

# D3S-001 in advanced solid tumors with *KRAS*<sup>G12C</sup> mutations: a phase 1 trial

Byoung Chul Cho; Shun Lu; Myung Ah Lee; Zhengbo Song; John Park; Sun Min Lim; Ziming Li; Jun Zhao; Gary Richardson; Yanqiao Zhang; Jun Zhang; Anwen Liu; Cheng Chen; Jia Wang; Jingtao Lu; Haopeng Rui; Qian Chen; Hui Wang; Jing Zhang; Zhi Jian Chen; Tony Mok

## Background

D3S-001 is a second-generation (2G) GDP-bound *KRAS* G12C inhibitor (G12Ci). Its high covalent potency and rapid target engagement kinetics correlated with robust anti-tumor activity preclinically and translated into promising clinical activity in a phase 1 first-in-human trial (FIH). Here we report clinical data from D3S-001 FIH trial (NCT05410145).

## Aim

The primary endpoints were safety and determination of the maximum tolerated dose. Secondary endpoints included pharmacokinetics, confirmed objective response rate (ORR) and disease control rate.

## Method

D3S-001 was evaluated in a phase 1a dose-escalation study in patients with advanced solid tumors harboring *KRAS*<sup>G12C</sup> mutation (*N* = 42) and a phase 1b expansion cohort of patients with non-small-cell lung cancer (NSCLC) whose disease progressed after prior G12Ci therapy (*N* = 20). D3S-001 was administered as monotherapy at 6 planned dose levels (50-900mg QD) from 3 countries.

## Results

D3S-001 demonstrated dose-dependent pharmacokinetics and no dose-limiting toxicities, and the maximum tolerated dose was not reached. Grade 3 treatment-related adverse events were reported in seven patients (16.7%) in the G12Ci-naive dose-escalation cohort and two patients (10.0%) in the G12Ci-pretreated NSCLC expansion cohort. There were no grade 4 or 5 treatment-related adverse events. D3S-001 600 mg was selected as the dose for further investigation based on pharmacokinetics. Confirmed ORR in the G12Ci-naive population was 73.5% overall (25 of 34), and 66.7% (14 of 21), 88.9% (8 of 9) and 75.0% (3 of 4) in patients with NSCLC, colorectal cancer and pancreatic ductal adenocarcinoma, respectively. Among patients with G12Ci-pretreated NSCLC, ORR was 30.0% (6 of 20) and disease control rate was 80.0% (16 of 20).

## Conclusion

This study demonstrates the safety and tolerability of D3S-001 monotherapy with promising antitumor activity. The phase 1b expansion phase is ongoing.