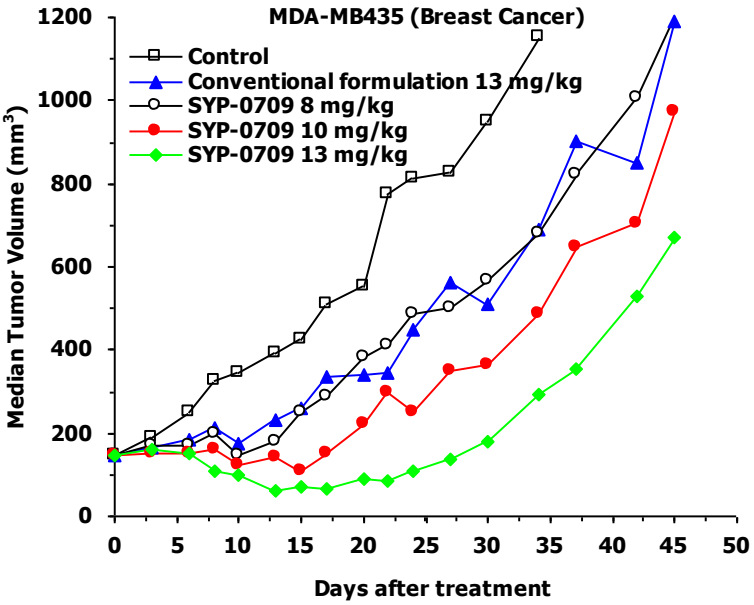
- Animal: Female nu/nu athymic mice with H1299 xenograft (8 weeks, ca. 20 g), n=5
- Group and Dose: Docetaxel-PNP (10 mg/kg)
  Docetaxel conventional formulation (10 mg/kg)
  via tail vein
- RESULT: Higher accumulation in tumor tissue



2. MTD (Maximum Tolerance Dose), In vivo Efficacy

- Animal: MDA-MB435 Xenograft tumor model, Cancer cell line: Human breast cancer cell line
- Group and Dose: Docetaxel-PNP (8, 10, 13 mg/kg),
- Docetaxel conventional formulation (13 mg/kg), 3 times/day x3 days
- RESULT: Similar MTD between Docetaxel-PNP and Docetaxel conventional formulation → 13 mg/kg
  Superior efficacy in animal tumor models at equivalent or lower dose



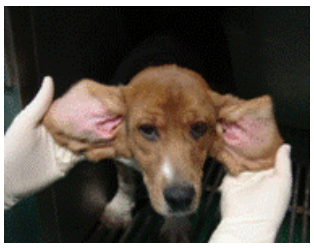


Pre-Clinical study

3. Hypersensitivity Study

- Animal : Beagle Dogs (n=3~4)
- Dosing Regimen : iv infusion for 30 minutes
- Dose: 0.35, 0.7, 1.4 mg/kg
- Sampling: 30 minutes after the start of iv infusion
- Premedication: Not treated
- RESULT: No hypersensitive reaction

• Docetaxel-PNP treated



• Conventional formula treated

- **Superior therapeutic profile preclinical studies compared with Docetaxel conventional formulation**
  - Desirable pharmacokinetic profile
  - Longer blood circulation: higher AUC & slower clearance
  - Higher accumulation in tumor tissue
- **Superior efficacy in animal models at equivalent or lower dose**
- **Possibly lower toxicity**
  Free from hypersensitivity reactions attributed to Tween-80

Phase I Clinical Study completed

1. Synopsis of the Study

- **Trial Objectives**
  - ✓ **Primary: the MTD and Recommended Ph II Dose**
  - ✓ **Secondary: the DLT and the PK on Day 1 of 1st cycle**
- **No. of Subjects: 3~6 patients for each group**
- **Dose level: 20 → 35 → 45 → 60 → 75 → 90 mg/m2**
- **Evaluation: DLT (only for 1st Cycle), MTD (2 DLTs in a dose level) Parmacokinetics, Safety, ORR**

2. Conclusion

- **MTD & Recommended Dose**
  - **MTD: tentatively 75 mg/m2**
  - **Recommended Dose: 45~60 mg/m2**
- **Pharmacokinetics**
  - **AUC: AUC of 60~80% dose in Docetaxel-PNP group is similar to the AUC in Taxotere® Group**
  - **T1/2: 1.5 to 2 times longer than Taxotere®**
- **Safety**
  - **Main adverse event: Neutropenia due to the long circulation in blood**
  - **Other adverse event (Diarrhea, Myalgia, Alopecia, Asthenia) : lower grade compared to Taxotere®**

Summary

1. Advantage of Docetaxel-PNP

- Enhanced stability of
  'Polymeric Nano-Particle containing Docetaxel' in blood
  → Longer blood circulation
  → Prolonged drug exposure to tumor cells
  → Superior efficacy
- Elimination of solubilizer-related hyper-sensitivity reactions
  → No Premedication

2. Current Status

- In Korea,
  - Phase I completed (Apr/2010 ~ Dec/2011)
  - Phase II ready
- To Worldwide
  - Open for Technology Transfer
  - Open to discuss various biz model based on Samyang's EU-GMP of oncologic drugs