Editorial Commentary

KRAS G12C inhibitors: also a new promising new targeted therapy in advanced pancreatic adenocarcinoma?

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Since the 2000s, major scientific advances have been made in the field of medical oncology thanks to the advent of genomic medicine. It has led to significant advances in molecular biology analysis capabilities, especially in DNA high-throughput sequencing technologies like next-generation sequencing (NGS). Those medical advances have been accompanied by the emergence of targeted molecular therapies which have revolutionized therapeutic strategies in many tumors. Those specific therapies may exhibit different characteristics and functions, depending on the targets on which they act (i.e., cell surface antigens, receptor/signal transduction pathways, growth factors) (1). As a result, they help to regulate cell cycle progression, cell death, metastatic dissemination and/or neo-angiogenesis. Nowadays, many targeted molecular agents have been approved by the Food and Drug Administration (FDA) [i.e., anti-epidermal growth factor receptor (EGFR), anti-platelet derived growth factor receptor (PDGFR), anti-vascular endothelial growth factor receptor (VEGFR), cyclin-dependent kinase (CDK) inhibitors, poly ADP-ribose polymerase (PARP) inhibitors] (1) and have demonstrated remarkable clinical success in the treatment of a wide range of advanced solid tumors. These agents mainly include small-molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) which differ according to their modes of action at the target level. These therapies can be mono-targeted (i.e., bevacizumab, anti-VEGF agent) or multi-targeted (i.e., regorafenib, anti-VEGFR/PDGFR/KIT agent).

Among the most common oncogenic alterations observed in human solid malignancies, *RAS* family oncogenes are one of the most frequently mutated genes (25% of human cancers) (2), and act as a driver of tumor initiation and maintenance. *KRAS* is the predominantly mutated isoform and accounts for 85% of *RAS* alterations, especially in codons 12 and 13 of *KRAS* (2). *KRAS* is a proto-oncogenic GTPase and *KRAS* activating mutations have been shown to increase tumor cell proliferation and decrease apoptosis. *KRAS* mutations have been described as one of the founder carcinogenic mutation in the genome in more than 80% of pancreatic ductal adenocarcinomas (PDACs) and more than 30% of colorectal cancer (CRC), biliary tract cancers and lung adenocarcinomas (3), prompting the interest in identifying specific anti-*KRAS* targeted (4) therapies for cancer treatment. *KRAS* G12D mutation appears to be the most identified alteration across tumor types (followed by G12V subtype), however it has been demonstrated that *KRAS* mutation pattern is tumor type specific. As an example, *KRAS* G12C mutation is by far the most frequently observed *RAS* alteration in non-small cell lung carcinoma (NSCLC) (30%) and is significantly less frequent in other tumor types (≤10%) (3). In the same way, *KRAS* G12D mutation incidence is the highest in PDAC (40%) and the lowest in NSCLC (3). *KRAS* mutations in codon 13

account for about 7% of PDAC and 10–15% of CRC.

For decades, intense efforts are being made to design *RAS* inhibitors targeted treatments. Ostrem and colleagues were the firsts who identified a novel switch-II pocket in the mutant *KRAS* G12C protein (5), leading to the recent emergence of *KRAS* G12C switch-II covalent inhibitors, which are oral highly selective, small-molecules, not suitable for others *KRAS* mutations in codons 12 and *KRAS* mutations in codon 13 (3). AMG-510 (sotorasib, 960 mg once daily, Amgen©, Southend Oaks, CA, USA) was the first *KRAS* G12C targeted therapy to enter clinical trials with first promising results in phase I/II (CodeBreaK 100, NCT03600883) in heavily pretreated cancer patients (6) (at least two previous lines of systemic therapy for metastatic disease), especially in NSCLC. Among this tumor subgroup (n=59), 32.2% of patients (n=19) had a confirmed objective response (complete or partial response) and 88.1% (n=52) had a disease control (objective response or stable disease) (6). In patients with CRC (n=42), 7.1% (n=3) had an objective response, and 73.8% (n=31) had a disease control. Among the 28 other included cases, 12 had PDAC, one of which had a confirmed partial response. There were no dose-limiting toxicity and no adverse event leading to early treatment discontinuation (6). Those promising results observed in heavily pre-treated patients with advanced solid tumors harboring a *KRAS* G12C mutation led to a phase II, for which the data were recently published. Regarding NSCLC, similar results were observed with an objective response in 46 patients (37.1%), including 4 (3.2%) complete response. Median progression-free survival (PFS) was 6.8 months [95% confidence interval (CI): 5.1 to 8.2], and median overall survival (OS) was 12.5 months (95% CI: 10.0 to could not be evaluated) (7). Results of the recent randomized phase III study in advanced NSCLC (CodeBreaK 200, NCT04303780) were published in March 2023 (8). This study met its primary endpoint: sotorasib significantly increased PFS [median (95% CI): 5.6 (4.3–7.8) *vs.* 4.5 months (3.0–5.7); hazard ratio (95% CI): 0.66 (0.51–0.86); P=0.0017] and had a more favorable safety profile compared with docetaxel (serious adverse events grade 3 or more: 33% *vs.* 40%), in previously pre-treated patients with advanced NSCLC harboring *KRAS G12C* mutation. By contrast, the available data on *KRAS* G12C-mutated metastatic CRC (mCRC) are currently less conclusive. In fact, among the 62 patients enrolled in CodeBreaK 100 phase II study, a partial response was observed in only 6 cases (9.7%) (9). *KRAS* G12C inhibitors exhibit only partial activity, lasting less than one year, and do not contribute to an extension of OS. One explanation could be that it has been demonstrated that reactivation may occur in the RAS-MAPK signaling pathway because of adaptive feedback mediated by EGFR (10). Therefore, the combination of an EGFR antibody with a *KRAS* G12C inhibitor could be an effective clinical strategy to mitigate EGFR reactivation in mCRC and might enhance the inhibition of *KRAS*-dependent signaling or overcome adaptive feedback to delay resistance and improve outcomes in these patients. The main studies assessing *KRAS* G12C inhibitors as monotherapy in human solid tumors are presented in *Table 1*.

Due to their scarcity (with the exception of NSCLC), survival data involving *KRAS* G12C targeted therapies in other advanced solid tumors remain limited, particularly for PDAC. PDACs are a major public health issue, with OS rate, all stages combined, being still <10% at 5 years (11). Recent therapeutic advances remain limited and FOLFIRINOX/NALIRIFOX is the standard of care in metastatic tumors with median OS of about only 11 months (11,12). Up until now, the only targeted therapy used in PDAC is PARP inhibitor in germline *BRCA* mutated unresectable PDAC with a disease control during platinum salt-based first-line therapy (13). It is estimated that *KRAS* G12C mutation occurs in approximately 1% to 2% of PDACs (14). According to European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) classification, only germline *BRAC1/2* mutation, microsatellite instability and *NRTK* fusion tests are currently recommended with a high level of evidence in PDAC (15). Level of evidence for *KRAS* mutations is only IIIA (potential clinically relevant with clinical benefit in other tumor entities). Nowadays, *KRAS* mutation in PDAC could be detected in tumor tissue as well as in blood samples (16).

In that context, the recent study by Strickler *et al.*, published in the *New England Journal of Medicine* (17), aimed to determine the safety profile and the efficacy of sotorasib as monotherapy in previously pre-treated patients with *KRAS* G12C-mutated PDAC, based on the data of CodeBreaK 100 phase I/II study (6). This prospective multicentric trial enrolled a total of 38 patients with *KRAS* G12C-mutated metastatic PDAC, from July 2019 to January 2021. The primary objectives of phase I were to evaluate the safety profile of sotorasib and to identify the recommended dose for phase II. In phase II, the primary endpoint was the objective response rate confirmed by centralized assessment. Phase I was performed in 12 patients, and 26 patients were enrolled in phase II. Included patients should have received at least one previous systemic therapy and be in a good

Table 1 Main studies assessing *KRAS* G12C inhibitors in human solid tumors as monotherapy

KRAS G12C inhibitor agent	Clinical trial	Cancer types	Main results
AMG-510 (sotorasib, 960 mg once daily)	Phase I/II (CodeBreaK 100, NCT03600883) (n=129) (6,8)	Advanced solid tumors	
		NSCLC (n=59)	Partial response: 37.1%, median PFS: 6.8 months
		CRC (n=42)	Partial response: 9.7%, median PFS: 4.0 months
	Pooled phase I/II (CodeBreaK 100, NCT03600883) (6)	PDAC (n=38)	Partial response: 21%, median PFS: 4.0 months
	Phase III (CodeBreaK 200, NCT04303780) (7)	Advanced NSCLC, compared to docetaxel (≥ L2) (n=116)	Median PFS: 5.6 vs. 4.0 months, P<0.05
MRTX849 (adagrasib, 600 mg twice daily)	Phase I/II (KRYSTAL-1, NCT03785249 (9)	Advanced solid tumors	
		NSCLC (n=116)	Partial response: 42.0%, median PFS: 6.5 months
		Locally advanced or mCRC (n=44)	Objective response rate: 22%, median PFS: 5.6 months
	Phase III (KRYSTAL-12, NCT04685135)	Advanced NSCLC, compared to docetaxel (≥ L2)	Ongoing
D-1553 (600 or 800 mg twice daily)	Phase I/II (NCT04585035)	Locally advanced or mCRC (n=24)	Objective response rate: 20.8%, median PFS: 7.62 months
GDC-6036 (divarasib, 400 mg once daily)	Phase I (NCT04449874)	Advanced solid tumors	
		NSCLC (n=60)	Objective response rate: 53.4%, median PFS: 13.1 months
		Locally advanced or mCRC (n=55)	Objective response rate: 29.1%, median PFS: 5.6 months
JNG-74699157	Phase I (NCT04006301) (n=10)	Advanced solid tumors	No significant clinical benefit
LY3499446	Phase I (NCT04165031) (n=5)	Advanced solid tumors	The study was early stopped due to an unexpected high rate of toxicities

NSCLC, non-small cell lung carcinoma; PFS, progression-free survival; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; mCRC, metastatic CRC.

general condition with an Eastern Cooperative Oncology Group performance-status score of ≤2. All patients received oral sotorasib at the dose of 960 mg once daily. In this largely pre-treated population with a poor prognosis, it is interesting to note that 21% of patients (n=8) had partial response with an encouraging duration of response of 5.7 months. Most of patients (n=24, 63%) had stable disease and tumor shrinkage of target lesions of any magnitude was observed in 30 patients (79%). Median PFS was 4.0 months (95% CI: 2.8 to 5.6) and median OS was 6.9 months (95% CI: 5.0 to 9.1). As observed in NSCLC or CRC, the safety profile of sotorasib was acceptable with 16% of grade 3 or more adverse events related to the treatment, consisting mostly in diarrhea and fatigue. No treatment-related adverse event was fatal or led to treatment discontinuation. Although those results are promising, this only concerns a minority of highly selected patients with non resectable PDAC. Those survival data, while limited, also appear to be similar to those previously observed in NAPOLI-1 phase III trial, with systemic chemotherapy treatment [nanoliposomal irinotecan (naliri) with fluorouracil and folinic acid] administrated in second line or more (18) (median OS: 6.1 months), questioning the value of sotorasib in PDAC. Nevertheless, it is worth noting that in NAPOLI-1 trial, only 34% of patients had received two or more previous line of treatment which is less than in CodeBreak 100 study

reported here (55%) (17). Few data concerning efficacy and safety of third-line treatment or more are available in advanced PDAC. In a study by Bachet *et al.* in which only 24 patients received a 3rd line of chemotherapy (L3), 16% experienced a partial response, 25% had stable disease and 33% had a progressive disease (19). Median OS from the beginning of L3 was 7.2 months. It should be mentioned that safety of sotorasib seems better than 2nd or 3rd line of chemotherapy with at least 30% of grade 3 or more adverse events. Moreover, authors highlighted that the objective response observed with sotorasib therapy in *KRAS* G12C-mutated PDACs (21%) was lower than in patients with *KRAS* G12C-mutated NSCLC (37.1%). Consequently, the clinical interest of sotorasib in patients with mutated *KRAS* G12C pre-treated PDAC cannot yet be applied in clinical practice and additional data from larger studies are needed to confirm those preliminary results.

Because those *KRAS* G12C targeted therapies achieve modest response and survival rates, various strategies have been developed in solid tumors in order to improve their anti-tumoral efficacy and/or to overcome resistance mechanisms. Several studies involving *KRAS* G12C inhibitors in combination with targeted or non-targeted therapies (i.e., immunotherapy) are therefore ongoing. In NSCLC, preclinical studies indicated that the *KRAS* G12C inhibitor adagrasib (MRTX849, Mirati©, San Diego, CA, USA), might recondition the tumor immune microenvironment and therefore might sensitize tumors to immune checkpoint inhibitor therapies (20). After showing promising result in phase Ib/II (overall response rate: 49%; disease control rate: 89%) (21), adagrasib in combination with pembrolizumab or alone is currently assessed in the dedicated first-line KRYSTAL-7 phase II/III trial *vs.* chemotherapy plus pembrolizumab (NCT04613596). The safety profile of this combination should be better assessed [(i.e., grade 3 cytolysis (8%) and lipase increasing (11%)] (22). Phase I/II combination strategies evaluating *KRAS* G12C inhibitors with other targeted therapies (i.e., EGFR, MEK/RAF, VEGF inhibitors) are still ongoing in various solid tumors and also demonstrated encouraging preliminary results with an acceptable safety profile, following the example of the association of adagrasib +/– cetuximab in heavily pre-treated patients with *KRAS* G12C-mutated mCRC. In KRYSTAL-1 study (10), a phase I/II nonrandomized trial, authors compared adagrasib monotherapy with adagrasib plus cetuximab. Both therapeutic strategies were well-tolerated and showed clinical activity, with more sustained responses with the combination as compared to adagrasib alone. Objective response rate was 23% (95% CI: 12% to 39%) in monotherapy arm *vs.* 46% (95% CI: 28% to 66%) in combination therapy arm. Median PFS were 5.6 (95% CI: 4.1 to 8.3) *vs.* 6.9 months (95% CI: 5.4 to 8.1), respectively. Adagrasib plus cetuximab is currently being investigated in second-line strategy in mCRC in phase III KRYSTAL-10 trial (NCT04793958) as well as sotorasib plus panitumumab in CodeBreak 300 trial (NCT05198934). Moreover, some clinical trials will start soon with a combination of chemotherapy (FOLFOX/FOLFIRI) plus anti-EGFR plus *KRAS* G12C inhibitors in first- and second-line setting of mCRC. In the same way, trials are underway to assess the contribution of a *KRAS* G12C inhibitor in combination with second-line chemotherapy [5-fluorouracil (5-FU) plus naliri] in advanced PDAC (NCT05251038), or in the event of therapeutic failure after standard therapies (NCT05288205).

In addition, the revolution brought by the emergence of selective inhibitors of *KRAS* G12C is being continued with the development of other highly specific *KRAS* inhibitors (i.e., *KRAS* G12D inhibitors, MRTX1133, Mirati©) (23) as well as pan-*KRAS* inhibitors (i.e., SOS1 inhibitors) which demonstrated interesting pre-clinical results. SOS1 is the guanine nucleotide exchange factor (GEF) and activator of RAS signaling pathway. Pan-KRAS SOS1 inhibitors bind to SOS1 and inhibit the interaction between KRAS and SOS1 proteins and effectively down-regulate active RAS mutated protein in tumor cells. SOS1 inhibitors also antagonize the negative feedback relief induced by RAF/MEK/ERK pathway inhibitor (24). Those new targeted-agents represent a viable approach for targeting all RAS-driven tumors, with currently ongoing phase I trials assessing SOS1 inhibitors safety and efficacy in advanced solid tumors [i.e., KRYSTAL 14 (NCT04975256) and NCT04111458 assessing both BI 1701963 SOS1 inhibitor, the first one of its class].

In conclusion, over the last few decades, major advances in genomic medicine have led to a better understanding of the different pathways of oncogenesis and consequently, to the emergence of personalized medicine in oncology. These major advances demonstrated that *RAS* (*KRAS*, *NRAS*, and *HRAS*) is one of the most frequently mutated gene family in cancers, enabling the recent advent of allele-specific covalent inhibitors against *KRAS* G12C mutant tumors. This improvement in knowledge is being continued with the current development of combination therapies or other specific (*K*)*RAS* inhibitors, in order to define in

the near future better approaches to treat all *RAS*-mutant tumors. The recent study reported here demonstrated an acceptable safety profile and significant efficacy of sotorasib as monotherapy in previously heavily pre-treated patients with *KRAS* G12C-mutated PDAC. Nevertheless, it concerns only a very small proportion of PDACs (1–2%) and survival results remain short (6.9 months), justifying evaluation of combination of *KRAS* G12C inhibitors plus chemotherapy in earlier lines in PDAC. Consequently, in addition to germline *BRCA* mutation, *KRAS* mutation has to be determine in all unresectable PDACs at diagnosis to allow the inclusion of these patients in future clinical trials.

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Footnote

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