Precision oncology for KRASG12C-mutant colorectal cancer

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Standfirst

Allele-specific inhibitors of KRAS^{G12C} are approved in non-small-cell lung cancer. Herein, we discuss recent results from the phase I/II KRYSTAL-1 trial of adagrasib alone and in combination with cetuximab in patients with *KRAS*^{G12C}-mutant metastatic colorectal cancer. The combination had promising efficacy, and if confirmed in later-phase trials, concomitant inhibition of EGFR and KRAS^{G12C} will present a new paradigm in precision oncology.

Refers to Yaeger, R. et al. Adagrasib with or without cetuximab in colorectal cancer with mutated *KRAS* G12C. *N. Engl. J. Med.* **388**, 44–54 (2022).

Globally, >1.9 million individuals were estimated to have been newly diagnosed with colorectal cancer (CRC) in 2022 (https://gco.iarc.fr/today/home). Approximately 45% CRCs harbour *RAS* mutations (https://www.cbioportal.org/); the current treatment options for *RAS*-mutant metastatic CRC (mCRC) comprise combination chemotherapy with a fluoropyrimidine, oxaliplatin and/or irinotecan, with optional addition of anti-angiogenic agents, in both the first-line and second-line settings[1]. Beyond the second line, neither of the approved treatments, TAS-102 (trifluridine–tipiracil) nor the multikinase inhibitor regorafenib, have produced meaningful objective response rates (ORR). To date, no targeted therapies have been approved for *RAS*-mutant mCRCs, which are inherently resistant to treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab.

After several decades of failed attempts to target *RAS*-mutant tumours, the G12C variant of KRAS is now druggable following the development of covalent inhibitors, such as sotorasib and adagrasib, that target the mutant cysteine residue to lock this oncogenic GTPase in its GDP-bound, inactive state. Both sotorasib and adagrasib have been approved by the FDA as single agents for the treatment of patients with *KRAS*^{G12C}-mutant non-small-cell lung cancer (NSCLC) who have received at least one prior line of treatment, based on ORRs of ~40% with the responses lasting a median of ~9 months.

The clinical development of KRAS^{G12C} inhibitors in mCRC has lagged compared with NSCLC. Approximately 2.5–3.5%mCRCs harbour *KRAS*^{G12C} mutations, with this subset accounting for ~50,000 new cases annually worldwide. Real-world studies have revealed that mCRCs harbouring such mutations are associated with worse prognosis than those harbouring other, non-G12C *KRAS* mutations[2].

Yaeger and colleagues[3] have recently reported that adagrasib monotherapy induced an ORR of 19%, a median response duration of 4.3 months and a median progression-free survival (PFS) duration of 5.6 months among 43 evaluable patients with chemorefractory *KRAS*^{G12C}-mutant mCRC enrolled in one of the phase II cohorts of the KRYSTAL-1 study. The modest clinical activity of single-agent adagrasib in this setting is in line with that of sotorasib, which produced a ORR of 9.7% in 62 heavily pretreated patients with *KRAS*^{G12C}-mutant mCRC included in one of the phase II cohorts of the CodeBreaK100 basket trial[4].

These results are reminiscent of those initially reported for *BRAF*-mutant cancers, with the BRAF inhibitor vemurafenib achieving ORRs >50% in patients with melanoma but only 5% in patients with mCRC[5]. The stark difference between the ORRs in CRC and melanoma, both harbouring the same *BRAF* mutation (V600E), was eventually explained by data from in vitro functional assays. This breakthrough came from mechanistic understanding of the peculiar characteristics of EGFR signalling in cancer cells with distinct histologies and embryological origins. We and others realized that in CRC cells bearing *BRAF*^{V600E} mutations, direct targeted inhibition of the BRAF oncoproteins results in reactivation of the RAS–MAPK signalling pathway through feedback stimulation of EGFR or other receptor tyrosine kinases, acting as a mechanism of primary adaptive resistance[6]. The same also applies to *KRAS*^{G12C}-mutant CRC, whereby profound and sustained MAPK pathway inhibition and antiproliferative effects are seen in preclinical models upon concomitant targeting of KRAS^{G12C} and EGFR, but not inhibition of either target alone[7].

This preclinical rationale led to the inclusion in KRYSTAL-1 of a pilot phase Ib cohort to investigate adagrasib in combination with cetuximab for the treatment of chemorefractory *KRAS*^{G12C}-mutant mCRC[3]. Concomitant KRAS^{G12C} and EGFR inhibition with adagrasib and cetuximab induced an objective response in 13 (46%) of 28 evaluable patients in this cohort, with a median response duration of 7.6 months[3]. Moreover, disease stabilization was seen in all of the remaining 15 patients, yielding a remarkable disease control rate (DCR) of 100%[3]. Early data from 40 patients with chemorefractory *KRAS*^{G12C}-mutant mCRC included in subprotocol H of the CodeBreaK 101 trial also demonstrated the promising antitumour activity of sotorasib in combination with panitumumab, which produced an ORR and a DCR of 30% and 93%, respectively[8].

Grade 3–4 treatment-related adverse events were seen in 15 (34%) of 44 patients with mCRC who received adagrasib monotherapy in KRYSTAL-1[3], with a safety profile similar to that previously observed in patients with NSCLC. The addition of

cetuximab did not substantially alter the safety profile of adagrasib but caused the typical adverse events seen with anti-EGFR monoclonal antibodies, including skin toxicities, hypomagnesaemia and infusion-related reactions[3]. Importantly, several adverse effects, including diarrhoea, nausea, vomiting, fatigue, elevated serum levels of liver enzymes and QT prolongation, were seen at similar frequencies in both the monotherapy and combination therapy arms[3]. Furthermore, no treatment-related deaths were reported[3].

Despite the manageable safety profile and encouraging clinical activity of adagrasib in combination with cetuximab several questions remain unaddressed. For example, no association between ORRs and molecular status of *TP53* or *PIK3CA* was found in an exploratory analysis[3], and no other data on potential predictive biomarkers have been reported. Future correlative analyses should consider both tumour and patient features, including tumour sidedness, methylomic and/or transcriptomic signatures and immunoscore as well as metabolomic profiles and influence of the microbiota.

Responses to targeted therapy are very often transient. The combinations of adagrasib plus cetuximab and sotorasib plus panitumumab results in a median PFS of 6.9 months and 5.7 months, respectively, in patients with chemorefractory *KRAS*^{G12C}-mutant mCRC[3,8]. Thus, as with other targeted therapies, acquired resistance almost inevitably ensues. Acquired mutations in *RAS*, *BRAF* or *MEK*, amplification of the *KRAS*^{G12C} allele or activation of receptor tyrosine kinases have been described as mechanisms of resistance in patients with *KRAS*^{G12C}-mutant upon disease progression on adagrasib or sotorasib monotherapy. Recently, the same molecular alterations have also been reported in circulating cell-free DNA from a small number of patients with mCRC and acquired resistance to these KRAS^{G12C} inhibitors in combination with cetuximab (n = 8) or panitumumab (n = 4), respectively[9].

From a clinical perspective, the phase III KRYSTAL-10 trial (NCT04793958) is comparing the combination of adagrasib and cetuximab versus standard chemotherapy regimens for the second-line treatment of patients with *KRAS*^{G12C}-mutant mCRC. By contrast, the phase III CodeBreaK 300 trial (NCT05198934) is further evaluating the combination of sotorasib and panitumumab versus investigator's choice of TAS-102 or regorafenib in patients with chemorefractory *KRAS*^{G12C}-mutant mCRC. Several ongoing phase I/II studies are also assessing KRAS^{G12C} inhibitors in combination with SHP2 inhibitors to test their ability to effectively suppress the MAPK pathway (NCT04330664; NCT04418661; NCT04449874; NCT04699188; NCT04720976; NCT05288205; NCT05480865). KRAS^{G12C} inhibitors have been shown to trigger immunogenic cell death, thereby inducing an immune-mediated antitumour response and synergizing with immune-checkpoint inhibitors in preclinical models[10], which provides a rationale for ongoing clinical studies exploring this combinatorial approach (NCT03600883; NCT03785249; NCT04699188; NCT04956640). Future proof-of-concept trials with a strong

translational component are likely to identify the best combination and sequence of treatments for the small subset of patients with *KRAS*^{G12C}-mutant mCRC.

In summary, the data from KRYSTAL-1 indicate that adagrasib monotherapy can induce partial responses in ~20% of patients with heavily pretreated *KRAS*^{G12}-mutant mCRC; however, concomitant EGFR blockade with the addition of cetuximab more than doubles the ORR[3]. Although this therapeutic strategy is clearly a relevant step to advance precision oncology for mCRC, the success of targeted therapies, including EGFR, HER2, BRAF and KRAS inhibitors, remains incremental and is not yet transformative for patients with mCRC.

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Competing interests

F.D.N. has received speaker's fees for Pierre Fabre for participating in an advisory board meeting relating to encorafenib. A.B. reports receiving commercial research grants from AstraZeneca, Boehringer Ingelheim and Neophore; is an advisory board member/unpaid consultant for Inivata and Neophore; has ownership interest in Neophore; and is an advisory board member/consultant for Guardant Health, Illumina, Inivata and Roche/Genentech.

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