### ABSTRACT

**Hepatocellular Carcinoma**
- 6th most common malignancy diagnosed worldwide
- Treatment options:
  - Surgical therapy: resection, cryoablation, and orthotopic liver transplantation
  - Non-surgical therapy: percutaneous ethanol injection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE)
  - Systemic treatment: targeted therapy and chemotherapy
  - Curative therapies such as resection, transplantation, or percutaneous therapy benefit only 25% of patients.
  - Majority of patients are not eligible for such therapies because of tumor extent or underlying liver dysfunction.
  - Improving treatment outcomes in patients with advanced stage hepatocellular carcinoma requires the development of agents with tolerable safety profiles.
  - Sorafenib has been the only systemic therapy as a first line therapy over the last decade.
  - Overall survival: 10.7 months.

**Tivozanib**
- Tivozanib is a novel and potent pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with potent activity against all 3 VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3).
- Previous studies performed in humans, tivozanib has shown strong anti-angiogenic and anti-tumor activity.
- Phase 1 and 2 studies on other cancers including RCC and CRC.
- Adverse events: fatigue (50.6%), nausea (40.7%), hand-foot syndrome (5.3%), elevated AST (15.8%), and grade 4 hypotension (5.3%).

**METHODS**

- This is a phase 1b/2 study with HCC patients (pts) having a measurable disease, Child-Pugh class A, and no prior systemic therapy. Phase 1b portion followed a modified 3 + 3 design; phase 2 portion was a two-stage, single arm, unblinded study. Adverse events were categorized based on CTCAE, and tumor imaging was assessed per RECIST.

**RESULTS**

- **Inclusion criteria**
  - Unresectable, measurable disease, Child-Pugh A
  - AST ≤ 5x ULN, UNR ≤ 2
  - Serum albumin ≥ 2.8 g/dL, Cr ≤ 1.5 x ULN
  - ANC ≥ 1,200/mm^3, platelets ≥ 60,000/mm^3, Hb ≥ 8.5 g/dL
  - ECOG ≤ 2

- **Exclusion criteria**
  - Any prior systemic therapy including anti-angiogenic therapy

- **Objectives**
  - To determine the safety of tivozanib
  - To determine OS and response rate by RECIST
  - To determine the change in alpha fetoprotein during therapy

- **Toxicity**
  - Hand-foot syndrome (5.3%), elevated AST (15.8%), and grade 4 hypotension (5.3%)

- **Conclusions**
  - Tivozanib is well tolerated and may have potential to improve progression-free survival (PFS) for at least 2 years.
  - Further studies are needed.

- **Tivozanib**
  - Oral vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with potent activity against all 3 VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3).

- **Phase 1b**
  - Dose escalation study (1 mg daily)

- **Phase 2**
  - Single-arm unblinded phase (total phase 2 sample size of 37)

- **Safety profile of tivozanib**
  - Well tolerated with no additional side effects reported in other studies

- **Secondary Objectives**
  - Safety profile of tivozanib

- **Response rate**
  - Partial response (PR) was seen in 4/19 (21%) and stable disease (SD) in 8/19 (42%): disease control rate was 63%.

- **Overall Survival (OS)**
  - 10.7 months, compared to 7.9 months with placebo
  - 66% of patients either need dose reductions or delay and discontinue it for reasons other than disease progression

- **DISCUSSION**

- **Tivozanib 1 mg daily was tolerated well with few severe adverse events leading to the discontinuation of the medication.**
- **4/19 patients showed a durable response longer than 2 years.**
  - This requires further research on the gene expression profile to understand the mechanism and patient population showing persistent response.
  - Biomarker driven studies including immune cell profiles are warranted.