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

Renuka V. Iyer1, Daneng Li2, Farshid Dayyani3, Alexandria T. Phan4, Michael N. Needle5, Thomas Adam Abrams6

Roswell Park Comprehensive Cancer Center, Buffalo, NY1; Department of Medical Oncology, City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA2; University of California Irvine, Division of Hematology/Oncology, Department of Medicine, Orange, CA3; UT Health North Campus Tyler, MD Anderson Cancer Center, Tyler, TX4; Aveo Oncology, Cambridge, MA5; Dana-Farber Cancer Institute, Boston, MA6

• 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

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

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)

Future Directions:

• Now enrolling Phase 2 to target an additional 30 patients

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