3081 **Poster Session**

First-time in-human study of VMD-928, an oral allosteric TrkA selective inhibitor targeting TrkA protein overexpression, in patients with solid tumors or lymphoma.

Vincent Chung, Ling Wang, Margaret S. Fletcher, Erminia Massarelli, Mihaela C. Cristea, Sailaja Kamaraju, Angela Tatiana Alistar, Chao Feng, You Li, Roger Lewis Whiting, Giuseppe Giaccone, David S. Hong, Jay Wu; City of Hope, Duarte, CA; VM Oncology, VM Pharma, Fremont, CA; MedAssessment, Inc, San Clemente, CA; City of Hope National Medical Center, Duarte, CA; Froedtert Health and Medical College of Wisconsin, Milwaukee, WI; Atlantic Health System, Morristown, NJ; VM Oncology, LLC, Fremont, CA; Weill Cornell Medical Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; VM Oncology, Fremont, CA

Background: Tropomyosin receptor kinase A (TrkA) is a protein encoded by the NTRK1 gene. Upregulation of TrkA signal transduction pathways, which can be caused by either NTRK1 gene fusions or intact TrkA protein overexpression, are oncogenic for multiple tumor types. This is clinically validated by demonstrated efficacy of ATP-competitive pan-TrkA/B/C inhibitors, larotrectinib and entrectinib for treatment of advanced solid tumors harboring NTRK1/2/3 gene fusions. VMD-928 is the first oral small-molecule TrkA (NTRK1) selective inhibitor with differentiated allosteric (ATP non-competitive) and irreversible mechanisms of action, acting as a molecular glue which sticks two TrkA proteins together and dose-dependently inhibits TrkA functions and downstream effectors, e.g. activated ERK, a hallmark of cancer. We conducted a first time in human phase 1 trial and completed the dose escalation phase. **Methods:** This is an open label, Phase 1 study investigating oral VMD-928 in adults with advanced solid tumors or lymphoma. The primary objective is to assess the safety and tolerability of VMD-928 and determine the recommended phase 2 dose. Secondary objectives include characterizing the pharmacokinetics (PK) and pharmacodynamics as well as assessing antitumor activity. **Results:** Non-biomarker-selected patients (n = 20) were accrued to 4 dose escalation cohorts ranging from 300 mg/day to 2400 mg/day. Three patients were accrued to the 2400 mg dose level with one DLT of elevated bilirubin, AST and ALT. The trough concentrations (Ctrough, ng/mL) ranged from 5.3 to 727. The dose was de-escalated to 1200 mg per day in divided doses and fifteen heavily pretreated patients were accrued with the following tumor types: adenoid cystic carcinoma, cholangiocarcinoma, lung cancer, pancreatic cancer, parotid, and squamous cell carcinoma of head and neck. There were no DLT's at this dose and one patient with adenoid cystic carcinoma had prolonged stable disease. Common adverse events related to therapy were dark stool (35%), elevated liver enzymes (25%, primarily at 2400 mg/day), fatigue, nausea or vomiting, and decreased appetite (20% each). **Conclusions:** VMD-928 was well tolerated with mainly gastrointestinal side effects. The recommended phase 2 dose (RP2D) is 600 mg twice (1200 mg) per day. The study is currently accruing in expansion cohorts to evaluate efficacy in biomarker-selected patients with tumors of TrkA protein overexpression. Tumor types with reported high TrkA protein expression including thymic carcinoma (98% with TrkA protein expression without NTRK1/2/3 gene fusions), mesothelioma (81%), squamous cell carcinoma of head and neck (80%), ovarian (80%), hepatocellular (72%), and squamous cell carcinoma of the lung (71%) are being accrued. Clinical trial information: NCT03556228. Research Sponsor: VM Oncology, LLC.

© 2021 by American Society of Clinical Oncology. Visit abstracts.asco.org and search by abstract for disclosure information.