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A phase Ib/II, multicenter, open-label, dose-escalation and dose-expansion study evaluating trastuzumab deruxtecan (T-DXd; DS-8201) monotherapy and combinations in patients with HER2-overexpressing gastric cancer (DESTINY-Gastric03)

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Background

For patients (pts) with HER2-overexpressing metastatic gastric cancer, trastuzumab + chemotherapy is a standard first-line option but provides only a modest overall survival (OS) benefit vs chemotherapy. T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and a membrane-permeable topoisomerase I inhibitor payload. Results from a phase I trial showed promising antitumor activity (confirmed objective response rate [ORR], 43.2%) in pts with heavily pretreated HER2+ metastatic gastric cancer who received T-DXd (5.4 or 6.4 mg/kg; Shitara K, et al. *Lancet Oncol*. 2019;20:827-836). Here we describe the phase Ib/II DESTINY-Gastric03 trial (NCT04379596) evaluating T-DXd monotherapy and combinations in pts with HER2-overexpressing gastric cancer.

Trial design

This is an open-label, multicenter, 2-part, phase Ib/II study in pts with HER2-overexpressing (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization positive) locally advanced, unresectable or metastatic gastric or gastroesophageal junction cancer. In part 1 (dose escalation), pts who had received prior trastuzumab-containing therapy will be assigned to 1 of 5 arms: (1) T-DXd + 5-fluorouracil (5-FU); (2) T-DXd + capecitabine (C); (3) T-DXd + durvalumab; (4) T-DXd + 5-FU or C + oxaliplatin (Ox); or (5) T-DXd + 5-FU or C + durvalumab. In part 2 (dose expansion), pts with no prior treatment for metastatic disease will be randomized across 4 arms: (1) T-DXd; (2) trastuzumab + 5-FU or C + Ox or cisplatin; (3) T-DXd + 5-FU or C ± Ox; or (4) T-DXd + 5-FU or C + durvalumab. In part 2, pts will be stratified by HER2 status. Primary endpoints are safety, determination of recommended phase II doses (part 1), and investigator-assessed confirmed ORR per RECIST v1.1 (part 2). Secondary endpoints include confirmed ORR (part 1), disease control rate, duration of response, progression-free survival (all per investigator), OS, safety (part 2), pharmacokinetics, and immunogenicity.

Clinical trial identification

NCT04379596.

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Legal entity responsible for the study

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