Efficacy of AKT inhibitor ARQ 092 compared with sorafenib in a cirrhotic rat model with hepatocellular carcinoma

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Introduction
• Hepatocellular carcinoma is the 5th most common cancer worldwide and the 2nd cancer related death.
• Developed on cirrhosis in 90% of the cases
• Only one approved drug in advanced cases: sorafenib
• PI3K/AKT/mTOR pathway activated in HCC >50% of the cases and in fibrogenesis

Aims
• Compare safety and efficacy of ARQ 092 with sorafenib in a rat cirrhotic model of HCC

Materials and methods (cont.)
• Treatment protocol:
  • Rat randomization in 3 groups
  • Oral gavage daily: sorafenib (20 mg/kg) continuously, ARQ 092 (15 mg/kg) one week on, one week off.
  • Weekly weighing
  • Histological analysis: fibrosis was assessed by red Sirius staining,
  • Tumor progression assessed by MRI:
  • Follow-up: 6 weeks
  • Morphological analysis (T2 weighted MRI): largest diameter of 5 target lesions

Results: Safety
• Adverse events
  • Sorafenib
    • Diarrhea
    • Loss of weight ≥10% and <20%
    • Loss of weight >20%
    • Hepatic encephalopathy
    • Sore spots
    • Tissue death

Materials and methods
• Animal model:
  • Fischer 344 male rats
  • Diethylnitrosamine IP every week (50 mg/kg) for 14 weeks

Results: Efficacy
• Tumor progression assessed by MRI:
  • Control
  • 100%
  • ARQ 092
  • 155.3% (30.0%)
  • Sorafenib
  • 180.2% (57.0%)

Materials and methods
• Activation of mTOR/P70S6K/AKT pathway in 50% of HCC

Results: Pathological analysis
• Mean number of tumors
  • Control
  • 96.8
  • Sorafenib
  • 37.9
  • ARQ 092
  • 155.3

Materials and methods
• PI3K/AKT/mTOR pathway activated in HCC >50% of the cases and in fibrogenesis

Results: Pathological analysis
• Mean sum of the 5 largest tumors (mm)
  • Control
  • 10.0
  • Sorafenib
  • 32.8

Materials and methods
• Results: Safety

Conclusions
• In this animal model of HCC on cirrhosis, ARQ 092
  • Is better tolerated than sorafenib
  • Has stronger antitumor effect than sorafenib
  • Reduces pAKT downregulation in vivo
  • Has anti-fibrotic effect
• Results warrant human testing of ARQ 092 in this setting