TPS3178 **Poster Session**

Trial in progress: Phase 1 study of the selective protein degrader ASP4396 in patients with locally advanced or metastatic solid tumors with *KRAS G12D* mutations.

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Background: *KRAS G12D* is the most common *KRAS* mutation at codon 12 found in solid tumors and is difficult to target. There are no approved therapies directly targeting *KRAS G12D*. Targeted protein degradation is emerging as a promising therapeutic approach for undruggable targets. ASP4396, a novel protein degrader, targets KRAS G12D-mutated protein for degradation via the ubiquitin-proteasome system. This mode of action may offer higher efficacy and safety compared with inhibitors by blocking both enzymatic and scaffolding functions of proteins and by higher target selectivity. This first-in-human study aims to evaluate the safety and efficacy of ASP4396 in patients with advanced solid tumors with *KRAS G12D* mutations (NCT06364696). **Methods:** This Phase 1, open-label, multicenter, dose-escalation and dose-expansion study of ASP4396 is enrolling adult patients with locally advanced (unresectable) or metastatic solid tumors with documented *KRAS G12D* mutations who have ≥ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1, ECOG performance status of 0 or 1, adequate organ function, and who did not respond or who are ineligible for standard therapies. Tumor-specific dose expansion cohorts may be enrolled at the maximum tolerated dose (MTD) and/or candidate recommended phase 2 dose (RP2D). Patients who received prior treatment targeting KRAS G12D will be excluded. Primary endpoints are safety and tolerability (assessed by dose-limiting toxicities [DLTs], adverse events, laboratory and other standard tests), and RP2D and/or MTD of ASP4396. Secondary endpoints are antitumor activity (objective response rate, duration of response, disease control rate, and progression-free survival per RECIST v1.1 by investigator assessment; and overall survival), and pharmacokinetic/ pharmacodynamic assessments. In the dose escalation cohort, patients will receive increasing doses of ASP4396 intravenously in a 21-day cycle. The target enrollment for each dose level is set at 1 DLT-evaluable patient for dose levels 1–3 and ≥ 3 DLT-evaluable patients for each subsequent dose level. The study will consist of 3 periods: screening (up to 28 days), treatment (every 21-day cycle until treatment discontinuation criteria are met), and follow-up. Data will be summarized descriptively (mean, standard deviation, median) for continuous endpoints, and by counts and percentages for categorical endpoints. Study enrollment is ongoing. Clinical trial information: NCT06364696. Research Sponsor: Astellas Pharma Inc.