TPS9598 Poster Session

The MATRiX trial: A multicenter, randomized, phase II study of ATR inhibition (via tuvusertib) with or without avelumab in patients with advanced anti-PD-(L)1–refractory Merkel cell carcinoma.

Rashmi Bhakuni, Evan Thomas Hall, George Ansstas, Shailender Bhatia, Andrew Scott Brohl, Melissa Amber Burgess, Maya Dimitrova, Ling Gao, Jeffrey Joseph Ishizuka, Evan J. Lipson, Jose Lutzky, Ann W. Silk, Jina Yun, Isaac Brownell, Judy Murray, Yvonne Marie Mowery, Ted Gooley, Steven Gore, Suzanne Louise Topalian, Paul Nghiem; University of Washington Medicine Dermatology, Seattle, WA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; Division of Medical Oncology, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; UPMC Hillman Cancer Center, Pittsburgh, PA; NYU Langone Medical Center, New York, NY; UCI School of Medicine, Irvine, CA; Yale School of Medicine, New Haven, CT; Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Fred Hutchinson Cancer Center, Seattle, WA; United States National Institutes of Health, Bethesda, MD; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; UPMC Hillman Cancer Center, Department of Radiation Oncology, Pittsburgh, PA; Fred Hutchinson Cancer Research Center, Seattle, WA; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD

Background: Merkel cell carcinoma (MCC) is a rare neuroendocrine skin cancer driven by UV mutations or the Merkel cell polyomavirus (MCPyV).It is aggressive, with a high Ki-67 proliferative index.Despite an initial high response rate (~55%) to PD-1 pathway inhibitors, >50% of patients exhibit primary or acquired resistance.ATR (ataxia telangiectasia and Rad3-related) kinase, a critical cell cycle checkpoint regulator, ensures genome fidelity in cancer cells experiencing high replication stress, including MCC.Our preclinical findings suggest anticancer activity of ATR inhibition via transcriptional induction of NF-κB-associated proinflammatory mechanisms.The potent, selective, orally administered ATR inhibitor tuvusertib (M1774) has shown antitumor activity in patients with unresectable solid cancers in Phase I trials, with a recommended Phase II dose of 180 mg daily on an intermittent schedule.We hypothesize that tuvusertib ± anti-PD-(L)1,may induce tumor regression in advanced anti-PD-(L)1-refractory MCC. **Methods:** The multicenter, randomized Phase II MATRiX trial tests the safety and efficacy of tuvusertib monotherapy (Arm 1) and tuvusertib plus avelumab (Arm 2) in patients with metastatic MCC refractory to PD-(L)1 blockade. Patients with progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 within 120 days of their last anti-PD-(L)1 therapy are eligible. Subjects randomized to Arm 1 receive tuvusertib 180 mg QD on days 1-14 of each 21-day cycle. Subjects in Arm 2 also receive avelumab 1600 mg IV on day 1 of each 21-day cycle. Imaging studies performed 9 weeks after treatment initiation and every 12 weeks thereafter will be assessed per RECIST v1.1. Patients in Arm 1 with progressive disease may receive tuvusertib + avelumab. Treatment-emergent adverse events are graded per Common Terminology Criteria for Adverse Events version 5.0. The primary endpoint is progression-free survival (PFS). Between June 2024 and January 2025, 13 subjects were enrolled across 10 centers. With a targeted enrollment of 50 patients, this trial has 83% power to observe a statistically significant (one-sided level of 10%) difference in PFS if the true hazard ratio for failure is 2.0. A stratified (primary vs. acquired resistance) log-rank test will be used, and binary outcomes will be compared using a Mantel-Haenzel test. A Wieand-like futility rule will be used for an interim analysis after the 23rd event occurs. Tumor biopsies, blood, and stool specimens will be profiled to gain integrated insight into transcriptomic, proteomic, and metabolic signatures associated with immune-mediated therapeutic outcomes. This orthogonal approach to solid tumor immunotherapy, relevant to analogous cancers, will guide future combination strategies to better harness the anti-tumor immune response. Clinical trial information: NCT05947500. Research Sponsor: NCI Cancer Therapy Evaluation Program-Experimental Therapeutics Clinical Trials Network; P30CA015704.