A Phase 1, first-in-human study of DS9051, a novel targeted protein degradation molecule, in patients with advanced/metastatic adrenocortical carcinoma or metastatic castration-resistant prostate cancer

TPS3179

Manish R. Patel,[1] Benedito A. Carneiro,[2] Jean-Pierre Delord,[3] Johann de Bono,[4] Christian Ostheimer,[5] Kentaro Ito,[5] Yuichi Takahashi,[6] Di Shu,[5] Nasser Khan,[5] Antonio Tito Fojo,[7]* Karim Fizazi[8]*

[1]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, USA; [2]Legorreta Cancer Center at Brown University, Providence, RI, USA; [3]Université de Toulouse, IUCT-Oncopole, Toulouse, France; [4]The Royal Marsden, London, UK; [5]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [6]Daiichi Sankyo Co., Ltd., Tokyo, Japan; [7]Columbia University, New York, NY, USA; [8]Centre Oscar Lambret, University of Paris-Saclay, Lille, France. *ATF and KF are co-senior authors.

PLAIN LANGUAGE SUMMARY

Why perform this study?

- Metastatic castration-resistant prostate cancer and adrenocortical carcinoma are two different types of cancers that are difficult to treat, particularly when they have spread to other parts of the body or stopped responding to currently available therapies.[1,2] This means that there is a need for new and more effective treatments

What will this study determine?

- The main goal is to find out which doses of a potential new treatment called **DS9051** can be given safely to people with cancer[3]
- This will help researchers decide what doses of **DS9051** should be tested in future clinical studies[3]

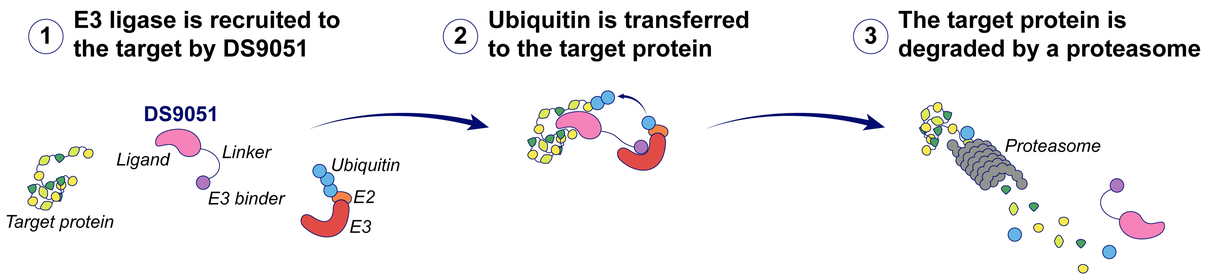
How will this study be performed?

- People with either metastatic castration-resistant prostate cancer who have been treated with standard treatments that are no longer working, or with advanced or metastatic adrenocortical carcinoma who cannot have surgery or radiation therapy, will be given **DS9051** at steadily increasing doses[3]
- At each dose level, the researchers will check if patients have any side effects before deciding whether to test the next higher dose[3]

BACKGROUND

- Metastatic CRPC typically progresses despite androgen deprivation and ARPI therapy, with or without taxanes[1]; biomarker-directed agents, such as PARP inhibitors and ^{177}Lu-PSMA-617, are only suitable for select patient populations[1]
- ACC is a rare and aggressive endocrine malignancy; treatment options in advanced ACC are limited beyond mitotane with or without standard chemotherapy, and prognosis is very poor[2]
- **DS9051** is a novel targeted protein degradation molecule (**Figure 1**)
  - **DS9051** has been designed to selectively degrade a key protein that is involved in the development and progression of both metastatic CRPC and ACC via a novel mechanism
  - Protein degraders have shown promising efficacy in various cancers, including metastatic CRPC, due to their ability to address otherwise undruggable targets by breaking down proteins instead of only inhibiting their enzymatic function[4]
- **DS9051-079** is a **first-in-human** study being conducted to evaluate **DS9051** therapy in patients with metastatic CRPC or advanced or metastatic ACC[3]

Figure 1. DS9051 proposed mechanism of action



- **DS9051** is a targeted protein degradation molecule consisting of a ligand that binds to the target protein, a linker, and a component that recruits E3 ligase
- **DS9051** acts as a bridge to link the target protein and E3 ligase, initiating ubiquitination and proteasomal degradation of the target protein

METHODS

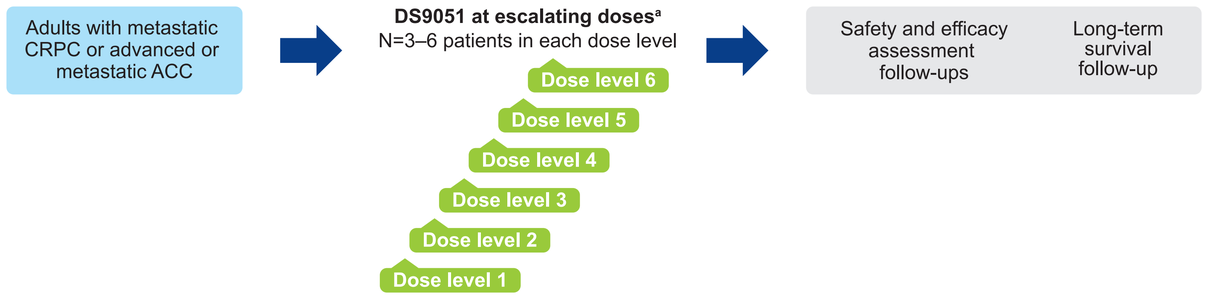
- **DS9051-079** (NCT07189403; EU CT 2025-521886-28-00) is a Phase 1, **first-in-human**, open-label, multicenter study of **DS9051**[3]
- Adults with metastatic CRPC, or advanced or metastatic ACC (**Table 1**)
  - Patients with metastatic CRPC must have:
    - Documented disease progression according to ≥1 of the following criteria: PSA progression per PCWG3 criteria, bone disease progression per PCWG3 criteria, or soft tissue disease progression per RECIST 1.1
    - Had ≥1 prior line of ARPI therapy for castration-sensitive or -resistant prostate cancer for ≥12 weeks
    - Had ≥1 prior line of chemotherapy or have refused or be ineligible for chemotherapy

Table 1. General key eligibility criteria

General key inclusion criteria	General key exclusion criteria
Adults aged ≥18 years, or the legal age of consent for study participation if >18 years	History of pituitary gland dysfunction
	Active or uncontrolled autoimmune disease requiring systemic treatment
	Any medical condition (other than the cancer) requiring a dose of concurrent systemic corticosteroid treatment >5 mg of prednisone and/or >100 µg of fludrocortisone per day (or equivalent)
Histologically confirmed diagnosis of ACC or adenocarcinoma of the prostate	Active infection or other medical conditions that would make corticosteroids contraindicated
	Spinal cord compression or clinically active central nervous system metastases
ECOG PS of 0 or 1 assessed ≤14 days prior to initiation of treatment (ECOG PS of 2 due to cancer pain is acceptable)	Unresolved toxicities from previous anticancer treatment
	Uncontrolled or clinically significant cardiovascular disease
	Known gastrointestinal disease or gastrointestinal procedures that may interfere with absorption of study treatment or intervention, including proton pump inhibitor and antacids
Adequate organ and bone marrow function within 14 days prior to initiation of treatment	History of another primary malignancy, except for: • Malignancy treated with curative intent and with no known active disease for ≥3 years • Non-melanoma skin cancer, lentigo maligna, or lentigo maligna melanoma, treated with curative intent and without evidence of disease • In situ carcinoma treated with curative intent and without evidence of disease • History of prostate cancer of Stage ≤T2cN0M0 without biochemical recurrence or progression

- Patients will receive **DS9051** orally at escalating doses, until radiographic disease progression as assessed by the investigator (per PCWG3 for metastatic CRPC, and RECIST 1.1 for ACC), or discontinuation for other reasons (**Figure 2**)
- The aim of the dose-escalation part of the study is to evaluate the safety and tolerability of **DS9051** and to determine the MTD and/or RDE
- Study endpoints are summarized in **Table 2**

Figure 2. DS9051-079 study design



[a]Dose escalation will be implemented using an accelerated titration design with single-patient cohorts at lower dose levels. In the event of a Grade ≥2 AE during the DLT evaluation period, the cohort size will be expanded to 3 patients, and the escalation/de-escalation rules will transition to the BOIN design to inform the MTD.[5,6] Per the BOIN design, at least 3 patients will be assigned to received DS9051 at a specific dose level. If the dose level is found to be safe by the BOIN design, escalation to the next higher dose level will continue.

Table 2. Study endpoints

Primary endpoints
Safety, including DLTs, TEAEs, and SAEs
Secondary endpoints
Objective response[a]
Disease control[a]
Clinical benefit[a]
DOR[a]
Pharmacokinetics

[a]By investigator per RECIST 1.1 for ACC or PCWG3 for metastatic CRPC.

Key statistical considerations

- Objective response rate, disease control rate, and clinical benefit rate will be summarized with their 95% CIs using the Clopper–Pearson method
- Time to event variables, including progression-free survival and DOR, will be summarized and presented graphically using the Kaplan–Meier method, with median event times and corresponding CIs presented using the Brookmeyer–Crowley method

Study status

- Enrollment began in November 2025 and is ongoing at sites in the USA (Florida and Rhode Island) and France (Toulouse), with plans for enrollment to open in additional sites and countries

REFERENCES

1. Hatano K, et al. *World J Mens Health*. 2023;41:769–784.
2. Chukkalore D, et al. *Oncologist*. 2024;29:738–746.
3. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT07189403. Accessed May 14, 2026.
4. Békés M, et al. *Nat Rev Drug Discov*. 2022;21:181–200.
5. Liu S and Yuan Y. *J R Stat Soc C*. 2015;64:507–523.
6. Yuan Y, et al. *Clin Cancer Res*. 2016;22:4291–4301.

ABBREVIATIONS

ACC, adrenocortical carcinoma; **AE**, adverse event; **ARPI**, androgen receptor pathway inhibitor; **BOIN**, Bayesian optimal interval; **CI**, confidence interval; **CRPC**, castration-resistant prostate cancer; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **MTD**, maximum tolerated dose; **PARP**, poly (ADP-ribose) polymerase; **PCWG3**, Prostate Cancer Working Group 3; **PSA**, prostate-specific antigen; **RDE**, recommended dose for expansion; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **TNM**, tumor node metastasis; **USA**, United States of America.

ACKNOWLEDGMENTS

Funding for this study was provided by Daiichi Sankyo, Inc.
Medical writing support was provided by Rachael Bailey, PhD, of BOLDSCIENCE, Inc., and was funded by Daiichi Sankyo, Inc.
Editorial support was provided in accordance with Good Publication Practice guidelines (https://ismpp.org/gpp-2022).

DISCLOSURES

Manish Patel has received (institutional) research funding from Accutar Biotech, AbbVie, Abdera Therapeutics, Adagene, Agenus, Allorion Therapeutics, Apollo, Astellas Pharma, AstraZeneca, Artios, Avenzo Therapeutics, BioNTech, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb/Celgene, Compugen, Conjupro Biotherapeutics, Cullinan Oncology, Cyteir, D3 Bio, Daiichi Sankyo, Genentech/Roche, Georgiamune, Hotspot Therapeutics, Immune-Onc Therapeutics, Immunitas, Immunogen, Incyte, Janssen, Kineta, Kura Oncology, Lilly, Loxo, Macrogenics, Medlink, Merck, Moderna Therapeutics, Novartis, Nurix, Olema Oncology, OnCusp Therapeutics, Pfizer, Prelude Therapeutics, Ribon Therapeutics, Seven and Eight Biopharmaceuticals, Step Pharma, Sutro Biopharma, Syndax, Systimmune, TeneoBio, Vividion Therapeutics, Zai Lab, and Zymeworks; has provided leadership for ION Pharma; and has had a consulting or advisory role for Accutar Biotech, Daiichi Sankyo/UCB Japan, Johnson & Johnson/Janssen, Kura Oncology, Mitsubishi Tanabe Pharma, and Shivanka Research.

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–June 2, 2026; Chicago, IL, USA.

MPatel@flcancer.com