

Comparison of In Vivo Efficacy of Nanoencapsulated Paclitaxel with Taxol and Abraxane

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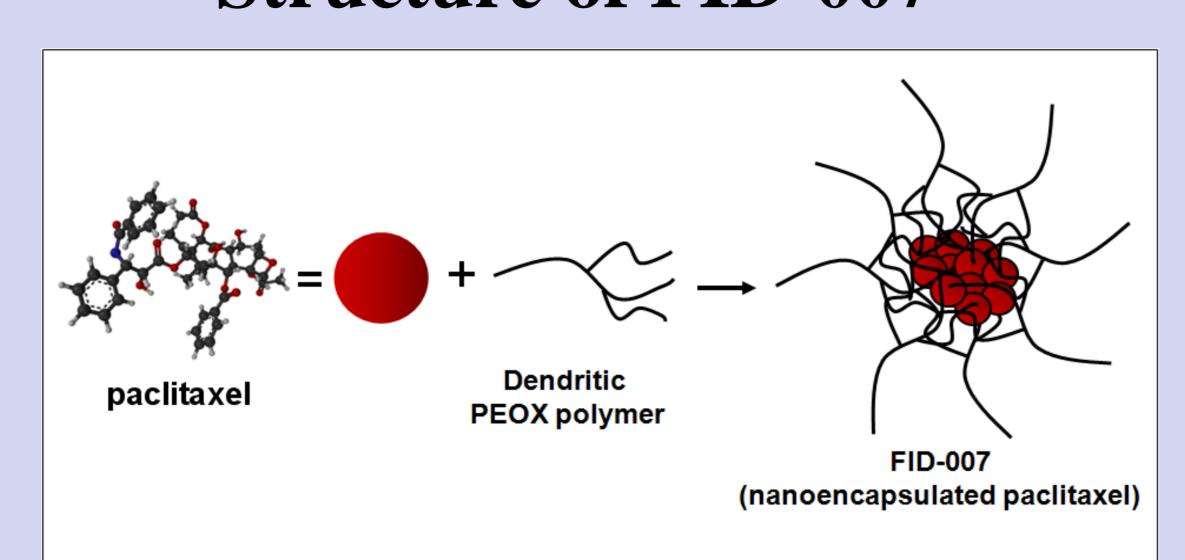
Introduction

- FID-007 is nanoencapsulated paclitaxel
- Paclitaxel is used in the treatment of breast, lung, and ovarian cancers.
- Paclitaxel is water insoluble and therefore difficult to deliver to cancer cells
- By nanoencapsulating paclitaxel with non-toxic and non-immunogenic PEOX polymers, the following benefits may be attained:
 - improve water solubility
 - reduce toxicity
 - prolong blood circulation time
 - enhance therapeutic efficacy

Available taxane-based drugs:

- 1. Taxol: paclitaxel in an ethanol/Cremaphor EL surfactant Limitations: Toxicity and allergic reactions
- 2. Abraxane: paclitaxel attached to human albumin, reduces toxicity and improves solubility. Limitations: Cardiotoxic, temporary loss of vision

Structure of FID-007



Particle Size with Dilution

Concentration, dilution	FID-007 (nm)	Abraxane (nm)
5 mg/mL	122	176
5 mg/mL, 1:10	67	141
5 mg/mL, 1:100	26	133
5 mg/mL, 1:1000	32	18

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Comparison Studies

FID-007 was compared to Taxol and Abraxane in several in vitro and in vivo studies:

- 1. Cytotoxicity to normal human fibroblast, A549 lung cancer, MDA-MB-231 triple negative breast cancer, and OV-90 ovarian cancer cell lines
- 2. Pharmacokinetic (PK) profile in mice
- 3. Single dose maximum tolerated dose (MTD) in CD-1 mice
- 4. Multiple dose MTD in Scid mice
- 5. In vivo efficacy in reducing xenograft tumor growth in mice using gemcitabine-resistant head and neck, pancreatic, breast, and ovarian cancer cell lines.

Cytotoxicity Studies

FID-007 showed cytotoxicity to A549 lung cancer, MDA-MB-231 triple negative breast cancer, and OV-90 ovarian cancer cell lines similar to Taxol and Abraxane. It was not cytotoxic to normal human fibroblast cells.

Maximum Tolerated Dose (MTD) Studies

Single dose MTD (CD-1 mice)

FID-007: 175 mg/kg Taxol: >20 mg/kg Abraxane: >180 mg/kg

Multi-dose MTD (CD-1 mice): FID-007: 100 mg/kg

Multi-dose MTD (Scid mice): FID-007: 30 mg/kg

In Vivo Efficacy in Mouse Xenograft Tumors

Human cancer cell lines were grown as xenograft tumors in each side of torsos of Scid mice (20 mice each cancer, sex appropriate):

A549 Lung Cancer

KB-Gem Gemcitabine-resistant Head and Neck Cancer Mia-Paca Pancreatic Cancer MDA-MB-231 Triple-Negative Breast Cancer

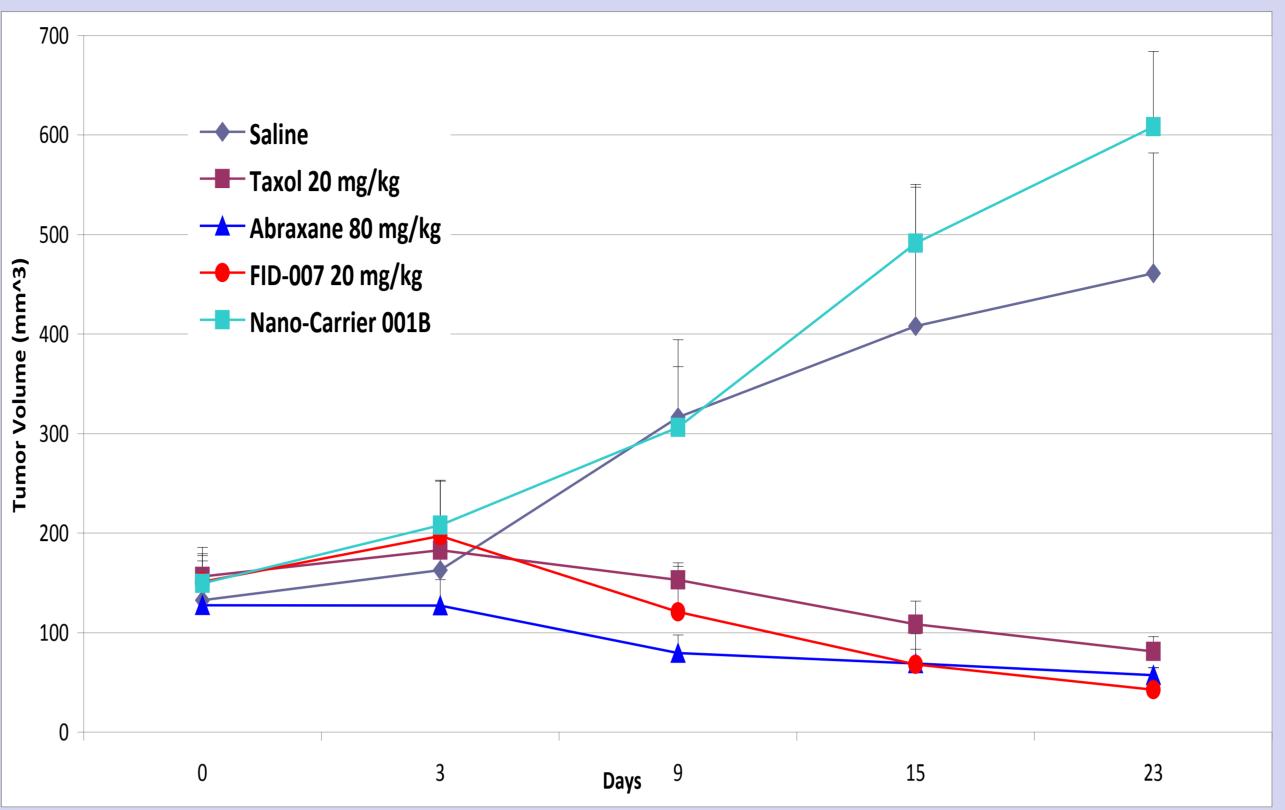
OV-90 Ovarian Cancer

Tumors were allowed to grow 7-9 days. Mice were randomly divided among treatment groups:

- 1. FID-007, 20-25 mg/kg
- 2. Taxol, 20 mg/kg
- 3. Abraxane, 20 80 mg/kg
- 4. Saline
- 5. Polymer (NanoCarrier-001B), 140 mg/kg

Drugs or control were administered IV via the tail vein every 3 days for a total of 4 treatments. Drugs were equitoxic based on MTD. Mice were euthanized 21 days after last treatment for all cancers except for breast cancer (10 days after last treatment).

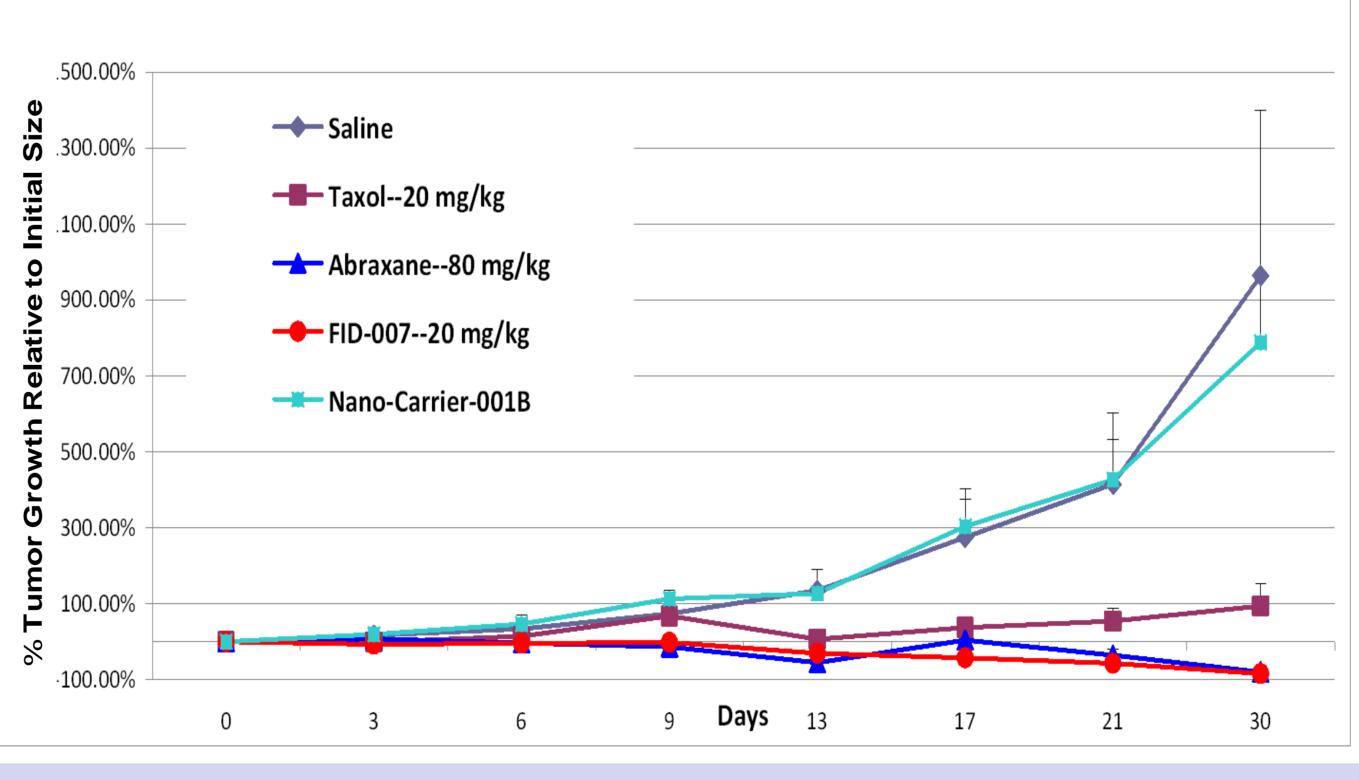
In Vivo Efficacy against Triple Negative MDA-MB-231Breast Cancer

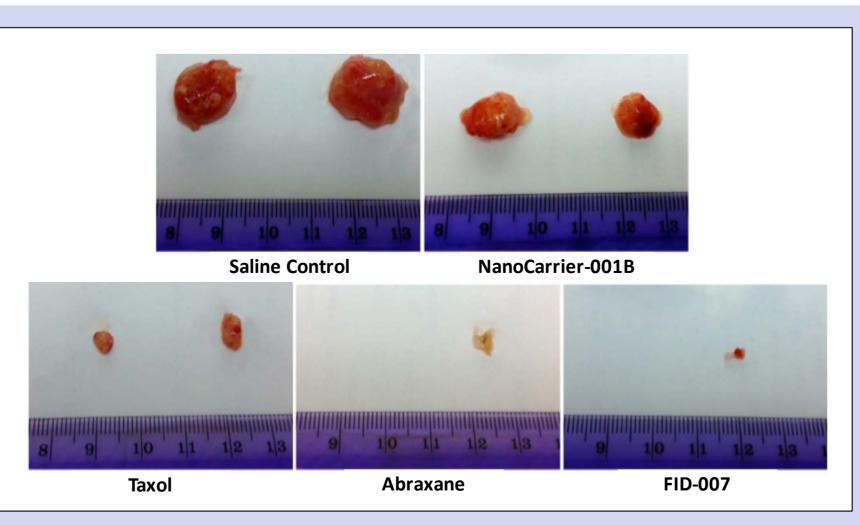




Representative images of excised breast tumors

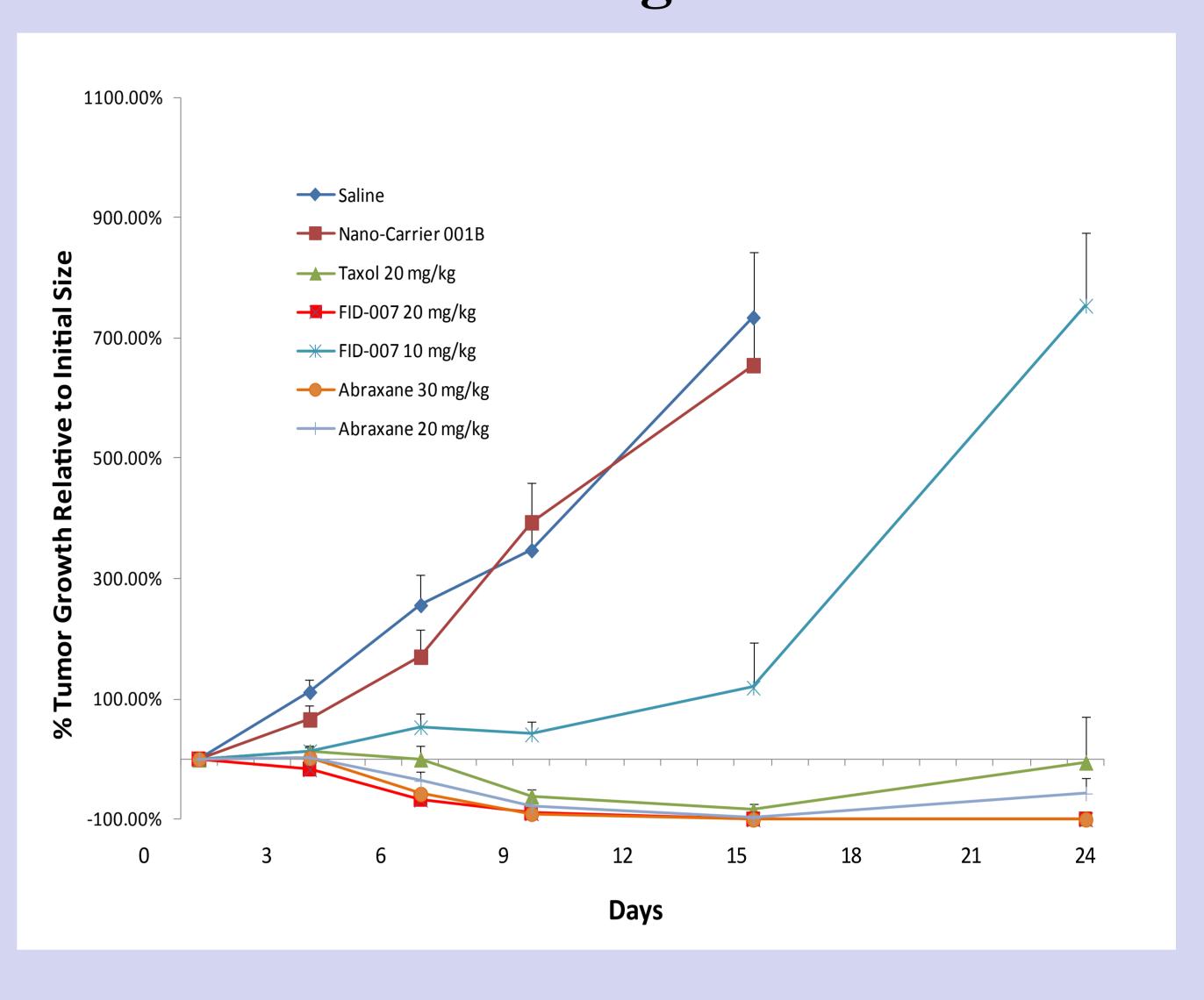
In Vivo Efficacy against OV-90 Ovarian Cancer





Representative images of excised ovarian tumors

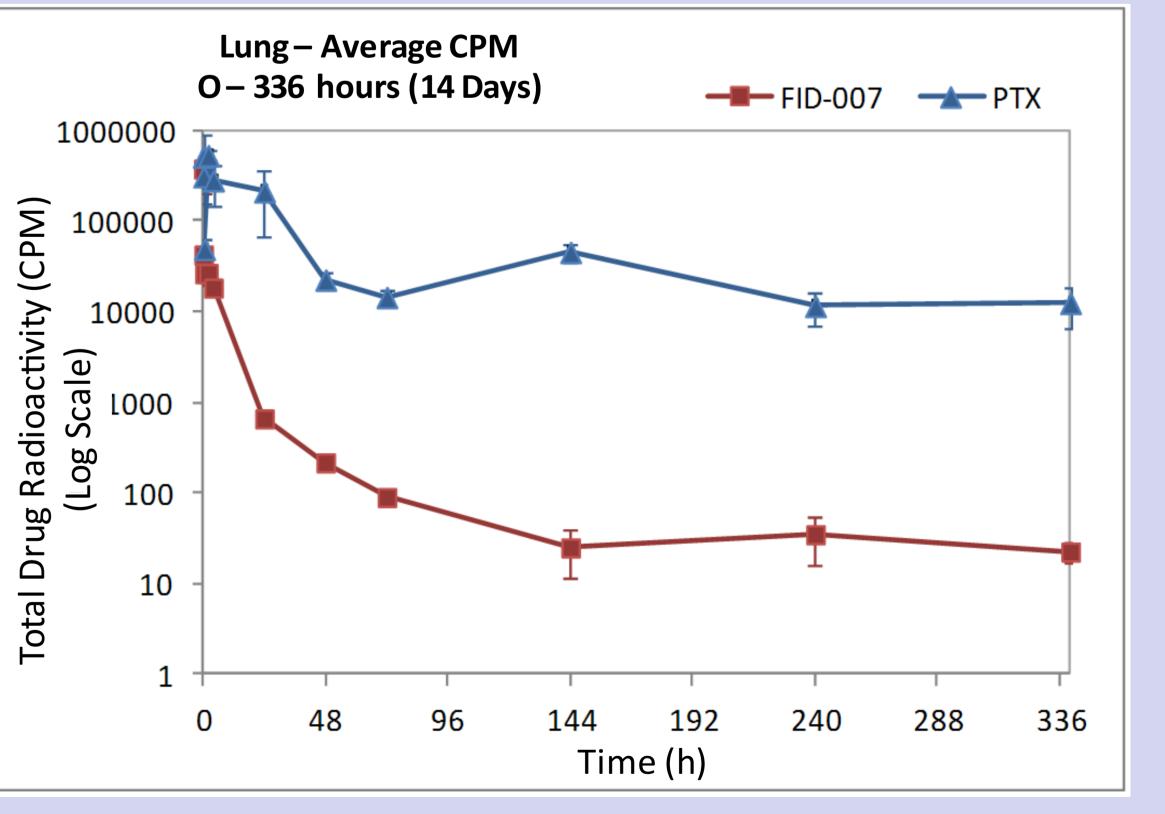
In Vivo Efficacy against A549 Human Lung Cancer



FID-007 was also significantly better than Taxol and as good as or better than Abraxane in controlling the growth of KB-Gem Gemcitabine-resistant Cancer and Mia-Paca Pancreatic Cancer in xenograft models.

Tissue Distribution in Mice

The distribution of FID-007 in major organs was compared to that of Paclitaxel over a period of 14 days after treatment of mice with radiolabeled drug



Shown above is the drug distribution of FID-007 and Paclitaxel (PTX) in lung tissue. Similar results were obtained in liver, kidney and spleen

Conclusions

- 1. Paclitaxel encapsulated with our polymers showed significantly lower toxicity than Taxol and similar toxicity to Abraxane in in vivo MTD studies.
- 2. The new drug, FID-007 showed better efficacy than Taxol and similar efficacy to Abraxane in reducing human Gemcitabine-resistant head & neck tumors, lung, pancreatic, breast, and ovarian tumors in mouse xenograft models.