A Phase 1, first-in-human study of DS-2243, an HLA-A*02/NY-ESO–directed bispecific T-cell engager, in patients with advanced solid tumors

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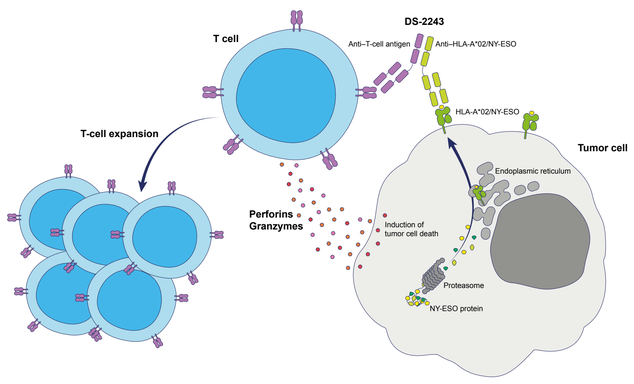
OBJECTIVES

- DS2243-054 (NCT06644755) is a Phase 1, first-in-human, open-label, multicenter, 2-part, dose-escalation and -expansion trial of DS-2243 monotherapy in adult patients with advanced or metastatic HLA-A*02/NY-ESO–positive synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), squamous or adenocarcinoma non-small cell lung cancer (NSCLC), or urothelial carcinoma (UC)[1]
  - The primary objectives of Part 1 (dose escalation) are to evaluate the safety and tolerability of DS-2243 and determine the MTD and/or RDE(s)
  - The primary objectives of Part 2 (dose expansion) are to evaluate the safety and efficacy (ORR) of DS-2243 at the RDE(s)

INTRODUCTION

- DS-2243 is a bispecific T-cell engager with an effectorless Fc region[2]
  - DS-2243 is designed to target both HLA-A*02/NY-ESO–expressing tumor cells and T cells, redirecting T-cell–mediated cytotoxicity toward the tumor (**Figure 1**)
  - DS-2243 has exhibited robust antitumor activity in preclinical studies
- NY-ESO-1 and LAGE-1 are homologous proteins commonly expressed in various tumor tissues but not in normal tissues other than the testis and placenta (which have low expression of class I and II HLA),[3–6] and thus have potential as tumor-specific therapeutic targets
  - Tumor types with prevalent NY-ESO-1 and/or LAGE-1 expression include SS, MRCLS, NSCLC, and UC[3–5]
- This first-in-human study is being conducted to evaluate DS-2243 monotherapy in patients with advanced or metastatic solid tumors[1]

Figure 1. DS-2243 mechanism of action[1,2]



- DS-2243 is a bispecific antibody engineered to engage specifically both HLA-A*02/NY-ESO–expressing tumor cells and T cells[2]
  - Both NY-ESO-1 and LAGE-1 proteins undergo intracellular proteolytic processing to generate the same highly immunogenic NY-ESO peptide[3,4,7]
  - The NY-ESO peptide is presented on the cell surface in association with HLA-A*02 major histocompatibility complex molecules[7]
- DS-2243 is designed to redirect T-cell–mediated cytotoxicity toward tumor cells[2]

METHODS

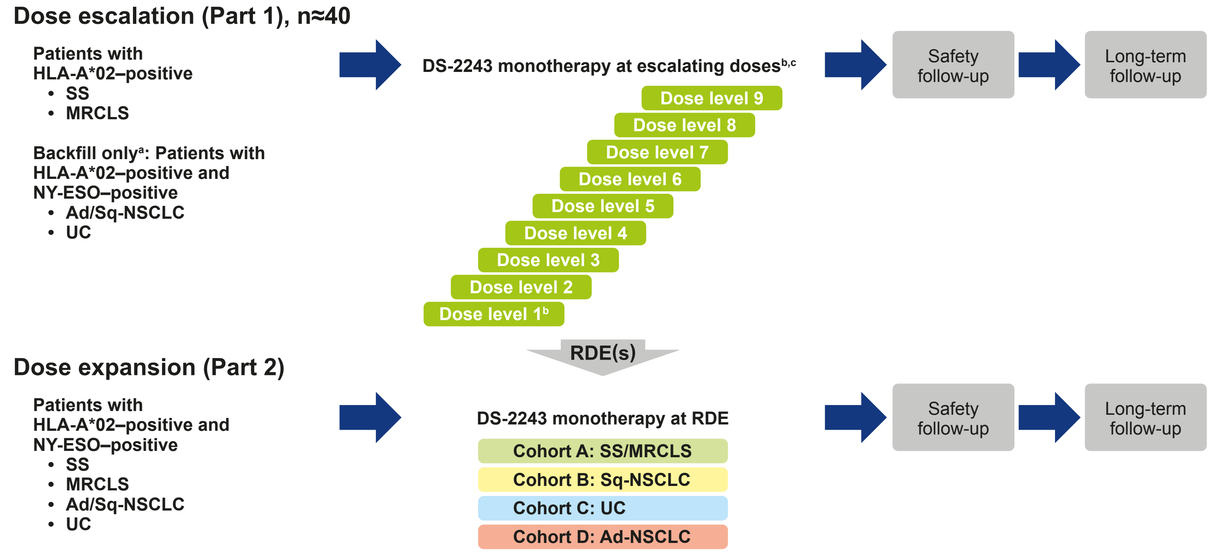
- DS2243-054 (NCT06644755) is a Phase 1, first-in-human, open-label, multicenter, 2-part, dose-escalation and -expansion trial of DS-2243[1]
- Patients must be adults (aged ≥18 years or above the local age of consent if higher) and have HLA-A*02–positive advanced or metastatic SS, MRCLS, squamous or adenocarcinoma NSCLC, or UC, and be unable to tolerate standard-of-care therapies, or have relapsed disease after or be refractory to such therapies (**Table 1**)[1]
  - Patients with NSCLC or UC in the dose-escalation part, and all patients in the dose-expansion part, must have NY-ESO protein expression confirmed in tumor tissue by IHC in a central laboratory
- Patients will receive DS-2243 as monotherapy until radiologic or clinical progression, unacceptable toxicity, withdrawal of consent, or discontinuation for other reasons (**Figure 2**)

Table 1. Key eligibility criteria[a]

Key inclusion criteria	Key exclusion criteria
Adults aged ≥18 years or the legal age of consent for trial participation if >18 years	Prior therapy targeting NY-ESO-1
HLA-A*02:01, 02:02, 02:03, 02:04, 02:05, 02:06, 02:09, 02:10, or 02:11 positive	Known symptomatic CNS metastases, leptomeningeal disease, or cord compression
One of the following histologically or cytologically documented cancers: • Advanced (metastatic or unresectable) SS or MRCLS • Metastatic or unresectable locally advanced NSCLC (squamous or adenocarcinoma) or UC	History of or active autoimmune disease. Participants with type I diabetes mellitus/hypothyroidism only requiring hormone replacement and participants with skin disorders not requiring systemic treatment may be enrolled as an exception
Patients with NSCLC or UC in Part 1 and all patients in Part 2: NY-ESO protein expression confirmed in tumor tissue by IHC in a central laboratory	HIV infection; in Part 2 only, participants with virologic suppression who are on a controlled antiretroviral regimen may be eligible
Disease relapsed from, refractory to, or intolerant to standard-of-care therapies	Active or uncontrolled hepatitis B or C infection
Has measurable disease assessed by CT/MRI per RECIST 1.1	Unresolved toxicities from previous anticancer treatment
Willing and able to provide adequate pretreatment or archival tumor tissue sample	Uncontrolled or clinically significant cardiovascular disease
ECOG performance status 0 or 1	Any previous, current, or uncontrolled clinically relevant illness, medical condition, psychological condition, surgical history, physical finding, or laboratory abnormality that, in the investigator's opinion, could affect the safety of the participant; alter the absorption, distribution, metabolism, or excretion of the trial intervention; or confound the assessment of trial results
Meets the required baseline local laboratory data within 14 days prior to start of study intervention administration	

[a]Eligibility criteria should follow the protocol approved in the respective country.

Figure 2. DS2243-054 study design



[a]Patients with Ad/Sq-NSCLC and UC will be enrolled in Part 1 only as backfill after dose escalation has determined doses to be further tested. [b]Dose escalation will be implemented using an accelerated titration design with single-participant cohorts at lower dose levels. In the event of a Grade ≥2 adverse event during the DLT evaluation period or upon the observation of clinical activity such as tumor shrinkage, the cohort size will be expanded to 3 participants, and the escalation/de-escalation rules will transition to the BOIN design to inform the MTD.[8,9] If the dose level is found to be safe by the BOIN design, escalation to the next higher dose level will continue. Up to ~9 additional participants may be enrolled at each dose level already deemed to be safe to attain additional safety and efficacy information to guide selection of optimal biologically effective RDE(s). [c]In Part 1, an appropriate step-up dose regimen (frequency, the number of steps, and dose levels for each step) may be considered, along with premedication for cytokine release syndrome, which could include intravenous hydration, antipyretics, and dexamethasone.

- Dose escalation (Part 1) aims to evaluate the safety, tolerability, preliminary antitumor activity, PK, and immunogenicity of DS-2243 and to determine the MTD and/or RDE(s)
- Dose expansion (Part 2) will evaluate the safety, preliminary antitumor activity, PK, and immunogenicity of DS-2243 at the RDE(s) in tumor-specific cohorts
- Study endpoints are summarized in **Table 2**
- Part 1 began in November 2024, and is enrolling in the USA (Massachusetts, Tennessee, and New York) and Europe (Belgium, France, and the Netherlands), with plans for enrollment to open in additional sites and countries
- Study completion is expected in August 2029

Table 2. Study endpoints

Primary	Secondary
Safety, including DLTs (Part 1 only) and TEAEs	ORR (Part 1 only), DCR, DOR, TTR, PFS all assessed by the investigator per RECIST 1.1
ORR (Part 2 only) as assessed by the investigator per RECIST 1.1	OS
	PK
	Immunogenicity

Key statistical considerations

- ORR and DCR will be summarized with 95% CI using the Clopper-Pearson method
- Time to event variables, including DOR, PFS, and OS, will be represented graphically using the Kaplan–Meier method, with median event times and corresponding CIs estimated using the Brookmeyer–Crowley method

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ABBREVIATIONS

Ad/Sq, adenocarcinoma/squamous cell carcinoma; **BOIN**, Bayesian optimal interval principle; **CI**, confidence interval; **CNS**, central nervous system; **CT**, computed tomography; **DCR**, disease control rate; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **Fc**, fragment crystallizable; **HIV**, human immunodeficiency virus; **HLA(-A*02)**, histocompatibility leukocyte antigen (A*02); **IHC**, immunohistochemistry; **LAGE-1**, L antigen family member 1; **MRCLS**, myxoid/round cell liposarcoma; **MRI**, magnetic resonance imaging; **MTD**, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **NY-ESO(-1)**, New York esophageal squamous cell carcinoma (1); **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **RDE(s)**, recommended dose(s) for expansion; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SS**, synovial sarcoma; **TEAE**, treatment-emergent adverse event; **TTR**, time to response; **UC**, urothelial carcinoma.

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DISCLOSURES

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