Phase 1b/2 study of tivozanib in patients with advanced inoperable hepatocellular carcinoma

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ABSTRACT

Background:
Sorafenib has been the only FDA-approved medication for inoperable HCC (iHCC) as first line. Agents with better tolerability and potential to improve progression-free-survival (PFS) are needed. Tivozanib (TIVO) is an inhibitor of vascular endothelial growth factor (VEGF) tyrosine kinase, inhibiting angiogenesis critical in HCC.

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, un-blinded study. Adverse events were categorized based on CTCAE, and tumor imaging was assessed per RECIST.

Results: At 3 centers with IRB approval, 21 eligible pts were enrolled. In phase 1b, 8 pts were enrolled at a starting dose of 1mg once daily q21days with one week off. Upon escalation to 1.5 mg, two pts had dose limiting toxicities (DLTs, grade 3 mucositis and hypertension) and came off study without completing the DLT period. The dose of TIVO was de-escalated to 1 mg, and the accrual of remaining patients to phase 2 portion occurred at 1 mg. In a total of 19 pts, median follow up was 16.9 months (mo). The primary endpoint of median PFS and PFS at week 24 were 5.5 mo and 47%. 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) at 6 and 12 mo was 58% and 25%. Median OS was 7.5 mo. Four pts have remained on TIVO for > 2 years. Viral loads of hepatitis B and C remained stable during the study. Adverse events (AEs) related to TIVO included grade 3 fatigue (15.8%), decreased appetite (5.3%), pulmonary embolism (10.5%), hand-foot syndrome (5.3%), elevated AST (15.8%), and grade 4 hypertension (5.3%).

Conclusions:
TIVO is tolerable at 1 mg in iHCC. In few pts, TIVO had deep and durable responses. Biomarker driven studies of TIVO in the context of immunotherapy are warranted. Clinical trial information: NCT01835223. Acknowledgment: We appreciate support from NCCN.

BACKGROUND

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), and radiation
  - Systemic medication treatment including 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, 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

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-angiogenesis and antitumor activity.
- Phase 1 and 2 studies on other cancers including RCC and CRC.
- Adverse events: fatigue (50.6%), nausea (40.7%), diarrhea (35.8%), stomatitis (33.3%), vomiting (24.7%), decreased appetite (23.5%), hypertension (22.2%), thrombocytopenia (16.0%), neutropenia (12.3%), and blood triglycerides increased (11.1%).

OBJECTIVES

- **Primary Objective**: Progression-free-survival (PFS) at 24 weeks per RECIST
- **Secondary Objectives:**
  - To determine the safety of tivozanib
  - To determine the OS and response rate by RECIST
  - To determine the change in viral load (HBV and HCV) during therapy
  - To determine the change in alpha fetoprotein during therapy

STUDY DESIGN

- **Multicenter phase 1b/2 study**
  - **Phase 1b**: dose escalation study (goal of between 6 and 18 patients)
    - Modified 3+3 design (starting at 1 mg – down to 0.5 mg, or up to 1.5 mg)
  - **Phase 2**: single arm, unblinded (total phase 2 sample size of 37)

- **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

RESULTS

- 3 centers with IRB approval accrued patients
  - Roswell Park Comprehensive Cancer Center
  - Case Comprehensive Cancer Center
  - Cleveland Clinic Taussig Comprehensive Cancer Institute
- The first patient in July 2013; enrollment of the last patient in Nov 2016

- In phase 1b
  - 8 patients were enrolled
  - Starting dose: 1 mg once a day every 21 days with one week off
  - Escalation to 1.5 mg daily, two patients developed dose limiting toxicities with grade 3 mucositis and hypertension → excluded from the study
    → Dose de-escalated to 1 mg daily
  - 2 patients treated with 0.5 mg daily, 4 patients with 1 mg daily

- In phase 2
  - The accrual of remaining patients to phase 2 with 1 mg daily

- A total of 19 patients were analyzed.

Primary Objective - PFS

- PFS responders within 24 weeks are defined as those who remain alive without evidence of disease progression for at least 24 weeks after enrollment= 9 PTS
- One patient with delayed positive 24 weeks scan is treated as NON PFS responder (this patient had 24 week scan at week 25)
- One patient who died without disease progression is treated as NON PFS responder
- PFS at 24 weeks was 47%
- Median PFS: 5.5 months
- **Of note, 4 patients have no disease progression longer than 2 years**

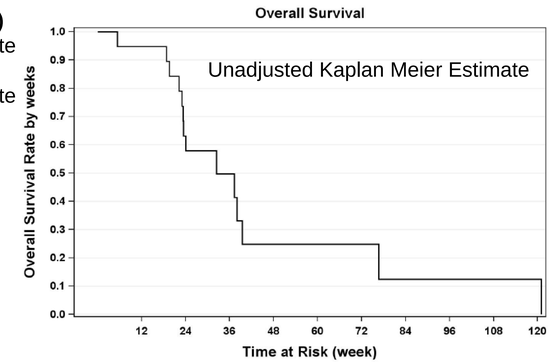
Secondary Objectives

- **Safety profile** of tivozanib
  - Well tolerated with no additional side effects reported in other studies
  - The most common adverse events with gastrointestinal symptoms including nausea, vomiting, diarrhea, constipation, and stomatitis

Adverse events (possibly, probably, or definitely related to tivozanib (n=19)

System	Events	Any grade #	Any grade %	Grade 1 #	Grade 1 %	Grade 2 #	Grade 2 %	Grade 3 #	Grade 3 %	Grade 4 #	Grade 4 %
GI	Nausea	7	36.8	4	21.1	3	15.8	0	0.0	0	0.0
	Vomiting	6	31.6	5	26.3	1	5.3	0	0.0	0	0.0
	Diarrhea	11	57.9	7	36.8	4	21.1	0	0.0	0	0.0
	Constipation	4	21.1	2	10.5	2	10.5	0	0.0	0	0.0
	Stomatitis	5	26.3	4	21.1	1	5.3	0	0.0	0	0.0
	Dyspepsia	1	5.3	1	5.3	0	0.0	0	0.0	0	0.0
General	Fatigue	14	73.7	5	26.3	6	31.6	3	15.8	0	0.0
	Pyrexia	1	5.3	1	5.3	0	0.0	0	0.0	0	0.0
Nutritional	Decreased Appetite	12	63.2	5	26.3	6	31.6	1	5.3	0	0.0
Cardiovascular	Hypertension	3	15.8	1	5.3	1	5.3	0	0.0	1	5.3
Pulmonary	Pulmonary Embolism	2	10.5	0	0.0	0	0.0	2	10.5	0	0.0
Hematologic	Anemia	1	5.3	1	5.3	0	0.0	0	0.0	0	0.0
	Thrombocytopenia	4	21.1	4	21.1	0	0.0	0	0.0	0	0.0
	Lymphopenia	2	10.5	1	5.3	1	5.3	0	0.0	0	0.0
Dermatologic	Hand-foot Syndrome	3	15.8	2	10.5	0	0.0	1	5.3	0	0.0
Hepatic	Elevated AST	4	21.1	1	5.3	0	0.0	3	15.8	0	0.0
	Elevated ALT	4	21.1	3	15.8	0	0.0	1	5.3	0	0.0
	Elevated AP	4	21.1	1	5.3	1	5.3	2	10.5	0	0.0
	Elevated Bilirubin	4	21.1	0	0.0	2	10.5	2	10.5	0	0.0

Overall Survival (OS)
- 26 weeks survival rate
  - 0.58 (0.33-0.76)
- 52 weeks survival rate
  - 0.25 (0.07-0.49)
- Median follow up : 16.9 mo
- Median survival : 7.5 mo



Response rate
Partial response: 4/19 (21%), stable disease in 8/19 (42%)
→ Disease control rate of 63%

Viral load (HBV and HCV)
- HBV tested (n=12), HBV positive patients (n=2)
  - No significant change in HBV viral load during the course of treatment
- HCV tested (n=10), HCV positive patients (n=3)
  - No significant change in HCV viral load during the course of treatment

Alpha fetoprotein (AFP)
Responders including 4 patients having a persistent response showed significant decrease in AFP for more than 2 years
- For example, one patient – AFP from 8,452.6 (Aug 2014) to 3.4 (Dec 2017)

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.

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