TPS8649 Poster Session

Onkoras-101: A phase 1a/1b open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of BBO-8520 in subjects with advanced KRAS^{G12C} mutant non-small-cell lung cancer.

Benjamin J. Solomon, Wallace L. Akerley, Vinod Ganju, Jun Zhang, Alex Adjei, Melissa Lynne Johnson, Alexander I. Spira, Lei Deng, Edward B. Garon, So Yeon Kim, Richard Frank, Lyudmila Bazhenova, Rasha Cosman, Rachel Roberts-Thomson, Christos Karapetis, Yong Ben, Foster Gonsalves; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Huntsman Cancer Institute, Salt Lake City, UT; PASO Medical, Frankston, Australia; University of Kansas Medical Center (KUMC), Westwood, KS; Cleveland Clinic, Cleveland, OH; Sarah Cannon Research Institute, Nashville, TN; NEXT Virginia, Fairfax, VA; Fred Hutchinson Cancer Center, Seattle, WA; UCLA Health, Santa Monica, CA; Smilow Cancer Hospital, New Haven, CT; Norwalk Hospital, Norwalk, CT; University of California, San Diego, Ideker Laboratory, La Jolla, CA; The Kinghorn Cancer Centre, Darlinghurst, Australia; The Queen Elizabeth Hospital, Woodville South, Australia; Flinders Medical Centre, Flinders, Australia; BridgeBio Oncology Therapeutics, Palo Alto, CA; BridgeBio Oncology Therapeutics, Brooklyn, NY

Background: BBO-8520 is a first-in-class, potent, selective, directly binding, orally bioavailable, covalent inhibitor of KRAS^{G12C}. It is effective against both the active GTP-bound (ON) state and the inactive GDP-bound (OFF) state of KRAS^{G12C}. BBO-8520 is being developed to treat patients with advanced cancer harboring the KRAS^{G12C} mutation. The oncogenic KRAS^{G12C} mutation results in an increased abundance of KRAS^{G12C} in the active GTP-bound (ON) state. While recent approvals of KRAS^{G12C}-targeted therapies provide a new treatment option for patients with KRAS^{G12C}-driven cancers, these agents exclusively target the GDP-bound (OFF) state of the protein, enabling the emergence of heterogeneous adaptive resistance. Thus, there is an urgent need for agents that can provide durable treatment benefit. **Methods:** This first-in-human, multicenter, open-label, Phase 1a/1b study evaluates the safety, tolerability, pharmacokinetics and preliminary antitumor activity of BBO-8520 as monotherapy and in combination with pembrolizumab in subjects with advanced non-small-cell lung cancer (NSCLC) with a KRAS^{G12C} mutation. BBO-8520 is administered orally once daily, in a 21-day treatment cycle. Patients enrolled in the trial must have histologically documented locally advanced or metastatic NSCLC with a KRAS^{G12C} mutation. Patients with treated or stable brain metastases are allowed to participate in the study. During Phase 1a dose escalation, BBO-8520 will be evaluated at escalating doses as monotherapy and in combination with pembrolizumab. The primary objective of Phase 1a is to evaluate the safety and tolerability of BBO-8520 monotherapy or in combination with pembrolizumab and determine the optimal dose(s) for Phase 1b dose expansion. Patients with KRAS^{G12C} -mutant NSCLC who have received prior treatment with KRAS^{G12C} (OFF) inhibitors are allowed to participate in Phase 1a. During Phase 1b dose expansion, BBO-8520 will be evaluated as monotherapy in expansion cohorts of: (1) patients with advanced NSCLC and prior treatment with KRAS^{G12C} (OFF) inhibitors; and (2) patients with advanced NSCLC and no prior treatment with KRAS^{G12C} inhibitors. BBO-8520 will also be evaluated in combination with pembrolizumab in an expansion cohort of patients with advanced NSCLC and no prior treatment with immune checkpoint or KRAS^{G12C} inhibitors. The primary objective of Phase 1b is to verify safety and tolerability of BBO-8520 monotherapy and in combination with pembrolizumab and evaluate antitumor activity (objective response rate evaluation). Clinical trial information: NCT06343402. Research Sponsor: BridgeBio Oncology Therapeutics.