UCI 趙 Chao Family Comprehensive Cancer Center

# A Phase 1 Study of the Combination of Pitavastin (Pita) with Gemcitabine and nab-paclitaxel in patients with Unresectable Pancreatic Adenocarcinoma (uPDAC)

**Jennifer Valerin**[1,2], David Fruman[2,3], Sophie Hasson[1], Tanvi Chichili, Farshid Dayyani[1,2], Christopher Halbrook[2,3]

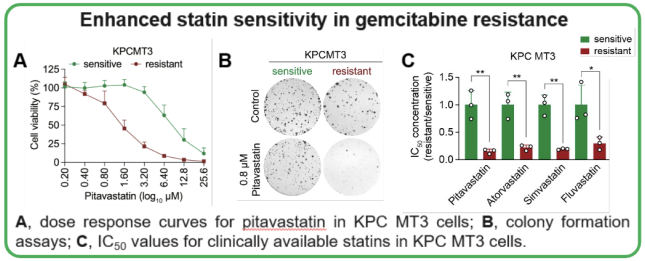
1. Department of Medicine - Division of Hematology/Oncology, University of California Irvine
2. Chao Family Comprehensive Cancer Center, University of California Irvine
3. Department of Molecular Biology and Biochemistry, University of California Irvine

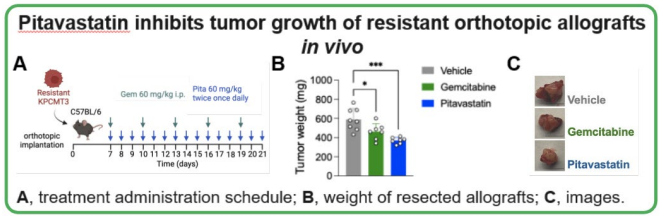
# Background

- Pancreatic cancer  remains one of deadliest major cancers driven by lack of response and acquisition of resistance to current treatments
- Current SOC for uPDAC: gemcitabine and nab-paclitaxel combination shows synergy and safety over single agent chemo: (PMID: 24131140) improved PFS, OS and RR

**Role of HMG-CoA inhibitors in PDAC:**

- Preclinical observation: acquired gemcitabine resistance in pancreatic cancer cells required metabolic rewiring



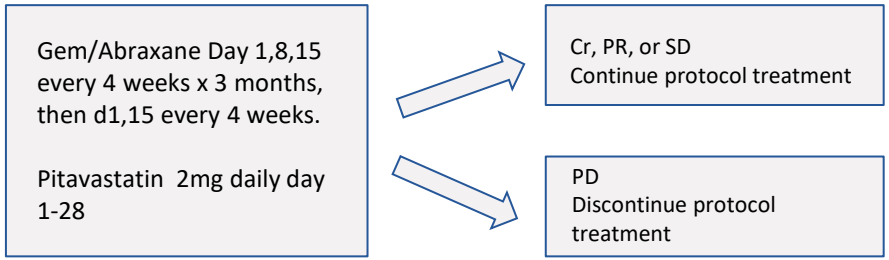

- Inhibition of HMG-CoA reductase reduces synthesis of isoprenoids which bind to Ras protein involved cell growth, proliferation, differentiation, and cancer development signaling pathways (PMID 25220658)
- In vitro, inhibition of tumor spheroid growth, induction of apoptosis and necrosis (PMID 29180851)

**Gemcitabine and Pitavastatin combo in pre-clinical  studies:**

- In vitro, synergistically suppressed proliferation of MIA PaCa-2 cells through sub-G1 and S phase cell cycle arrest, activation of apoptosis/necrosis, and activation of cellular metabolism and autophagy (PMID 32606957)
- In vivo, inhibited tumor growth in Mia PaCa-2 xenografts (PMID 32606957)

# Hypothesis

- The combination of Pitavastatin (HMG-CoA reductase inhibitor) with Gemcitabine and nab-paclitaxel is feasible and tolerable and via sub-G1 and S phase cell cycle arrest, activation of apoptosis/necrosis and other crucial cytotoxic mechanisms, might improve outcomes in uPDAC.




Abbreviations:
uPDAC: unresctable Pancreatic Adenocarcinoma, SOC: Standard of Care, DL: Dose Levels,
Pita: Pitavastatin, RP2D: Recommended phase II dose

# Trial Design

- Single center, prospective, open label, non-randomized phase 1B trial (3+3 design)

**Main Eligibility**
- 1L + uPDAC
- ECOG 0-2
- appropriate organ function

**Treatment**
- Gemcitabine and nab-paclitaxel: Day 1,8,15 every 4 weeks x 3 months, then d1,15 every 4 weeks.
- Pitavastatin: Day 1-28 every 4 weeks.
    - DL -1: Pita 1 mg
    - DL 0: Pita 2 mg
    - DL +1: Pita 4 mg

**Primary objective**
- Primary endpoint: RP2D of Pitavastatin in combination with Gemcitabine and nab-paclitaxel in treatment of uPDAC.

**Secondary objectives**
- PFS, OS, ORR (in patients with measurable disease)

**Total number of pts to be enrolled:**
- min= 8, max= 12 (includes number of anticipated screen failures)

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# Thank You

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