PHASE 2 MULTI-COHORT CLINICAL STUDY EVALUATING DISTAMAB VEDOTIN ALONE AND IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH HER2-EXPRESSING UNRESECTABLE OR METASTATIC UROTHELIAL CARCINOMA (RC48G001, TRIAL IN PROGRESS)

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Background Urothelial carcinoma (UC) is the 10th most diagnosed cancer worldwide, with a mortality rate of 1.9 per 100,000. Nearly 50% of patients cannot tolerate the standard cisplatin-based first-line (1L) chemotherapy, which presents a strong need to improve outcomes in both 1L and later lines of therapy.

Human epidermal growth factor receptor 2 (HER2) overexpression has been reported in multiple malignant tumors, including UC, and may be associated with poor outcomes. No HER2-directed therapies are currently approved for the treatment of urothelial carcinoma.

Distamab vedotin (DV; RC48-ADC) is an investigational antibody–drug conjugate comprised of a novel HER2-directed monoclonal antibody, distamab, conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable linker. DV elicits antitumor activity through multimodal mechanisms of action including MMAE-directed cytotoxicity, bystander effect, and immunogenic cell death. DV is conditionally approved in locally advanced unresectable or metastatic urothelial carcinoma (LA/mUC) and gastric cancer in China and was granted Breakthrough Therapy designation by the FDA.

Methods RC48G001 (NCT04879329) is a phase 2, multicohort, open-label, multicenter trial to evaluate DV in patients with HER2-expressing LA/mUC.

Patients are enrolled in 3 cohorts based on prior treatment and tumor HER2 expression by immunohistochemistry (IHC) and gene amplification (via in situ hybridization [ISH]), assessed centrally. Cohorts A and B are enrolling patients who have received prior systemic therapy (1 or 2 lines, including platinum-containing chemotherapy) and whose tumors are HER2-positive (IHC 3+, or 2+ and ISH-positive) or HER2-low (IHC 2+ and ISH-negative, or IHC 1+), respectively. Cohort C is enrolling first-line treatment-naive patients in the LA/mUC setting, whose tumors have HER2-positive or HER2-low expression.

Cohorts A and B will evaluate DV as monotherapy (intravenous [IV] administration, once every 2 weeks [Q2W]). Cohort C will evaluate DV (IV, Q2W) +/- pembrolizumab (IV, Day 1 of each 6-week cycle).

Patients in all cohorts must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group Performance Status of 0-1 in Cohorts A and B, and 0-2 in Cohort C.

The primary endpoint is confirmed objective response rate (cORR) assessed by blinded independent central review (BICR). Secondary endpoints include cORR by investigator assessment, overall survival, duration of response, progression-free survival, disease control rate per RECIST v1.1 by BICR and investigator assessment, safety, and pharmacokinetic parameters.

Enrollment for all cohorts is ongoing in North America and Europe, and planned in Latin America, Asia-Pacific, and Israel.

Trial Registration NCT04879329

REFERENCES

Ethics Approval The trial is being conducted in compliance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. All patients, or their legal representatives, provided informed consent. All participating sites have been approved by a corresponding institutional review board or independent ethical committee per the participating institution.