TPS4215 **Poster Session**

RHEA-1: First-in-human (FIH) study of AZD9793, a first-in-class CD8-guided T cell-engager (TCE) for glypican-3-positive (GPC3+) advanced or metastatic hepatocellular carcinoma (HCC).

Stephane Champiat, Patrick Grierson, Jason Chia-Hsun Hsieh, Masafumi Ikeda, Yu-Yun Shao, Changhoon Yoo, Cristina Bergamaschi, Sarah Blanchette, Lyndon Kirby, Anna Krotkova, Elie Pommier, Maria Trissal, Frederick Goldberg, Bharat Burman, Stephen Lam Chan; Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Oncology, School of Medicine, Washington University, St. Louis, MO; Division of Hematology/Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan; Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; Department of Oncology, ASAN Medical Center, Seoul, South Korea; AstraZeneca, Gaithersburg, MD; AstraZeneca, Waltham, MA; AstraZeneca, Durham, NC; AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Baltimore, MD; AstraZeneca, New York, NY; Department of Clinical Oncology, Chinese University of Hong Kong, Ma Liu Shui, Hong Kong

Background: GPC3 is an oncofetal protein expressed in 70–80% of HCC and is associated with poor prognosis. Preliminary clinical research on GPC3-specific CAR-T treatment has validated GPC3 as a therapeutic target in HCC. Its expression is largely confined to the surface of tumor cells, making it an ideal target for TCEs. AZD9793, a trispecific IgG1 monoclonal antibody, is a first-in-class CD8-targeted TCE that directly engages tumor-infiltrating T cells and GPC3+ tumors, forming a bridge that activates T cells leading to tumor cell lysis and T cell proliferation. AZD9793 promotes potent GPC3+ HCC cell killing through preferential engagement of CD8+ T cells, while minimizing CD4+ T cell activation and unwanted cytokine release. The novel mechanism of action combines bivalent GPC3 binding, CD8-biased engagement, and low-affinity T cell receptor binding to improve cytotoxicity and reduce the risk of cytokine release syndrome compared with other TCEs. **Methods:** RHEA-1 is the FIH trial of AZD9793 monotherapy. Eligible patients in this modular, Phase I/II, open-label, multicenter study are adults (≥18 years old) with prospective centrally determined GPC3+ advanced or metastatic HCC with ≥1 measurable lesion by RECIST v1.1, who have received ≥1 line of prior systemic treatment and have an ECOG performance status of 0 or 1. Patients with hepatitis B are eligible if they receive antiviral treatment to ensure adequate viral suppression before enrollment and for ≥6 months after the study; and with hepatitis C if they are being managed per local practice. The study includes Module 1 (intravenous AZD9793) and Module 2 (subcutaneous AZD9793), each comprising dose escalation (Part A) and dose expansion (Part B). Module 1 Part A1 (fixed dose) will start with an accelerated titration design and will then switch to a modified toxicity probability interval-2 algorithm after the first 4 dose cohorts or earlier if dose-limiting toxicities (DLTs) are reported. Part A2 (step-up dosing) may open in either Module based on emerging safety data from Part A1. Part B may be initiated in one or both Modules. Primary endpoints include safety and tolerability in terms of DLTs (only in dose escalation) and adverse events to establish maximum tolerated dose, optimal biological dose, and recommended phase II dose; and objective response rate (only in dose expansion) by investigator assessment (IA) per RECIST v1.1. Secondary endpoints include preliminary efficacy (only in dose escalation) in terms of response and progression-free survival by IA, as well as overall survival (only in dose expansion), pharmacokinetics, immunogenicity, and CD8+ T cell infiltration pre- and post-treatment. No formal statistical hypothesis is proposed; all variables will be reported descriptively. The study (NCT06795022) is currently enrolling in the US and APAC. Clinical trial information: NCT06795022. Research Sponsor: AstraZeneca.