An open-label phase 1 study of DCC-2812 monotherapy in patients with advanced genitourinary cancers

Abstract: TPS4639

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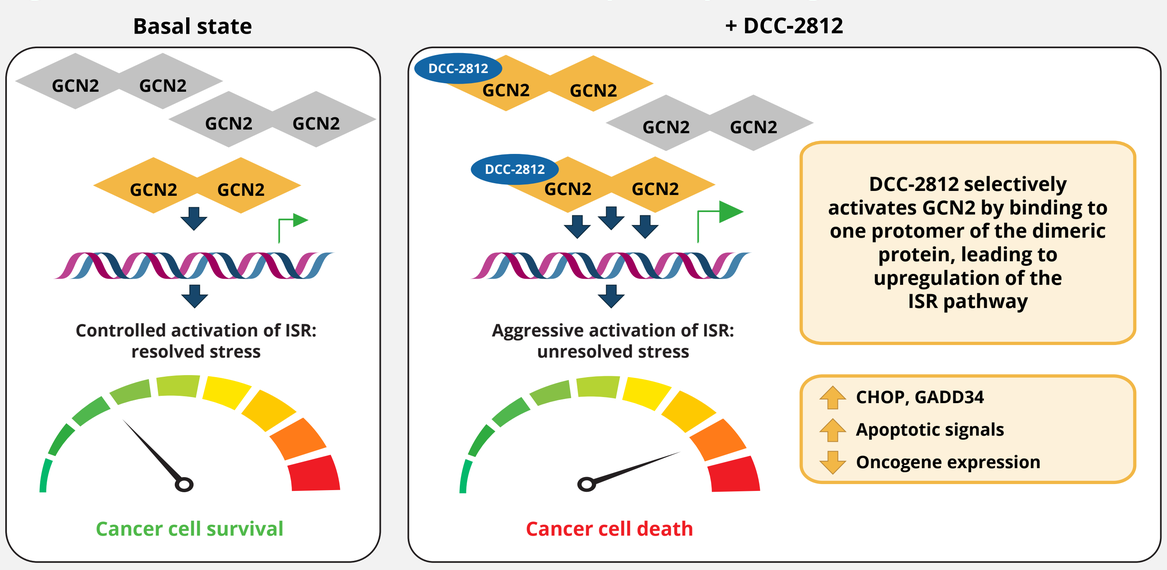
Introduction

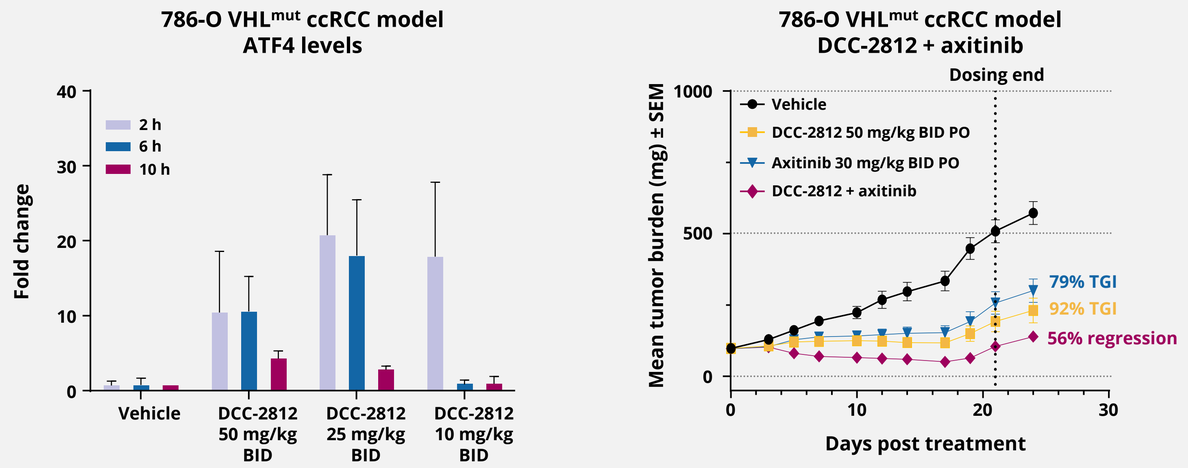
- The integrated stress response (ISR) is a major adaptive cellular response pathway that cancer cells depend on to survive in the context of oncogenic pathway activation and high proliferative demand[1-3]
  - The ISR is tightly regulated by stress-sensing kinases, including general control nonderepressible 2 (GCN2)[1-4]
- Under a controllable level of cellular stress, moderate activation of GCN2 promotes adaptation to nutrient and oxygen deficiency, supporting cancer cell survival[1-3]
- In contrast, excessive GCN2 activation in response to unresolvable stress leads to the induction of pro-apoptotic genes and cancer cell death, making this pathway a promising therapeutic target (**Figure 1**)[1-3]
- DCC-2812 is an investigational, potent, and selective activator of GCN2 and thus the ISR pathway in cancer cells[5,6]
- In preclinical studies, DCC-2812 upregulated the ISR pathway and demonstrated single-agent antitumor activity in a variety of cancer cell lines, including those of renal and urothelial origin[5,6]
- DCC-2812 also inhibited tumor growth in vivo in xenograft models of renal cell carcinoma (RCC) and urothelial cell carcinoma (**Figure 2**)[6]
- Here, we describe an ongoing phase 1 study evaluating DCC-2812 as a monotherapy in patients with advanced genitourinary cancers

Figure 1. DCC-2812 activates GCN2 and the ISR pathway leading to cancer cell death[5,6]



CHOP, CCAAT/enhancer-binding protein (C/EBP) homologous protein; GADD34, growth arrest and DNA damage-inducible protein 34; GCN2, general control nonderepressible 2; ISR, integrated stress response.

Figure 2. DCC-2812 upregulates the ISR pathway via ATF4 and inhibits tumor growth in vivo in xenograft models of ccRCC, renal papillary cancer, and bladder cancer[6]

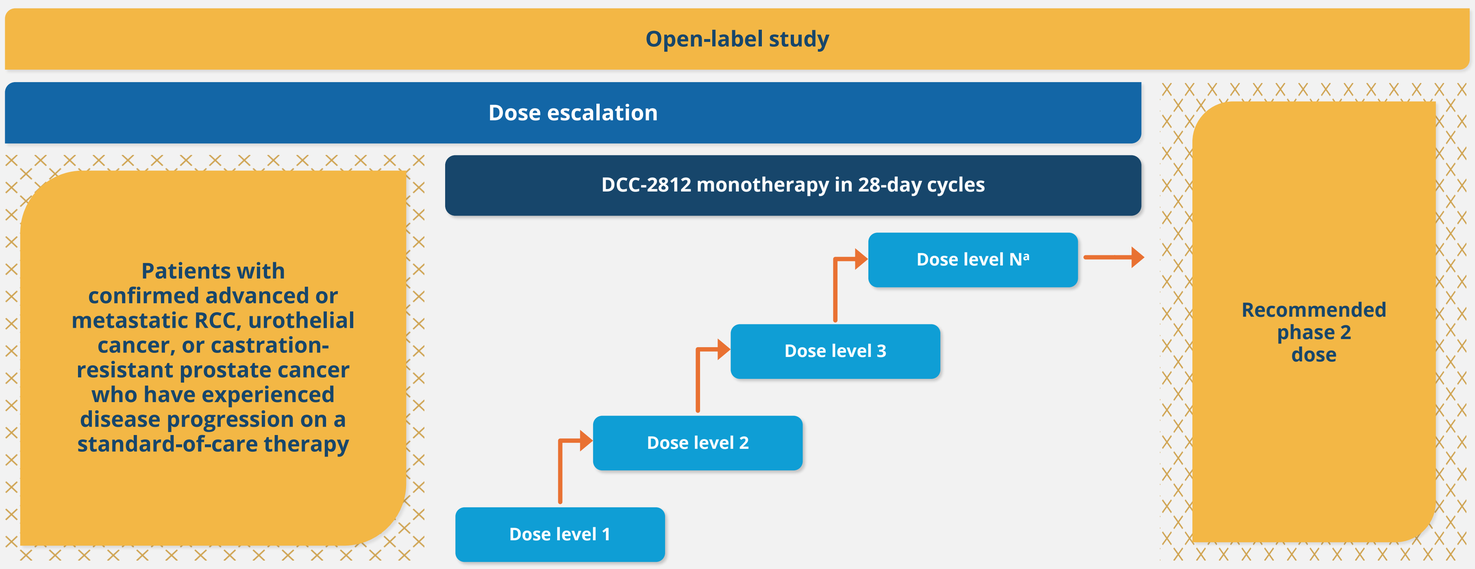


ACHN, human renal adenocarcinoma cell line; ATF4, activating transcription factor 4; BID, twice daily; ccRCC, clear cell renal cell carcinoma; c-Met, cleaved proto-oncogene encoding the hepatocyte growth factor receptor; IP, intraperitoneal; ; ISR, integrated stress response; mut, mutant; PO, by mouth; Q7D, every 7 days; SEM, standard error of the mean; TGI, tumor growth inhibition; VHL, Von Hippel-Lindau.

Methods

- This is a multicenter, open-label, phase 1 dose-escalation study evaluating the safety and preliminary antitumor activity of DCC-2812 in adult patients (≥18 years) with histologically or cytologically confirmed advanced or metastatic RCC, urothelial cancer, or castration-resistant prostate cancer (NCT06966024)

Figure 3. Study design



[a]Escalation will continue per Bayesian optimal interval design as long as no dose-limiting toxicities are identified or until the maximum tolerated dose is reached. All safety data will be considered when the next dose level is decided by the Cohort Review Committee.
RCC, renal cell carcinoma.

Primary outcome measures

- Dose-limiting toxicities during cycle 1
- Treatment-emergent adverse events (TEAEs), serious adverse events, and dose modifications due to TEAEs

Secondary outcome measures

- Radiographic objective response rate and radiographic duration of response per Response Evaluation Criteria in Solid Tumors version 1.1 or Prostate Cancer Working Group 3 criteria, if applicable
- Pharmacokinetics

Key eligibility criteria

INCLUSION

- Male or female ≥18 years of age
- Have histologically or cytologically confirmed advanced or metastatic renal cell carcinoma, urothelial cancer, or castration-resistant prostate cancer
- Have experienced disease progression on or be intolerant of standard-of-care therapies
- If a female is of childbearing potential, must have a negative pregnancy test prior to enrollment and all participants agree to follow the contraception requirements
- Adequate organ function and electrolytes
- Ability to take oral medication

EXCLUSION

- Received any prior anticancer therapy (other than LHRH agonists/antagonists for prostate cancer) or any investigational therapy within a specified timeframe prior to the first dose of DCC-2812
- Have impaired cardiac function
- Received major surgery within 28 days of first dose of DCC-2812

LHRH, luteinizing hormone–releasing hormone.

- The study is currently recruiting patients at multiple sites in the United States

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Please scan to access the clinicaltrials.gov site for this study (NCT05957367).