A Phase 1/2 Study of VS-7375 in Advanced *KRAS* G12D-Mutant Solid Tumors, Including Cholangiocarcinoma

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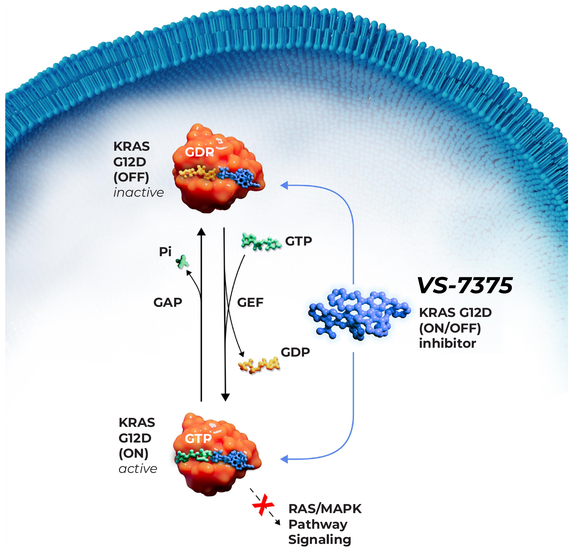
BACKGROUND

- Cholangiocarcinoma (CCA) is a global health problem with a rising incidence, accounting for approximately 15% of all primary liver cancers worldwide[1,2]
- Surgical resection remains the only potentially curative treatment; however, the majority of patients present with advanced-stage disease, thereby limiting curative options[3,4]
- As a result, there is a substantial unmet need for the development of effective systemic therapies[3,4]
- Therapeutic strategies are increasingly focused on targeted approaches guided by next-generation sequencing[3,4]
- Kirsten rat sarcoma virus homolog (*KRAS*) mutations are reported in ≥16% of CCA cases, with *KRAS* G12D representing the most prevalent variant, accounting for approximately 40% of *KRAS*-mutant tumors[5,6]
- VS-7375 is a potent, highly selective, oral, noncovalent, small molecule that acts as a dual *KRAS* G12D inhibitor by suppressing both the active (ie, ON) and inactive (ie, OFF) states of *KRAS* G12D[7] (**Figure 1**)

Figure 1. VS-7375 Mechanism of Action



GAP, GTPase-activating protein; GDP, guanosine diphosphate; GEF, guanine-nucleotide exchange factor; GTP, guanosine triphosphate; *KRAS*, Kirsten rat sarcoma virus homolog; MAPK, mitogen-activated protein kinase; RAS, rat sarcoma virus.

- In preclinical studies, VS-7375 was correlated with better in vivo efficacy and durability and more rapid and durable suppression of phosphorylated extracellular signal-regulated kinase signaling compared to ON-only rat sarcoma virus inhibitors and achieved exposures corresponding to maximal tumor regressions[7]

OBJECTIVE

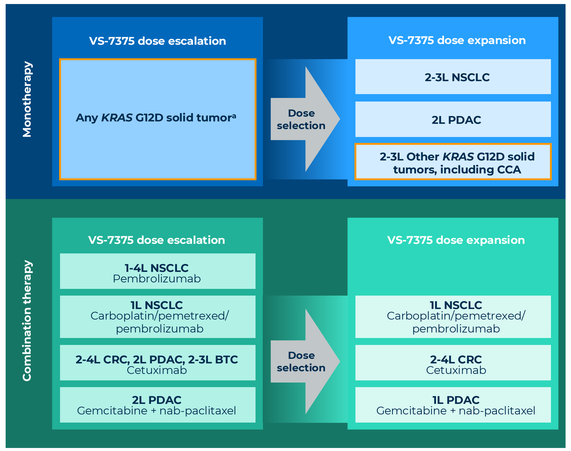
- To describe the study design of TARGET-D 101, an ongoing phase 1/2, open-label, multicenter study (NCT07020221), assessing the safety and efficacy of VS-7375 in participants with advanced *KRAS* G12D-mutated solid tumors, including CCA[8]

METHODS

Study Design

- The TARGET-D 101 study is a dose escalation and expansion study evaluating VS-7375 as monotherapy and in combination therapy for patients with *KRAS* G12D mutant solid tumors (**Figure 2**)

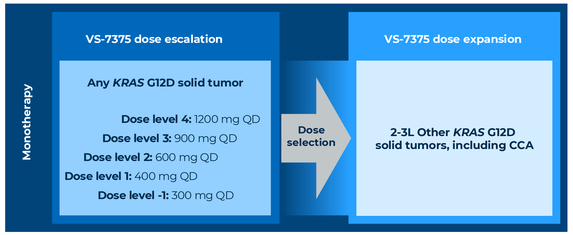
Figure 2. TARGET-D 101 Study Design



Orange rectangles indicate cohorts highlighted in this presentation.
[a]Patients who received 1-3 prior lines of therapy.
BTC, biliary tract cancer; CCA, cholangiocarcinoma; CRC, colorectal cancer; *KRAS*, Kirsten rat sarcoma virus homolog; L, line; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

- This poster focuses on the cohorts which include patients with CCA (**Figure 3**)
- The solid tumor monotherapy dose escalation phase will assess the safety, tolerability, pharmacokinetics, and preliminary anticancer activity of VS-7375 in patients with any previously treated advanced solid tumor harboring a *KRAS* G12D mutation who have received 1-3 prior lines of systemic therapy
- The solid tumor monotherapy dose expansion phase (solid tumors other than pancreatic ductal adenocarcinoma, non-small cell lung cancer, and colorectal cancer) will assess the anticancer activity of VS-7375 at the recommended phase 2 dose(s) in advanced solid tumors harboring a *KRAS* G12D mutation, including biliary tract cancer, in patients who have received 1-2 prior lines of therapy and have no available therapies with proven clinical benefit

Figure 3. Study Design for Dose Escalation and Dose Expansion Cohorts With Solid Tumors, Including Patients With CCA



CCA, cholangiocarcinoma; *KRAS*, Kirsten rat sarcoma virus homolog; L, line; QD, once daily.

Participant Population

- Eligibility criteria for all participants and for those with other solid tumors, including CCA, are shown in **Table 1**

Table 1. Key Inclusion and Exclusion Criteria for Participants With Solid Tumors, Including CCA

Key inclusion criteria	Key exclusion criteria
All participants • Aged ≥18 years • Histologic or cytologic evidence of solid tumor harboring a *KRAS* G12D mutation[a] • Measurable disease according to RECIST v1.1 • ECOG performance status of 0 or 1 • Adequate organ function **Dose expansion cohort for patients with solid tumors, including CCA** • Locally advanced unresectable or metastatic solid tumor not being evaluated in other cohorts • 1-2 prior lines of standard systemic therapy	**All participants** • Major, nondiagnostic surgical procedure ≤4 weeks prior to study day 1 or anticipation of a major surgical procedure during the study • Received chemotherapy, targeted therapy, or radiotherapy (excluding palliative radiation) ≤4 weeks or ≤5 half-lives of the drug or immunotherapy ≤4 weeks prior to study day 1 • Treatment with an investigational drug ≤4 weeks or ≤5 half-lives of the drug prior to study day 1 • History of treatment with a direct RAS inhibitor • Received a strong CYP3A4 inhibitor or inducer ≤14 days or ≤3 half-lives of the drug prior to study day 1 • Use of proton pump inhibitors ≤7 days and H_2 receptor antagonists ≤1 day prior to study day 1 • Symptomatic, untreated, or actively progressing known central nervous system metastases

[a]If feasible, mutation status should be determined using a validated next-generation sequencing or polymerase chain reaction testing method using fresh biopsy.
CCA, cholangiocarcinoma; CYP3A4, cytochrome P450 3A4; ECOG, Eastern Cooperative Oncology Group; H_2, histamine 2; *KRAS*, Kirsten rat sarcoma virus homolog; RAS, rat sarcoma virus; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Endpoints and Clinical Assessments

- Primary and secondary endpoints and corresponding outcome measures for all participants and for those with other solid tumors, including CCA, are shown in **Table 2**

Table 2. Primary and Secondary Endpoints and Outcome Measures

Endpoint	Outcome measures
VS-7375 dose escalation	
Primary endpoints	AEs, dose-limiting toxicities, abnormal vital signs, physical examination, electrocardiogram parameters, ECOG performance status, clinical laboratory results, and dose interruptions/reductions
Secondary endpoints	Pharmacokinetic parameters
	Confirmed ORR, DCR, and DOR per RECIST v1.1 by investigator assessments. Tumor response endpoints may also be evaluated using BICR assessments
VS-7375 dose expansion	
Primary endpoint	Confirmed ORR by BICR per RECIST v1.1
Secondary endpoints	Confirmed ORR by investigator assessment; DOR, BOR, DCR, and PFS per RECIST v1.1; and overall survival
	AEs, abnormal vital signs, physical examination, electrocardiogram parameters, ECOG performance status, clinical laboratory results, and dose interruptions/reductions
	Pharmacokinetic parameters

AE, adverse event; BICR, blinded independent central review; BOR, best objective response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Clinical Trial Status

- This trial is currently enrolling patients
- For more information go to https://clinicaltrials.gov/study/NCT07020221

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Patient-Friendly Lay Summary

What is this study about?

- This study is testing a new treatment for people with certain cancers that have a specific genetic change called a *KRAS* G12D mutation
- The goal is to learn the safest dose, understand side effects, and see how well the treatment works—either on its own or combined with other cancer treatments

What medicine is being tested?

- The main drug being studied is VS-7375, an investigational (not yet approved by the US Food and Drug Administration) medicine taken by mouth
- It is designed to block *KRAS* G12D and may help slow or stop cancer growth
- Some participants may also receive other approved cancer treatments (like chemotherapy, targeted therapy, or immunotherapy) together with VS-7375, depending on the study group

Who is eligible to participate?

- You may be able to join if you
  - Have an advanced solid tumor (such as cholangiocarcinoma)
  - Your tumor has a *KRAS* G12D mutation (confirmed by testing)
  - Have received certain prior treatments (requirements depend on the study group)
- Your study doctor will determine if you qualify and which part of the study is right for you

What happens during the trial?

- You will take VS-7375 tablets by mouth every day
- You will have regular clinic visits for check-ups, blood tests, and scans to see how your cancer is responding
- You can continue receiving treatment as long as you are benefiting and tolerating it as determined by the study doctor

TARGET-D 101

Poster presented at Cholangiocarcinoma Foundation Annual Conference. May 1-3, 2026, Salt Lake City, Utah.