Sotorasib as Fourth-Line Treatment in Pancreatic Cancer: A Case Report and Literature Review

IFEANYI DAVID ONUKOGU, MD; GEORGIO MEDAWAR, MD; YASHVIN ONKARAPPA MANGALA, MD; RITESH RATHORE, MD

ABSTRACT

The molecular pathogenesis of exocrine pancreatic cancer involves mutations K-RAS, TP53, CDKN2A, and SMAD4. The KRAS oncogene leads to constitutively active tumor cell proliferation and is present in 90% of unresectable or metastatic pancreatic adenocarcinomas. Of these, the G12C variant of K-RAS genes accounts for 1–2% of mutations.

A 65-year-old woman initially diagnosed with T3N0M0 pancreatic adenocarcinoma, underwent six cycles of neo-adjuvant chemotherapy with mFOLFIRINOX followed by Whipple procedure. Her pathological stage was T4N2. She then received adjuvant mFOLFIRINOX but unfortunately her disease progressed through multiple lines of chemotherapy. Molecular analysis by Next Generation Sequence(NGS) panel revealed KRAS G12C mutation. Based on this mutational status, she was started on Sotorasib to which she had clinical response lasting for about 11 months prior to disease progression.

Off-label use of Sotorasib as fourth-line treatment in our patient with KRAS G12C mutated pancreatic cancer was efficacious and relatively well tolerated.

KEYWORDS: KRAS mutation, targeted therapy, Sotorasib, Pancreatic cancer

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, in both men and women.[1] It is caused by a series of inherited and acquired mutations that lead to interruption of signal transduction, leading to the arrest of G1/S cell cycle.[2] KRAS (Kirsten Rat Sarcoma Virus) is a GTPase-mediated cellular signal transducer protein that plays a key role in the activation of the mitogen-activated protein kinase (MAPK) pathway resulting in intranuclear gene activation that leads to cell proliferation and growth.[2,3] Studies have shown that mutation in KRAS results in hyper-activation of KRAS, thus resulting in constitutively active MAPK signaling. This causes unregulated cell proliferation, which eventually results in cancer development.[3]

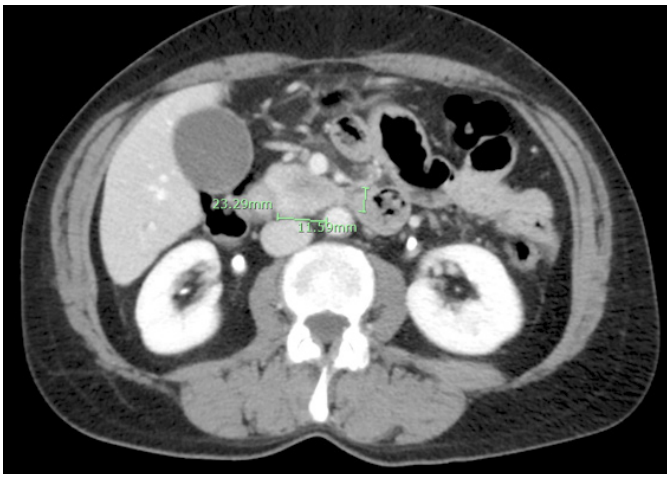
KRAS oncogene was first discovered in the 1980s and is the most frequently mutated oncogene in human solid cancers.[4,5] In a retrospective study of 79,004 patients with various cancers who underwent next-generation sequencing, the KRAS mutation was present in 13,758 patients and was more prevalent in females, patients older than 60 years of age, and those with a history of smoking.[6] KRAS G12C, a subtype of KRAS, was seen in 11.9% of cases while other KRAS variants were seen in 88.1% of cases.[6] The KRAS G12C mutation was most prevalent in patients with non-small-cell lung cancer (9%), appendiceal cancer (3.9%), colorectal cancer (3.2%), tumor of unknown origin (1.6%), small bowel cancers (1.43%), and pancreatic cancers (1.3%).[6] Decades of unsuccessful research attempts for a KRAS-targeted therapy deemed it a non-druggable mutation until recent advances that led to the discovery of mutant-specific KRAS-G12C inhibitors, Adagrasib and Sotorasib.[4] Targeting KRAS-G12C mutated pancreatic adenocarcinoma is a newly explored area.

CASE PRESENTATION

A 65-year-old woman with no past medical history presented in October 2019 to the emergency department with nausea and vomiting and was diagnosed with acute pancreatitis for which conservative management was initiated.

A subsequent abdomen/pelvis CT scan showed 1.2 x 2.3 ill-defined hypodensity in the uncinate process of the pancreatic head **(Figure 1).** This finding was confirmed by an

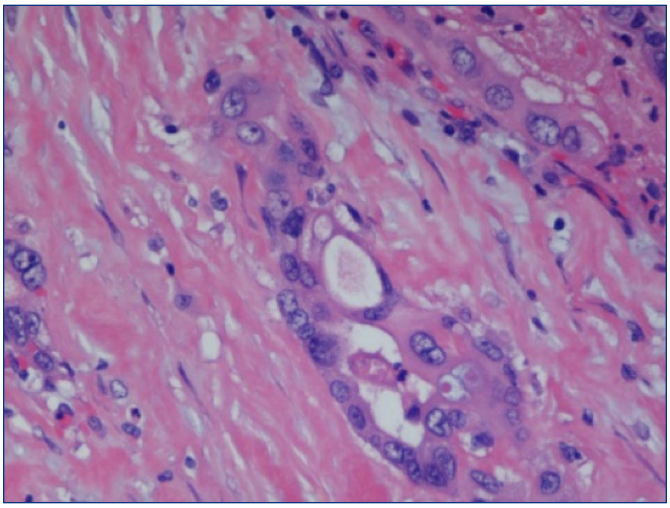
Figure 1. Initial abdomen/pelvis CT scan
(10/10/19) showing an ill-defined hypodensity in the uncinate process of the pancreatic head up to 1.2 x 2.3 cm with pancreatic ductal dilatation.



abdomen MRI and the portal vein, splenic vein, superior mesenteric vein (SMV), superior mesenteric artery (SMA), and common hepatic artery were patent. Chest CT scan showed only a 4 mm right apical lung nodule, which was likely benign. An Endoscopic Retrograde Cholangiopancreatography (ERCP) with biliary sphincterotomy and stent placement was performed. Endoscopic US-guided biopsy of the pancreatic head mass showed crowded clusters of malignant glandular cells with enlarged nuclei, prominent nucleoli, and irregular nuclear membrane, consistent with pancreatic adenocarcinoma. The initial CA 19-9 level was 611.9 U/mL.

In December 2019, the patient began six cycles of neoadjuvant chemotherapy with mFOLFIRINOX for her stage IIA borderline resectable pancreatic head adenocarcinoma. Restaging CT imaging in March 2020 showed stable disease and in April 2020, she underwent a Whipple procedure with R1 resection. The tumor was found to involve the SMV, so the SMV was resected and reconstructed (with a harvest of the left proximal saphenous vein). Pathology review showed the stage as pathological T4N2 (5/19 positive lymph nodes) well-differentiated adenocarcinoma with positive SMA margin **(Figure 2).** The tumor involved peripancreatic tissue, distal bile duct, ampulla, duodenal wall, vascular lumen attached, and superior mesenteric vein. Mutational analysis showed wild-type BRCA 1 and 2 and normal immunohistochemistry expression of MLH1, MSH2, MSH6, and PMS2. The patient was considered to have clinical stage 3 disease with positive margins at resection, so the decision was made to start adjuvant concomitant chemoradiotherapy utilizing oral capecitabine.

Figure 2. (H&E stain, 40x magnification)
The glands have simple architecture and are lined by malignant cuboidal epithelium composed of large cells with pleomorphic nuclei and abundant densely eosinophilic cytoplasm, consistent with chemotherapy cytopathic effect.



She was then transitioned to adjuvant FOLFIRINOX and completed six more cycles. Repeat CT imaging in October 2020 showed no local recurrence and the CA 19-9 was down to 4.5 U/mL. She was placed on regular imaging surveillance up until May 2021, when CA19-9 went up to 126.7 U/mL. Imaging showed new bilateral lung nodules, (largest 2.4 cm), and increased soft tissue fullness in the lateral aspect of the SMA and aorta with obliteration of the superior mesenteric vein (local regionally as well as distant recurrence of her pancreatic cancer). The patient was started on gemcitabine and nab-paclitaxel palliative chemotherapy. However, imaging after eight cycles showed progression of the disease with the Ca 19-9 level increasing to 336 U/mL. The patient was next transitioned to FOLFIRI (with liposomal irinotecan) in January 2022 and after four cycles were administered, there was still disease progression on CT imaging and CA 19-9 increasing to 540 U/mL **(Figure 3).** Next-generation sequencing of the pancreaticoduodenectomy specimen revealed presence of KRAS G12C mutation. Subsequently, in May 2022, the patient was started on oral Sotorasib 960 mg once daily. A repeat CT scan after three months on therapy in July 2022 showed marked improvement in the pulmonary nodules and decreased size of the pancreatic mass along with a decreased in the CA 19-9 level to 19.9 U/mL. Due to grade 3 diarrhea, the Sotorasib was dose reduced to 720 mg daily. Follow-up CT imaging in September and December 2022 showed sustained partial response.

Unfortunately, in March and April 2023, the patient lost response with repeat CT chest/abdomen/pelvis with IV contrast from 03/2023 demonstrating disease progression with multiple pulmonary nodules, new liver lesions and worsening soft tissue mass involving pancreatic head and uncinate process with infiltration through the retroperitoneum encasing SMA and right hepatic artery. The treatment and response summary are summarized in **Table 1.**

Figure 3. (H&E stain, 20x magnification)
Metastatic pancreatic ductal adenocarcinoma to regional lymph node.

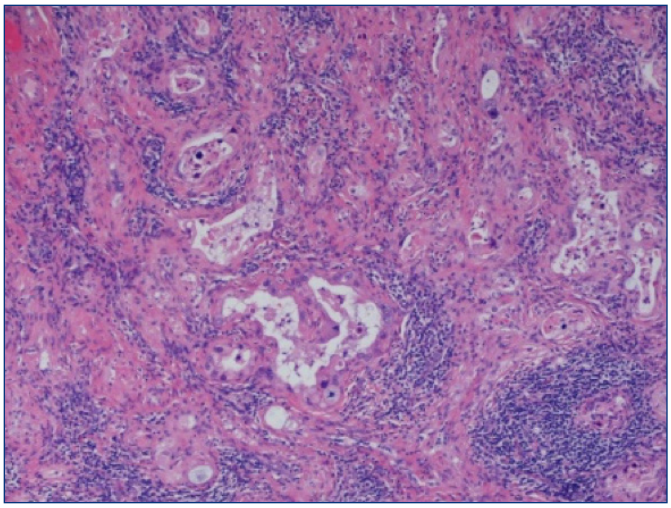


Table 1. Our patient's treatment/response summary

Pre-treatment CA 19-9 (U/mL)	Treatment regimen	Duration of treatment	Lowest CA 19-9, on treatment (U/mL)	Duration of response
11/08/2019: 611.9	Perioperative FOLFIRINOX (6 cycles)	12/2019–10/2020 (surgery after 3 cycles)	01/04/2021: 7.5	15 months
05/05/2021: 126.7	Gemcitabine + Nab-paclitaxel (8 cycles)	05/2021–12/2021	10/05/2021: 15.6	~8 months
01/03/2022: 336.2	FOLFIRI (2 cycles)	01/2022–02/2022	01/25/2022: 540.2	No response.
03/09/2022: 255.7	Sotorasib	5/2022–03/2023	7/14/2022: 19.9	~11 months

Figure 4. Abdomen-Pelvis CT imaging

Pre-treatment with Sotorasib (5/2/2022): Increased size of ill-defined soft tissue mass involving the pancreatic head and uncinate process, measuring approximately 3.4 x 2.4 x 4.8 cm.

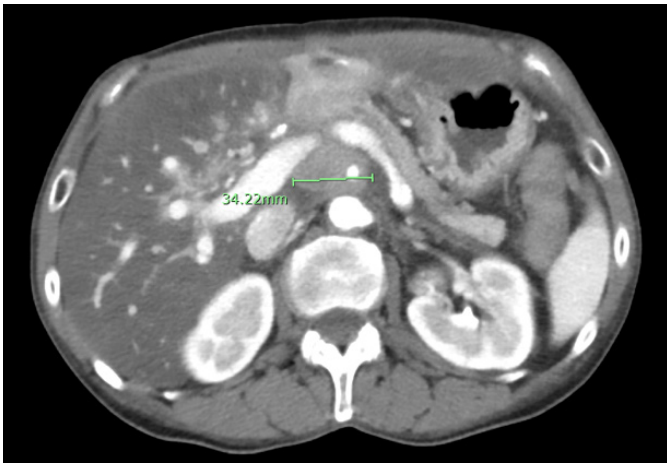
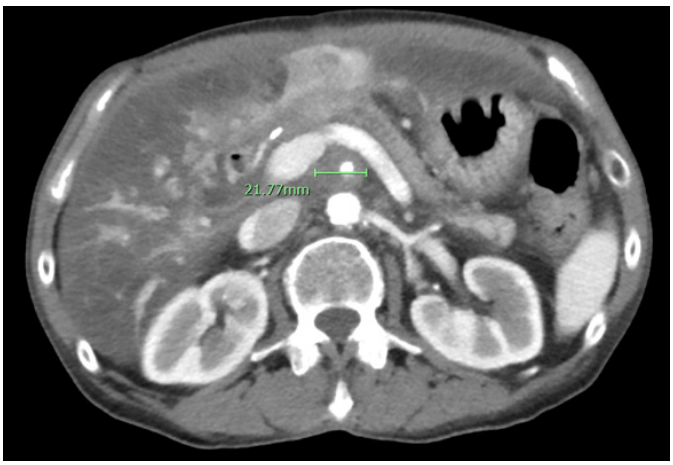


Figure 5. Abdomen-Pelvis CT imaging

Post-treatment with Sotorasib (7/7/2022): Decrease in the size of the ill-defined soft tissue mass in the pancreatic head/uncinate size measuring 2.2 x 2.1 x 4.3 cm.



DISCUSSION

KRAS is the most frequently mutated oncogene that occurs in solid malignancies, most commonly non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic ductal adenocarcinoma (PDAC).[7]

The KRAS G12C mutation occurs in approximately 1 to 2% of pancreatic cancers.[5] Physiologically, this point mutation favors the active form of the KRAS protein (GTP-bound KRAS) that increases the proliferation and growth of tumor cells. The mutated cysteine is located next to a pocket (P2) of the switch II region. This pocket is present only in the inactive form of KRAS (GDP-bound KRAS) and was used to develop specific, irreversible KRAS G12C small molecule inhibitors.[8] These drugs lock the KRAS G12C in the inactive GDP-bound state and demonstrated anti-tumor activity in pre-clinical setting.[8,9]

CodeBreak100 and KRYSTAL-1 trials are two large, multicenter, open-label basket trials that investigated the role of 2 KRAS G12C inhibitors Sotorasib and Adagrasib, respectively, in metastatic solid tumors harboring KRAS G12C mutation. In the CodeBreak100 trial, among advanced NSCLC patients, an ORR of 36% median duration of response was 10.0 months was observed with the use of Sotorasib.[10] In the KRYSTAL-1 trial, Adagrasib therapy in advanced in patients with KRAS G12C mutated NSCLC resulted in a median progression-free survival of 6.5 months and a median overall survival of 12.6 months with a median duration of response of 8.5 months.[11] Based on these results Sotorasib (960 mg once daily) and Adagrasib (600mg twice daily) received accelerated FDA approval for adult patients with KRAS G12C mutated locally advanced or metastatic NSCLC, in patients who have received at least one prior systemic therapy.

Early promising data on pancreatic cancer from these trials were recently reported. In the KRYSTAL-1 trial, Bekaii-Saab et al reported that of the 12 enrolled patients with KRAS G12C mutated pancreatic cancer, disease control rate (DCR) was seen in 100% with 50% of patients having at least a partial response (PR) with a median progression-free survival of 6.6 months.[12] Furthermore, an abstract by Strickler et al presented at the American Society of Clinical Oncology 2022 meeting showed that of 38 patients with KRAS-G12C mutated pancreatic cancer treated with Sotorasib in the CodeBreak100 trial, the disease control rate was 84.2% with an overall partial response rate of 21%, median progression-free survival of 4 months, and the median overall survival of 7 months with a median follow-up of 16.8 months.[7]

Concerning the safety profile, in the CodeBreak 100 trial, the safety analysis done on the pancreatic cancer subgroup showed that the most common any-grade adverse events

were abdominal pain (37%), diarrhea, and nausea (24% each). The most common grade 3 events were diarrhea and fatigue which were each reported in 5.3% and there were no grade ≥ 4 toxicities.[7]

In our case, the patient had a robust partial response to Sotorasib (960 mg daily) used as fourth-line treatment. The dose was reduced one level to 720 mg daily due to grade 3 diarrhea, a common side effect of this drug as mentioned above. The response duration lasted an estimated 11 months before developing disease progression with metastasis to lungs and liver. She was then referred for clinical trial.

CONCLUSION

There is a high unmet need for patients with metastatic pancreatic adenocarcinoma who have progressed through approved first and second lines of treatment. The current subsequent lines of therapies have not shown survival benefit in these patients. However, early data from the CodeBreak100 trial show that patients harboring KRAS G12c mutation derive clinical benefit with Sotorasib use.

In this report, we share the remarkable clinical benefit observed with specific targeted therapy approach using Sotorasib in stage IV pancreatic adenocarcinoma with KRAS G12c mutation, which reinforces the need to evaluate next-generation sequencing on all these patients to detect potentially targetable activating driver mutations. The treatment response in our patient was approaching one year, which is significantly higher than the median of 6–8 months noted in trials.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi:10.3322/caac.21708
2. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science (80-)*. 2008;321(5897):1801-1806. doi:10.1126/science.1164368
3. Pantsar T. The current understanding of KRAS protein structure and dynamics. *Comput Struct Biotechnol J*. 2020;18:189-198. doi:10.1016/j.csbj.2019.12.004
4. Krishnan T, Roberts-Thomson R, Broadbridge V, Price T. Targeting Mutated KRAS Genes to Treat Solid Tumours. *Mol Diagn Ther*. 2022;26(1):39-49. doi:10.1007/s40291-021-00564-0
5. Hong DS, Fakih MG, Strickler JH, et al. KRAS G12C Inhibition with Sotorasib in Advanced Solid Tumors . *N Engl J Med*. 2020;383(13):1207-1217. doi:10.1056/nejmoa1917239
6. Salem ME, El-Refai SM, Sha W, et al. Landscape of KRAS G12C, Associated Genomic Alterations, and Interrelation With Immuno-Oncology Biomarkers in KRAS -Mutated Cancers . *JCO Precis Oncol*. 2022;(6):1-10. doi:10.1200/po.21.00245
7. Strickler JH, Satake H, Hollebecque A, et al. First data for sotorasib in patients with pancreatic cancer with KRAS p.G12C mutation: A phase I/II study evaluating efficacy and safety. *J Clin Oncol*. 2022;40(36_suppl):360490. doi:10.1200/JCO.2022.40.36_suppl.360490
8. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. KRAS (G12C) inhibitors alloserically control GTP affinity and effector interactions Supplementary information. *Nature*. 2013;503(7477):1-27.
9. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575(7781):217-223. doi:10.1038/s41586-019-1694-1
10. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation . *N Engl J Med*. 2021;384(25):2371-2381. doi:10.1056/nejmoa2103695
11. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in Non–Small-Cell Lung Cancer Harboring a KRAS G12C Mutation . *N Engl J Med*. 2022;387(2):120-131. doi:10.1056/nejmoa2204619
12. Bekaii-Saab TS, Spira AI, Yaeger R, et al. KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRASG12C mutation. *J Clin Oncol*. 2022;40(4_suppl):519. doi:10.1200/JCO.2022.40.4_suppl.519

Authors

Ifeanyi David Onukogu, MD, Division of Hematology/Oncology, Roger Williams Medical Center/Boston University, Providence, RI.

Georgio Medawar, MD, Division of Hematology/Oncology, Medical University of South Carolina, Charleston.

Yashvin Onkarappa Mangala, MD, Division of Hematology/Oncology, Roger Williams Medical Center/Boston University, Providence, RI.

Ritesh Rathore, MD, Division of Hematology/Oncology, Roger Williams Medical Center/Boston University, Providence, RI.

Disclosures

All the above authors have no financial disclosures.

Correspondence

Ifeanyi David Onukogu, MD
Clinical Fellow,
Division of Hematology/Oncology
Roger Williams Medical Center
825 Chalkstone Ave.
Providence, RI 02908
401-456-5790
Fax 401-456-5765
ifeanylchukwu.onukogu@chartercare.org