**M402 Increases Gemcitabine Uptake into Pancreatic Tumors as a Result of Stromal Matrix Remodeling**

**Birgit C. Schultes1, Chia Lin Chu1, Alison Long1, Elaine Sun1, Elma Kurtagic1, Daniela Beccati1, Joel Pradines1, Paul Miller1, David Ryan2, Keith Flaherty2, James Roach1, Lynn Zhang1, Ganesh Kaundinya1**

1Momenta Pharmaceuticals, Cambridge, MA, USA; 2Massachusetts General Hospital, Boston, MA

**BACKGROUND**

- The striking histological feature of pancreatic adenocarcinoma (PDAC) is the presence and abundance of the fibrous stroma (desmoplasia) which presents a barrier of standard care chemotherapeutics (such as gemcitabine).
- The pancreatic tumor stroma is composed of tumor cells, activated fibroblasts (such as pancreatic stellate cells), inflammatory cells and extensive extracellular matrix molecules.
- The desmoplastic response involves the complex interplay between these main cell types, key heparin-binding growth factors (including sonic hedgehog (SHH), EGF, HB-EGF, TGFs, PDGF and FGFs) and degradative matrix enzymes such as MAMPs and heparanase.

**RESULTS**

- **Capan-2 Tumors Display a High Desmoplastic Response**
- **M402 Monotherapy Has a Dose-dependent Impact in the Capan-2 Model**
- **M402 and Combination Therapy Reduces Desmoplastic and SHH Signaling**
- **M402 Enhances the Efficacy of Gemcitabine in the Capan-2 Model**

**M402 Accumulates in the Tumor with Long Residence Time**

- M402 Accumulates in the Tumor with Long Residence Time
  - Capan-2 Tumors Display a High Desmoplastic Response
  - **M402 Increases Gemcitabine Delivery to the Tumor**

**M402 Enhances the Efficacy ofGemcitabine in the Capan-2 Model**

- **Primary Tumor Weights**
- **Gemcitabine at 30 mg/kg twice weekly (p) vs Week 1**

**M402 and Combination Therapy Enhances Tumor Perfusion**

- **Tumor Weight**
- **M402 treatment Week 6**
- **Gemcitabine treated Week 6**
- **I Calcin 3H2O**
- **E Calcin DAP**
- **DAP**

**CONCLUSIONS**

- **In the Capan-2 pancreatic cancer mouse model:**
  - M402 targeted the pancreatic tumor with long residence time.
  - Data indicate that M402 affects the stromal activation within the pancreatic tumor microenvironment.
  - Alone and in combination with gemcitabine, M402 showed a significant reduction in tumor size and fibrosis, accompanied by down-regulation of SHH, PDGF and TGF-beta pathways.
  - Tumors treated with M402 or the M402 + gemcitabine combination showed increased perfusion and microvessel penetration into the tumor centers as compared to large tortuous vessels restricted to the tumor rim in vehicle or gemcitabine monotherapy groups.
  - The effects on the tumor stroma and vasculature translated into increased incorporation of gemcitabine into the tumor DNA when mice were pre-treated with M402 vs. saline.
  - M402 is in Phase I clinical studies in advanced pancreatic cancer, in combination with gemcitabine and nab-paclitaxel.

**ACKNOWLEDGEMENTS**

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**M402 Monotherapy Has a Dose-dependent Impact in the Capan-2 Model**

- **Primary Tumor Weights**
  - **M402 at 10, 20, 40 mg/kg i.p. (x) vs Week 5**
  - Gemcitabine at 30 mg/kg twice weekly (p) from Week 1

**M402 Enhances the Efficacy of Gemcitabine in the Capan-2 Model**

- **Primary Tumor Weights**
  - **M402 treatment Week 6**
  - **Gemcitabine treated Week 6**

**M402 and Combination Therapy Enhances Tumor Perfusion**

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