EMERALD-1: A phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization.

Riccardo Lencioni, Masatoshi Kudo, Joseph Erinjeri, Shukui Qin, Zhenggang Ren, Stephen Chan, Yasuaki Ari, Jeong Heo, Ahn Mai, Jose Escobar, Yamil Alonso Lopez Chuken, Jung-Hwan Yoon, Won Young Tak, Tanita Suttichaimongkol, Mohamed Bouattour, Shi-Ming Lin, Magdalena Zotkiewicz, Gordon Cohen, Bruno Sangro; Department of Diagnostic and Interventional Radiology, University of Pisa School of Medicine, Pisa, Italy; Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; Department of Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, New York, NY; Cancer Centre of Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China; Zhongshan Hospital, Fudan University, Shanghai, China; State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, The Chinese University of Hong Kong, Hong Kong SAR, China; Department of Diagnostic Radiology, National Cancer Center, Chuo-Ku, Tokyo, Japan; Department of Internal Medicine, College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital, Busan, South Korea; General Surgery Department, Nhan Dan Gia Dinh Hospital, Ho Chi Minh City, Viet Nam; Hospital San Lucas Cardiológica del Sureste, Chiapas, Mexico; Can Oncology Centre, New León, Mexico; Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea; Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea; Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; Medical Oncology, AP-HP Hôpital Beaujon, Paris, France; Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan; Oncology Biometrics, Late Oncology Statistics, AstraZeneca, Warsaw, Poland; Global Medicines Development, AstraZeneca, Gaithersburg, MD; Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain

Background: For >20 years, TACE has been a standard of care for embolization-eligible uHCC; however, most people with uHCC treated with TACE progress within 1 year. Embolization creates a proinflammatory tumor microenvironment and increases VEGF signals; clinical studies have established the role of immune checkpoint inhibitors (ICIs; e.g. D) and VEGF inhibitors (e.g. B) in advanced HCC. Methods: In EMERALD-1 (NCT03778957; double-blind, global, Phase 3 study), participants (pts) with embolization-eligible uHCC, Child-Pugh A to B7 liver function, Eastern Cooperative Oncology Group performance status 0–1, and no evidence of extrahepatic disease were randomized 1:1:1 to the D+B+TACE, D+TACE, or TACE arms. TACE was cTACE or DEB-TACE (investigator choice). Pts received D (1500 mg) or placebo for D (Q4W) plus TACE. After completion of last TACE, pts received D (1120 mg) or placebo for D plus B (15 mg/kg) or placebo for B (Q3W). Primary endpoint was progression-free survival (PFS) for D+B+TACE vs TACE. Secondary endpoints included PFS for D+TACE vs TACE, overall survival (OS), objective response rate (ORR), time to progression (TTP), and safety for D+B+TACE or D+TACE vs TACE. PFS, ORR, and TTP were assessed by blinded independent central review (RECIST v1.1). Results: In total, 616 pts with BCLC Stage A (25.8%), Stage B (57.3%), and Stage C (16.1%) were randomized to D+B+TACE (n=204), D+TACE (n=207), or TACE (n=205). Demographic and baseline characteristics were generally balanced across arms. At final PFS analysis, the primary objective was met: PFS significantly improved for D+B+TACE vs TACE (median [m]PFS 15.0 vs 8.2 months [mo]; hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.61–0.98; p=0.032 [threshold 0.0434]). Results were consistent across most prespecified subgroups. The secondary endpoint of PFS for D+TACE vs TACE was not statistically significant (mPFS 10.0 vs 8.2 mo; HR, 0.94; 95% CI, 0.75–1.19; p=0.638). ORR was 43.6%, 41.0%, and 29.6%, and mTTP was 22.0, 11.5, and 10.0 mo for D+B+TACE, D+TACE, and TACE, respectively. No new safety signals were identified. In the D+B+TACE (n=154), D+TACE (n=232), and TACE (n=200) safety analysis sets, respectively, 32.5%, 15.1%, and 13.5% of pts had maximum Grade 3/4 treatment–related adverse events (TRAEs); 8.4%, 4.3%, and 3.5% discontinued due to TRAEs; and 0%, 1.3%, and 2.0% died due to TRAEs. Pts continue to be followed for OS. Conclusions: D+B+TACE is the first ICI-based regimen in a global Phase 3 trial to show statistically significant and clinically meaningful improvement in PFS, vs TACE, in pts with embolization-eligible uHCC. Safety was manageable and consistent with the safety profiles of D, B, and TACE in uHCC. D+B+TACE has the potential to set a new standard of care in uHCC. Clinical trial information: NCT03778957. Research Sponsor: AstraZeneca.