DEDUCTIVE: a Study of Tivozanib in Combination with Durvalumab in Subjects with Untreated Advanced Hepatocellular Carcinoma; Phase Ib results.

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Background/Methods:

- Tivozanib (T, a potent and selective VEGFR 1, 2 & 3 TKI) and durvalumab (D, a PD-L1 antibody) have both demonstrated single agent activity in HCC
- The combination of bevacizumab (VEGF-A Mab) with atezolizumab (PD-L1 inhibitor) has shown significant improvements in OS and PFS
- T blocks all three VEGF receptors, and has the potential to improve outcomes, compared to only blocking the VEGF-A ligand
- Reduction in Tregs after tivozanib treatment for HCC correlated with significant improvement in overall survival (OS)[1].
- The ph1 portion of this study combines T with D to establish the recommended phase II dose (RP2D) and provide preliminary safety and efficacy data

Methods:

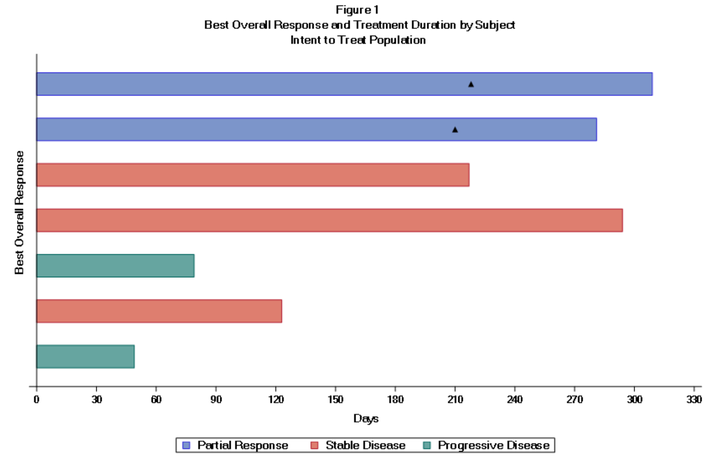
- Major eligibility criteria
  - Documented untreated advanced HCC, Child-Pugh Class A
  - Major exclusion criteria are co-infection with HBV and HCV and significant organ dysfunction
- The starting doses are T 1 mg orally for 21 days followed by 7 days off treatment and D 1500 mg intravenously every 28 days
- A DLT is generally defined as the occurrence of any Grade ≥3 adverse event (AE) per CTCAE v.5 in Cycle 1 that is at least possibly related to the investigational regimen
- The primary objective
  - Establish the RP2D and the safety and tolerability for this combination in patients with advanced HCC.
- Outcome measures will be AEs and cross-sectional imaging performed every 8 weeks

- **Use of Tivozanib, a selective, potent inhibitor of VEGFR 1, 2, & 3, has the potential to improve outcomes in HCC in combination with PD-L1 blockade**
- **RP2D is Tivozanib 1 mg p.o. on days 1-21 and Durvalumab 1500 mg i.v. on day 1 of every 28-day cycle**
- **The combination of T with D in patients with untreated advanced HCC is well tolerated**
- **2 of 7 patients in phase 1b responded**
- **Now Enrolling Phase 2**

Results:

- 7 patients were enrolled in Phase 1b
- Six were male; median age was 75 (range 40 to 82)
- One patient had mild elevation of LFTs and did not complete the 21-day course of T and was replaced
- No patient experienced a ≥ grade 3 AE in cycle 1
- 6 of 7 experienced an adverse drug reaction
- The most common ADRs, each seen in two of seven patients, were cough, diarrhea, fatigue, hypertension, and PPE (hand-foot syndrome)
- 1 SAE for grade 3 GI hemorrhage
- 2 of 7 achieved a PR (Figure 1 below)

Figure 1
Best Overall Response and Treatment Duration by Subject
Intent to Treat Population



Note : Triangle indicates the Best Overall Response.

Future Directions:

- Now enrolling Phase 2 to target an additional 30 patients

[1]Kalathil, ONCOIMMUNOLOGY 2020