A Phase 1, first-in-human study of DS5361, a small-molecule, nonsense-mediated mRNA decay inhibitor, in patients with advanced/metastatic solid tumors (Parts 1 and 2)

TPS2680

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PLAIN LANGUAGE SUMMARY

Why perform this study?

- Many cancers are now treated using immunotherapy, which helps the body's immune system to locate and attack cancer cells[1]
- Although immunotherapy provides benefits for people with cancer, the effects are not always long lasting[2]; using immunotherapy in combination with another drug may improve outcomes[3,4]

What will this study determine?

- The main goal is to find out which doses of a potential new treatment called **DS5361** can be given safely to people with cancer, either on its own or in combination with an immunotherapy drug called pembrolizumab[5]
- This will help researchers decide what doses of **DS5361** should be tested in future clinical studies[5]

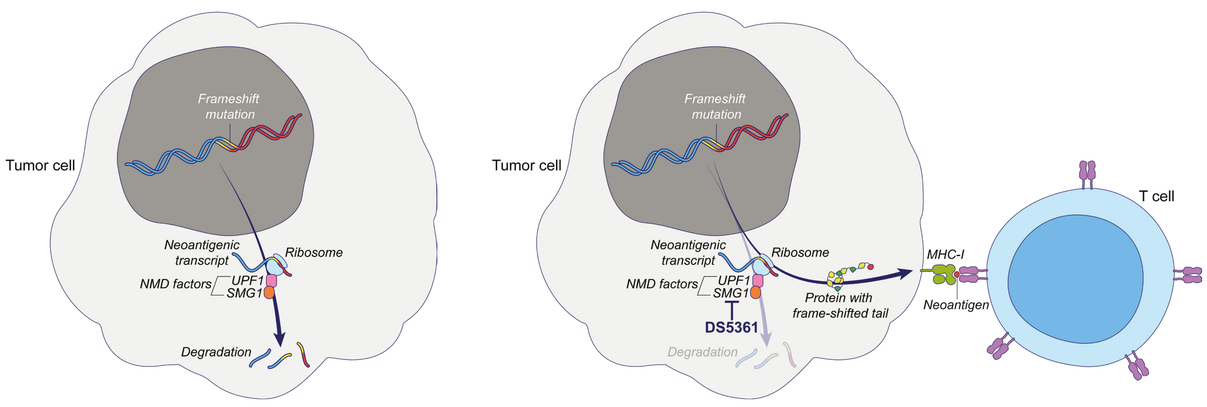
How will this study be performed?

- People with advanced cancer or cancer that has spread to other parts of the body will be given **DS5361** by itself or along with pembrolizumab at steadily increasing doses[5]
- At each dose level, the researchers will check if patients have any side effects before deciding whether to test the next higher dose[5]

BACKGROUND

- Despite the success of ICIs in the treatment of patients with advanced or metastatic solid tumors, only a minority experience meaningful long-term responses,[2] underscoring the need for novel therapies to maximize clinical benefit
- TMB-H and MSI-H are associated with improved efficacy of ICIs due to an increase in presentation of neoantigens, tumor-specific peptides displayed on tumor cell surfaces that are critical for antitumor immune responses[3,4]
- mRNAs harboring premature termination codons, including neoantigenic transcripts derived from frameshift mutations, are recognized and degraded by NMD, a crucial cellular surveillance system that prevents the translation of potentially harmful proteins[3,4]
- **DS5361** is a potentially first-in-class, orally available, small-molecule inhibitor targeting the serine/threonine kinase SMG1, a key component of the NMD mechanism[3]
  - **DS5361** is designed to activate antitumor immunity by inhibiting NMD, thereby increasing neoantigen levels (**Figure 1**). When administered in combination with ICIs, **DS5361** may enhance ICI efficacy
- In preclinical studies, **DS5361** enhanced antigen presentation and demonstrated immune-dependent antitumor efficacy, including T-cell activation; benefits in mouse models were also observed when **DS5361** was combined with ICIs
- **DS5361-061** is a **first-in-human** study being conducted to evaluate **DS5361** as monotherapy (Part 1) and in combination with pembrolizumab (Part 2) in patients with advanced or metastatic TMB-H and/or MSI-H solid tumors[5]

Figure 1. DS5361 proposed mechanism of action



- NMD is a crucial cellular surveillance system that degrades mRNA harboring frameshift mutations[2,3]
- **DS5361**, a small-molecule inhibitor of SMG1, is designed to inhibit NMD, leading to expression of neoantigenic proteins derived from frameshift mutations
- The resultant increased neoantigen presentation on tumor cells is postulated to activate antitumor immunity and enhance ICI efficacy

METHODS

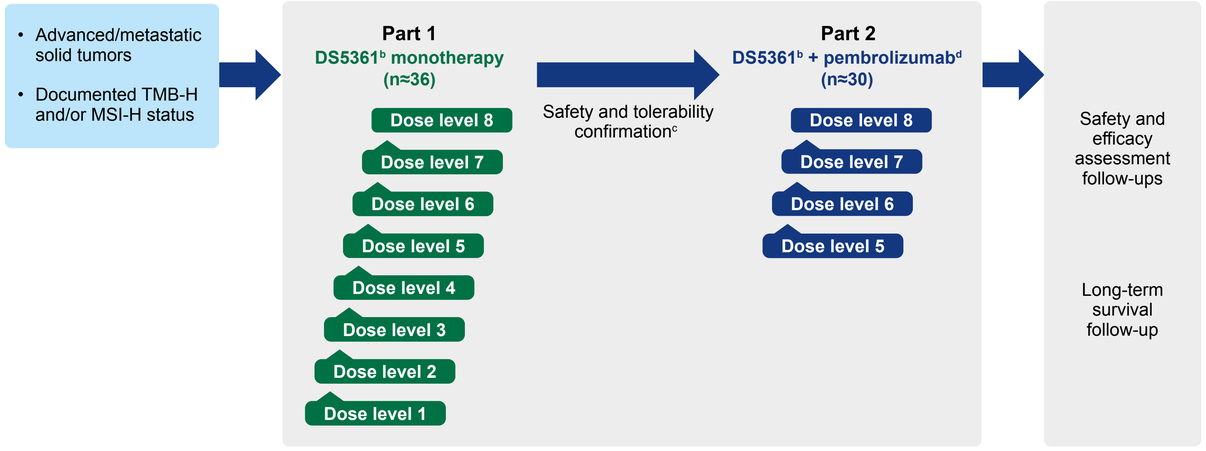
- **DS5361-061** (NCT07182591) is a Phase 1, **first-in-human**, open-label, multicenter, dose-escalation study of **DS5361** as monotherapy (Part 1) and in combination with pembrolizumab (Part 2)

Table 1. Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
Adults aged ≥18 years, or the legal age of consent for study participation if >18 years	Spinal cord compression or clinically active CNS metastases (untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms); history of leptomeningeal carcinomatosis
Histologically or cytologically documented recurrent, metastatic, or unresectable solid tumors refractory to standard treatment, for which standard treatment is intolerable, or for which no standard treatment is available	Uncontrolled or significant cardiovascular disease; cerebrovascular accident, transient ischemic attack, or other arterial thromboembolic event ≤6 months prior to enrollment
Documented TMB-H and/or MSI-H status per a validated or approved genomic test prior to treatment initiation	History of (noninfectious) ILD/pneumonitis that required corticosteroids; current ILD/pneumonitis or where suspected ILD/pneumonitis cannot be ruled out
Measurable disease according to CT/MRI per RECIST 1.1 as assessed by the investigator	Clinically severe pulmonary compromise (ie, requiring any supplemental oxygen)
ECOG PS 0 or 1	HIV infection; active or uncontrolled hepatitis B or C infection (screening test required for all)
Adequate organ and bone marrow function ≤14 days prior to initiation of treatment	Active, known, or suspected autoimmune disease; a diagnosis of immunodeficiency or receiving systemic steroid therapy (or any other form of immunosuppressive therapy) ≤14 days prior to initiation of trial intervention; prior organ transplantation including allogeneic stem cell transplantation
Patients with HNSCC only: documented HPV test results for oropharyngeal cancer	Evidence of severe or uncontrolled systemic disease

- Approximately 66 adult patients with advanced or metastatic solid tumors who are unable to tolerate standard treatment, or have disease that is refractory to standard treatment or for which no such treatment is available, will be enrolled across Parts 1 (n≈36) and 2 (n≈30)
  - All patients must have documented TMB-H and/or MSI-H status
  - Key eligibility criteria are presented in **Table 1**
- Patients will receive **DS5361** monotherapy (in Part 1) or **DS5361** in combination with standard-dose pembrolizumab (in Part 2), until radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or discontinuation for other reasons, or (for pembrolizumab only) for a maximum of 35 cycles (~2 years; **Figure 2**)
- Primary objectives of the dose-escalation part of the study are to:
  - Evaluate the safety and tolerability, and to determine the MTD of **DS5361** as monotherapy in Part 1
  - Evaluate the safety and tolerability, and to determine the MTD and/or the recommended dose(s) for expansion of **DS5361** in combination with pembrolizumab in Part 2
- Secondary objectives are to evaluate the preliminary antitumor activity and characterize the PK profile of **DS5361**
- Study endpoints are summarized in **Table 2**

Figure 2. DS5361-061 study design



[a]Part 1 and Part 2 will utilize the BOIN design to determine the MTD. [b]Administered at escalating doses. [c]Following the confirmation of safety and tolerability at dose level 6 in Part 1, dose escalation of DS5361 in combination with pembrolizumab will be initiated from dose level 5 in Part 2. Actual initial dose level in Part 2 may be amended based on clinical data. [d]Administered at a standard dose for up to 35 cycles.

Table 2. Study endpoints

Primary endpoints
Safety, including DLTs, TEAEs, and SAEs
Secondary endpoints
Objective response by investigator per RECIST 1.1
Disease control by investigator per RECIST 1.1
DOR by investigator per RECIST 1.1
PK profile of **DS5361**, including plasma concentrations and PK parameters

Key statistical considerations

- ORR and DCR will be summarized with their 95% CIs using the Clopper–Pearson method
  - ORR is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR
  - DCR is defined as the proportion of patients with a BOR of confirmed CR, confirmed PR, or SD
- DOR will be presented using the Kaplan–Meier method
  - DOR is defined as the time (month) from date of initial response (CR or PR) to the earlier date of the first objective documentation of radiographic disease progression or death due to any cause

Study status

- Enrollment began in October 2025 and is ongoing at sites in the USA (Florida, Rhode Island, and Texas) and Japan (Chiba and Tokyo), with plans for enrollment to open in additional sites and countries

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ABBREVIATIONS

BOIN, Bayesian optimal interval; **BOR**, best overall response; **CI**, confidence interval; **CNS**, central nervous system; **CR**, complete response; **CT**, computed tomography; **DCR**, disease control rate; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HIV**, human immunodeficiency virus; **HNSCC**, head and neck squamous cell carcinoma; **HPV**, human papillomavirus; **ICI**, immune checkpoint inhibitor; **ILD**, interstitial lung disease; **MHC-I**, major histocompatibility complex class I; **MRI**, magnetic resonance imaging; **mRNA**, messenger RNA; **MSI-H**, microsatellite instability-high; **MTD**, maximum tolerated dose; **NMD**, nonsense-mediated mRNA decay; **ORR**, objective response rate; **PK**, pharmacokinetic; **PR**, partial response; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SAE**, serious adverse event; **SD**, stable disease; **SMG1**, suppressor with morphogenetic effect on genitalia 1; **TEAE**, treatment-emergent adverse event; **TMB-H**, tumor mutational burden-high; **UPF1**, up-frameshift protein 1; **USA**, United States of America.

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