KRAS G12C inhibitors in metastatic colorectal cancer: a tale of two targets

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Sotorasib is an irreversible inhibitor of the *RAS* guanosine triphosphatase (GTP)ase, specifically targeting the mutation involving glycine 12 to cysteine in the Kirsten rat sarcoma viral oncogene homolog (*KRAS* G12C). It works by covalently binding to a pocket in the switch 2 region, trapping *KRAS* G12C in an inactive state (1). In 2021, sotorasib has been granted accelerated approval for the treatment of pretreated locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults with *KRAS* G12C mutation by the Food and Drug Administration (FDA). The approval was supported by a Phase 1/2 clinical trial (NCT03600883) in 124 patients, which demonstrated an overall response rate (ORR) of 36% [95% confidence interval (CI): 28% to 45%] with a median response duration of 10 months (2).

In colorectal cancer (CRC), the *KRAS* G12C sequence variant is found in 3–4% and is associated with poor prognosis (3-5). Sotorasib as a single agent in patients with *KRAS* G12C-mutated metastatic CRC (mCRC) showed a moderate ORR of 9.7% (6). In the Phase 1 escalation study (2), sotorasib was administered at doses of 180, 360, 720 and 960 mg. The response rate in mCRC was higher with the daily 960 mg dose compared to all other doses combined. Three patients (12.0%) had a confirmed objective response and 20 patients (80.0%) had disease control in the 25 patients receiving the daily 960 mg dose. No responses were observed at the reduced dose levels.

Recently, additional results on distinct *KRAS* G12C inhibitors have been reported. Yaeger *et al.* observed that adagrasib (7) induced an ORR of 19% in 43 patients. In a Phase 1 dose-escalation basket study, divarasib achieved a confirmed partial response in 29.1% (95% CI: 17.6% to 42.9%) of 55 patients with mCRC (8).

Several studies have shown that both high levels of basally active epidermal growth factor receptor (EGFR) signaling and adaptive feedback leading to overactivation of EGFR-RAS-mitogen-activated protein kinases (MAPK) signaling following *KRAS* G12C inhibition, may be the essential mechanisms of primary resistance to *KRAS* G12C inhibitors (9,10). Thus, combining a *KRAS* G12C inhibitor with a monoclonal antibody against EGFR may be more effective in the clinic. The reactivation of *MAPK* signaling, mediated by EGFR, is an adaptive feedback mechanism that constitutes a primary and acquired resistance mechanism to B-Raf proto-oncogene (*BRAF*) inhibitors monotherapy in *BRAF* V600E mCRC (11). A dual *BRAF*-EGFR blockade with cetuximab and encorafenib improved overall survival (OS), progression-free survival (PFS) and responses in

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previously treated *BRAF* V600E mCRC patients compared with other chemotherapy options (12).

The Phase 1b trial published by Kuboki *et al.* in 2024 (13) is designed to evaluate the safety and efficacy of the combination. Of sotorasib plus panitumumab in refractory mCRC and *KRAS* G12C mutation, utilizing a planned dose de-escalation scheme. The *KRAS* G12C was confirmed by local molecular testing. The study includes two cohorts: a dose exploration cohort and an expansion cohort. Patients were enrolled in the United States and Japan from June 24, 2020, to December 21, 2021. The primary objectives for both cohorts were safety and tolerability. Safety was measured by the occurrence of adverse events and dose limiting toxicities (DLTs) within the first 4 weeks. The initial doses explored (level 1) were sotorasib 960 mg orally, once daily (OD) and panitumumab 6 mg/kg, once every two weeks (Q2W), which are the standard doses of both drugs. Secondary endpoints included efficacy and pharmacokinetics.

In all, 48 patients (eight in the dose-finding cohort and 40 in the extension cohort) were treated. No DLTs were observed in the exploration cohort. Thus, all the patients in both cohorts received dose level 1. Treatment-related adverse events (TRAEs) of any grade and grade ≥3 and of any grade occurred in 13 (27%) and 45 (94%) patients, respectively. The most common grade 3 TRAEs were rash (6%), acneiform dermatitis (4%) and hypomagnesemia (4%). Nevertheless, no TRAEs led to discontinuation of sotorasib, although panitumumab was discontinued in one patient.

In the dose-finding cohort, one *KRAS*-G12C inhibitor-naive had a confirmed partial response (ORR =12.5%; 95% CI: 0.3% to 52.7%). The disease control rate (DCR) was 75.0% (95% CI: 34.9% to 96.8%). Five patients had received prior sotorasib treatment as single drug and 80% achieved stable disease. In the expansion cohort, the ORR was 30% (95% CI: 16.6% to 46.5%), with a DCR of 92.5% (95% CI: 79.6% to 98.4%). The duration of response was 5.3 months (95% CI: 2.8 to 7.4 months). Of note, the response evaluation was based on investigator assessment. With a median follow-up of 16.7 months, the median PFS was 5.7 months (95% CI: 4.2 to 7.7 months), and the median OS was 15.2 months (95% CI: 12.5 to not estimable). Regardless of primary tumor location (left or right), sotorasib plus panitumumab showed similar efficacy. No data have been reported regarding other clinical factors, as sex, time from initial diagnosis of metastases, number of metastatic sites, or presence of liver metastases.

The exploratory endpoints included an assessment of genomic alterations at baseline, based on a comprehensive analysis of circulating-free DNA (cfDNA). The *KRAS* G12C sequence variant was found in 41 out of 43 patients, although with a very low variant allelic frequency (VAF; 0.0009 to 0.5810). Concurrent genomic alterations, which may condition the potential response to anti-EGFR and/or sotorasib, were found in *PIK3CA* (28%), *EGFR* (26%), *BRAF* non-V600 (19%) and *ARID1A* (14%). Although the number of patients is limited, the authors suggest that the presence of alterations in *BRAF* or *ARID1A* could be associated with worse PFS, but do not provide data regarding other alterations found in cfDNA. Finally, pharmacokinetic analysis showed that sotorasib exposure was similar in all patients, enrolled at centers in Japan or the United States.

The efficacy and safety and efficacy results of sotorasib combined with panitumumab have been reinforced and validated in other Phase 1/2 clinical trials evaluating other combinations of *KRAS* G12C inhibitors and anti-EGFR agents. In the Phase 1/2 trial KRYSTAL-1, adagrasib and cetuximab were evaluated in 32 patients (7). TRAEs of grade 3 or higher were reported in 16%. Cetuximab was discontinued due to toxicity in 16%. The ORR was 46% (central review), with a median PFS of 6.9 months. Combining divarasib and cetuximab in a Phase 1 study (14) achieved a response rate (determined by the investigator) of 62.5% in 24 patients who have not received prior treatment with another *KRAS* G12C-targeting agent. The median PFS was 8.1 months. TRAEs resulted in 4 patients (13.8%) having to reduce the dose of divarasib, with no discontinuations. Cetuximab was suspended in one patient (3.4%).

Approximately 88% of patients in the adagrasib-cetuximab study (7) and 77.3% of patients in the divarasib-cetuximab study (14) showed a reduction in *KRAS* G12C VAF with the treatment, based on serial cfDNA analysis, but these assessments were performed at different time points. Future studies could analyze whether early and serial evaluation of *KRAS* G12C VAF in cfDNA would aid in titrating the appropriate dose of the specific inhibitor in combination with anti-EGFR for each patient.

Moreover, data from randomised Phase 3 trial (CodeBreaK 300) confirmed that sotorasib plus panitumumab resulted (15) in longer PFS than standard treatment (regorafenib or trifluridine/tiparacil) in chemorefractory mCRC (median number of previous lines =2). In this trial, sotorasib was evaluated at two doses, (960 mg OD in 53 patients and 240 mg OD in 53 patients) in combination with panitumumab (6 mg/kg Q2W). Patients

were included form 76 sites across 12 countries. Radiologic assessment was performed by blinded independent central review. The median PFS was 5.6 months (95% CI: 4.2 to 6.3 months), 3.9 months (95% CI: 3.7 to 5.8 months) and 2.2 months (95% CI: 1.9 to 3.9 months) in the 960-mg sotorasib-panitumumab, 240-mg sotorasib-panitumumab, and control groups, respectively. The hazard ratio (HR) for PFS (primary end point) in the 960-mg sotorasib plus panitumumab group as compared with the control group was 0.49 (95% CI: 0.30 to 0.80; P=0.006), and the HR for the 240-mg sotorasib plus panitumumab group was 0.58 (95% CI: 0.36 to 0.93; P=0.03). The ORR was 26.4% (95% CI: 15.3% to 40.3%), 5.7% (95% CI: 1.2% to 15.7%), and 0% (95% CI: 0.0% to 6.6%) in the 960-mg sotorasib plus panitumumab, 240-mg sotorasib plus panitumumab, and control groups, respectively. However, no formal comparison of doses of sotorasib 960 *vs.* 240 mg was made. At the time of publication, the data on OS were not mature. The HRs in the sotorasib plus panitumumab group as compared with the control group were 0.77 and 0.91 for the 960 and 240 mg subgroups respectively.

In the various trials with *KRAS* G12C inhibitors, the proportion of women appears to be higher (ranging from 50% to 73%) than in other trials conducted in mCRC in the third or subsequent lines (16-19): CORRECT, 38–40%; RECOURSE, 39–38%; SUNLIGHT, 49.6–54.5%; FRESCO2, 39–47%. These discrepancies could be explained by differences in the incidence of *KRAS* G12C mutations or in the prognosis of this mutation according to gender (20). It remains to be seen whether the efficacy of anti-*KRAS* G12C drugs will differ according to gender. In the subgroup analysis of the CodeBreaK 300 (15), the HR for PFS in the female cohort was 0.35 (95% CI: 0.17 to 0.73) in the 960-mg sotorasib plus panitumumab group as compare with the control group and 0.63 (95% CI: 0.31 to 1.27) in the 240-mg sotorasib plus panitumumab group as compared with the control group.

Phase 1b trial results presented by Kuboki *et al.* (13) suggest that effectively blocking *KRAS* G12C in mCRC is "a tale of two targets". Moreover, Phase 3 results support the combination of sotorasib 960 mg plus panitumumab as a new treatment option in mutated *KRAS* G12C chemo refractory mCRC patients. The doublet of *KRAS* G12C and EGFR blockade is also currently being studied in an earlier line of treatment in randomized trials CodeBreaK 301 (ClinicalTrials.gov; NCT06252649) and KRYSTAL-10 (ClinicalTrials.gov; NCT04793958) in mCRC and even in the pre-operative setting in resectable *KRAS* G12C CRC (ClinicalTrials.gov; NCT05845450).

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