**RATIONALS FOR COX-2 INHIBITOR IN PANCARCINOMA**

- COX-2 over expressed in >80% of pancreatic cancer
- COX-2 over expression correlated with poor survival in pancreatic cancer
- COX-2 and EGFR signaling regulate the dominant ERK/MAPK, AKT and β-catenin pathway in pancreatic cancer
- β-catenin activity is implicated in genitalia resistance
- Therefore a combination of a COX-2 inhibitor, an EGFR inhibitor and gemcitabine may be of benefit in pancreatic cancer patients

**APRICOXIB (TGI01)**

- Primary endpoint: Progression free survival (PFS)
  - A randomized, placebo-controlled, single blinded study will be initiated at 80% power at an alpha=0.05 significance level to detect a difference of 18% between the progression free survival in the COX-2 inhibitor and placebo arm
  - Secondary endpoint: Safety, tolerability, overall survival (OS), exploratory analysis of PFS in the 25% of patients who had at least a 50% drop from baseline PGE-M

**PHASE II RANDOMIZED PLACEBO CONTROLLED STUDY IN PANCARCINOMA: CANCER-KEY ELIGIBILITY CRITERIA**

- 1st line recurrent locally advanced or metastatic adenocarcinoma of the pancreas
- Must have not received prior chemotherapy except as part of chemoradiotherapy for 1st T3 disease
- ECOG PS 0, 1, 2

**PHASE II PANCREATIC: TREATMENT EMERGENT ADVERSE EVENTS BY ORGAN SYSTEM (≤10 INCIDENCE)**

- **PHASE II PANCREATIC: TREATMENT EMERGENT ADVERSE EVENTS BY ORGAN SYSTEM (10 INCIDENCE)**
  - **Patient OI**
    - **Cytotoxicity**
      - Adverse events to be sought
    - **Cardiac**
      - MI
    - **Nervous System**
      - Nausea
    - **Musculoskeletal**
      - Arthritis
    - **Gastrointestinal**
      - Diarrhea
    - **Hematological**
      - Lymphopenia
    - **Skin**
      - Rash
    - **Nephrology**
      - Kidney failure

**MOLLEULAR BASIS OF SYNERGISTIC EFFECTS OF ELOXITIN AND GEMCITABINE IN PANCREATIC CANCER**

- COX-2 has a well defined role in carcinogenesis
- It correlates with high grade tumors, advanced stage, metastases and poor survival
- COX-2 is a marker of poor response to therapy
- COX-2 inhibition is associated with an improvement in survival

**COX-2 HAS A WELL DEFINED ROLE IN CARCINOGENESIS**

- Inhibits prostaglandin synthesis
- Promotes angiogenesis
- Inhibits apoptosis
- Enhances cell proliferation
- Promotes cell migration
- Inhibits tumor immune recognition
- Interacts with multiple pathways involved in cancer

**APRICOXIB IS A POTENT AND SELECTIVE COX-2 INHIBITOR**

- IC50 for COX-2 (nM): 45, 38, 0.36, 1.0
- COX-2 expression correlated with poor survival in pancreatic cancer

**PHASE II PANCREATIC: PATIENT DEMOGRAPHICS**

- **Population**
  - \( \geq 23 \) patients
  - \( \geq 19 \) sites
  - \( \geq 30 \) patients

**CONCLUSIONS**

- This study represents the first combination of a COX-2 inhibitor with erlotinib and gemcitabine in 1st line advanced pancreatic cancer patients
- This triple combination inhibits key survival pathways in pancreatic cancer and thus may benefit patients
- The triple combination is well tolerated with a side effect profile consistent with an advanced pancreatic cancer population treated with these classes of drugs
- The study is open and continues to enroll