Safety and efficacy of D-1553 in KRAS G12C-mutated colorectal cancer: results from a phase I/II study

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Background

KRAS G12C mutation is an oncogenic driver that occurs in 3-4% of colorectal cancer (CRC). D-1553 is a novel oral and potent KRASG12C inhibitor. This phase I/II open-label study (NCT04585035) is an international multicohort study evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of D-1553 in patients (pts) with KRAS G12C mutated locally advanced or metastatic solid tumors. The phase I part was conducted to determine the recommended phase 2 dose (RP2D) of D-1553. The phase II part enrolled multiple expansion cohorts of different cancer types. Here we report preliminary data from pts with locally advanced unresectable or metastatic CRC receiving ≥ RP2D of D-1553 monotherapy.

Aim

- To assess the safety and tolerability of D-1553 single agent and in combination with immunotherapy/chemotherapy or targeted therapy in subjects with advanced or metastatic solid tumors with KRasG12C mutation
- To determine the DLT, MTD and RP2D of D-1553 single agent and in combination with immunotherapy/chemotherapy or targeted therapy in subjects with advanced or metastatic solid tumors with KRasG12C mutation

Methods

Pts with locally advanced unresectable or metastatic CRC with progression after standard treatment were enrolled in the Phase I and Phase II parts of the study. Pts were required to have KRAS G12C mutations in tumor or ctDNA samples and no prior KRAS G12C directed therapy. The current analysis includes CRC patients who were treated with D-1553 at RP2D (600 mg BID) and above (800 mg BID) as monotherapy. The endpoints of the study include clinical activity, safety and PK.

Results

As of 30 December 2022, 24 pts with previously heavily treated locally advanced or metastatic CRC (54.2% male; median age, 61.5 years [range 44, 74]; ECOG PS 0/1: 45.8%/54.2%) were enrolled and received D-1553 600 mg (n=23) or 800 mg (n=1) BID monotherapy. 95.8% of pts had stage IV disease. 66.7% had ≥ 2 prior lines of therapy (median: 2 [range, 1, 6]). Median treatment duration was 5.75 (range 1.51, 11.83) months (mo) with a median follow-up of 6.64 (range 2.46, 13.11) mo.

Confirmed ORR was 20.8% (5/24) (95% CI: 7.1%-42.2%), and DCR was 95.8% (23/24). Median PFS was 7.62 mo (95% CI, 2.89 to 9.53 mo). At the data cutoff date, 37.5% (9/24) of pts remain on study treatment. Treatment-related adverse events (TRAEs) of any grade occurred in 50% (12/24), most were grade 1 or 2 in severity. Two pts had grade 3/4 TRAEs (alanine aminotransferase increased, diarrhoea, hypertension and hypokalaemia). No TRAEs were fatal or resulted in D-1553 discontinuation. The most common (≥ 5%) TRAEs (any grade) were increased alanine aminotransferase or aspartate aminotransferase, increasedbilirubin, diarrhea, hypothyroidism and nausea.

Conclusion

D-1553 demonstrated a tolerable safety profile and promising monotherapy activity in pts with heavily pretreated locally advanced or metastatic CRC and KRAS G12C mutations. This study is ongoing to further evaluate the safety and efficacy of D-1533 as monotherapy and in combination with cetuximab or chemotherapy in pts with locally advanced or metastatic CRC.

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