A phase 1, 2-part, multicenter, first-in-human, dose-escalation and dose-expansion study of DS-1103a with trastuzumab deruxtecan (T-DXd) in patients with advanced solid tumors

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INTRODUCTION

- Therapeutic advances with immune checkpoint inhibitors have rapidly emerged and improved outcomes for patients with various types of cancer; however, many challenges and unmet needs remain[1]
- Growing evidence demonstrates that tumor-associated macrophages in the tumor microenvironment promote cancer cell proliferation and immunosuppression[2]
  - Prohibiting the interaction between cancer cells and these macrophages may be the key to tumor suppression and cancer treatment[2]
- Blockade of the signal regulatory protein α (SIRPα)-CD47 interaction is a promising pathway to restore the antitumor immune functions of macrophages and reduce tumor growth[3,4]
- DS-1103a, a recombinant humanized immunoglobulin G4 anti-SIRPα antibody, blocks the SIRPα-CD47 pathway by binding to the major human variants of SIRPα
- Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate consisting of an anti–human epidermal growth receptor 2 (HER2) antibody and topoisomerase I inhibitor payload, is approved for the treatment of various cancers, including breast cancer, non-small cell lung cancer, and gastric cancer[5]
- In nonclinical studies, DS-1103a enhanced trastuzumab- or T-DXd–induced antibody-dependent cellular phagocytosis (ADCP), suggesting a potential benefit of the combination
  - Antimouse SIRPα antibody (a surrogate of DS-1103a) enhanced T-DXd antitumor efficacy in a syngeneic mouse model[6]
  - In a quantitative systems pharmacology model, the starting dose of DS-1103a for use in future first-in-human studies (100 mg intravenously [IV] every 3 weeks) in combination with T-DXd was determined both in vitro and in vivo based on the achievement of intratumoral occupancy and induced ADCP activity[7]
- This phase 1 study will assess the preliminary safety and efficacy of DS-1103a in combination with T-DXd in advanced solid tumors (ClinicalTrials.gov Identifier: NCT05765851)

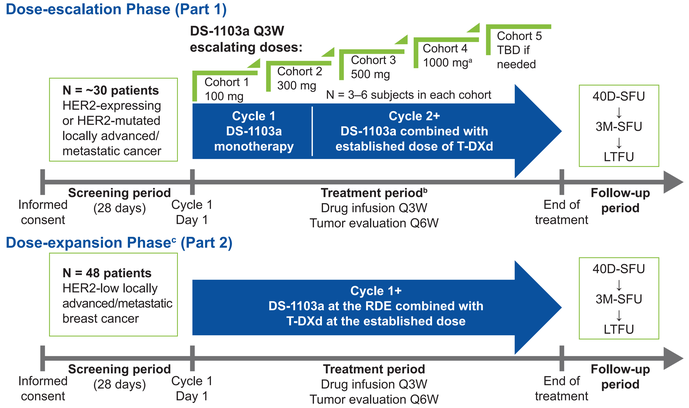
OBJECTIVES

- To investigate the safety and tolerability and determine the recommended dose for expansion (RDE) of DS-1103a in combination with T-DXd
- To further evaluate the safety and the efficacy of DS-1103a at the RDE in combination with T-DXd in patients with HER2-low metastatic breast cancer

METHODS

- This is a phase 1, global, multicenter, first-in-human, 2-part, dose-escalation and dose-expansion study designed to evaluate DS-1103a in combination with T-DXd in patients with advanced (unresectable or metastatic) HER2-expressing/HER2-mutated solid tumors
- The study design is displayed in **Figure 1**
- Dose-escalation (Part 1) will enroll approximately 30 patients with pathologically documented HER2-expressing (eg, immunohistochemistry [IHC] 1+ or greater) or HER2-mutated (with activating mutation determined by next-generation sequencing or other appropriate analysis techniques) advanced solid tumors not amenable to standard of care
- Dose-expansion (Part 2) will enroll approximately 48 patients with HER2-low (IHC 2+/in situ hybridization [ISH]– or IHC 1+ [ISH– or untested]) breast cancer who received 1 to 2 prior lines of chemotherapy in the recurrent or metastatic setting
- Key inclusion criteria
  - Adults ≥18 years of age at the time of informed consent
  - The presence of ≥1 measurable lesion based on computed tomography or magnetic resonance imaging per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the investigator
  - Eastern Cooperative Oncology Group performance status of 0 or 1
- Key exclusion criteria
  - Prior treatment with an anti-CD47 or anti-SIRPα therapy
  - An inadequate treatment washout period prior to the start of study treatment, defined as follows:
    - Major surgery: ≤4 weeks (or ≤2 weeks for low-invasive cases)
    - Radiation therapy, including palliative stereotactic radiation therapy to the chest: ≤4 weeks
    - Palliative stereotactic radiation therapy to other anatomic areas: ≤2 weeks
    - Received any systemic agent from a previous treatment regimen or clinical study within the specified time frame prior to administration of study treatment
- Study drug(s) administration
  - In Part 1, DS-1103a monotherapy will be administered via IV infusion starting on Cycle 1 Day 1, with a proposed starting dose of 100 mg
    - Starting on Cycle 2 Day 1, T-DXd (5.4 mg/kg) will also be administered via IV infusion
  - In Part 2, patients will receive an RDE of DS-1103a, as established by Part 1, in combination with T-DXd starting on Cycle 1 Day 1
- The anticipated total duration of the study is expected to be approximately 44 months

Figure 1. Study design



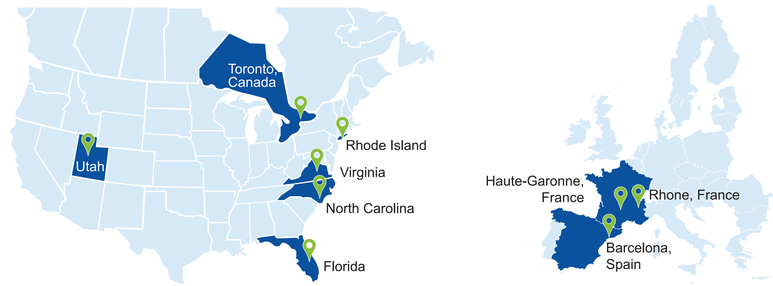
HER2, human epidermal growth receptor 2; Q3W, every 3 weeks; Q6W, every 6 weeks; T-DXd, trastuzumab deruxtecan; TBD, to be determined; D, day; M, month; SFU, safety follow-up; LTFU, long-term follow-up; RDE, recommended dose for expansion.
[a]Use of a DS-1103a dose >1000 mg may be allowed depending on the observed safety, pharmacokinetic and pharmacodynamic data and the recommendation of the Bayesian optimal interval design.
[b]The dose-limiting toxicity evaluation period includes Cycles 1 and 2 in Part 1.
[c]Further discussion with health authorities on the study design of Part 2 is planned prior to commencing dose expansion.

- Endpoints and evaluations
  - In Part 1, the primary endpoint will be to investigate the safety and tolerability of DS-1103a and to determine the RDE of DS-1103a in combination with T-DXd
  - In Part 2, the primary endpoint will be to further evaluate the safety and tolerability of DS-1103a at the RDE in combination with T-DXd and determine the objective response rate (ORR)
    - The ORR will be assessed by blinded independent central review per RECIST v1.1
  - Secondary endpoints include the antitumor activity of DS-1103a in combination with T-DXd, the pharmacokinetic profile of DS-1103a, and the incidence of antidrug antibodies against DS-1103a
  - Safety evaluations will include endpoints such as dose-limiting toxicities, treatment-emergent adverse events (TEAEs), serious adverse events, adverse events of special interest, and TEAEs leading to study drug discontinuation

ENROLLMENT STATUS

- First patient dosed: June 2023
- Estimated primary completion: June 2026
- Enrolling and planned recruitment sites (**Figure 2**)

Figure 2. Global map of enrolling and planned recruitment sites



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DISCLOSURES

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