



Rare *ROS1-CENPW* gene in pancreatic acinar cell carcinoma and the effect of crizotinib plus AG chemotherapy: A case report

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Abstract

BACKGROUND

This is the first report of an *ROS1-CENPW* fusion gene in pancreatic malignancies.

CASE SUMMARY

A 77-year-old woman with a pancreatic tumor and multiple liver metastases was admitted to our hospital. Genetic testing revealed the presence of the *ROS1-CENPW* fusion gene, a rare fusion gene that has not been previously reported in the field of pancreatic cancer. The patient received crizotinib plus AG (albumin paclitaxel plus gemcitabine) chemotherapy. After treatment, the patient's condition stabilized, and her prognosis was good.

CONCLUSION

The *ROS1-CENPW* gene treatment regimen used in this case is an excellent treatment option that provides new hope for patients with advanced pancreatic cancer and similar genetic mutations. To date, owing to the rarity of the *ROS1-CENPW* fusion gene, our team has encountered only a single case. Therefore, the efficacy of crizotinib plus AG chemotherapy in patients with pancreatic acinar cell carcinoma harboring the *ROS1-CENPW* fusion gene requires further validation.

Key Words: *ROS1-CENPW*; Pancreatic acinar cell carcinoma; Crizotinib; Gemcitabine; Albumin paclitaxel; Case report

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Core Tip: *ROS1-CENPW* is a novel fusion gene locus in pancreatic acinar cell carcinoma that has not been previously reported. We detected this rare fusion gene in a 77-year-old female patient with pancreatic acinar cell carcinoma. We adopted the treatment regimen of crizotinib combined with AG chemotherapy (gemcitabine 1000 mg/m² plus albumin paclitaxel 125 mg/m²). A good therapeutic effect was achieved.

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INTRODUCTION

Pancreatic cancer is a highly aggressive disease with insidious onset, rapid progression, and poor prognosis[1]. Its molecular features include genomic instability and a high oncogene and tumor suppressor gene mutation rate[2]. Pancreatic cancer has a unique tumor cell microenvironment and immunosuppressive properties[3,4]; therefore, chemotherapy alone is of little benefit due to cytotoxicity and drug resistance[5]. Personalized medical treatments targeting specific genes have attracted considerable attention due to their high efficacy and unique status in pancreatic cancer treatment[6]. Unfortunately, *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, highly expressed in pancreatic cancer, have not shown satisfactory results as clinical therapeutic targets[7,8].

Pancreatic acinar cell carcinoma (PACC) is a rare pancreatic tumor that secretes various exocrine enzymes such as trypsin and lipase. Compared to pancreatic tumors arising from the ductal epithelium, PACC accounts for less than 2% of all pancreatic tumors. Metastatic PACC is generally incurable[9]. Therefore, developing personalized treatment plans for individual patients has become a priority. The discovery and reporting of the *ROS1-CENPW* locus may present a new unique approach for the targeted therapy of pancreatic cancer.

CASE PRESENTATION

Chief complaints

Appetite loss, weight loss, fatigue, and abdominal pain for more than 1 year.

History of present illness

A 77-year-old woman presented to our hospital complaining of appetite loss, weight loss, fatigue, and abdominal pain accompanied by radiating shoulder pain. These symptoms had persisted for more than 1 year.

History of past illness

No previous history of hypertension, diabetes, cardiovascular and cerebrovascular diseases; No history of hepatitis, tuberculosis, malaria and other infectious diseases; No history of blood transfusion, trauma, surgery; No history of food and drug allergy.

Personal and family history

The patient was born and raised in Jiaying, Zhejiang; No history of smoking or drinking; No history of exposure to radioactive substances. No familial genetic history.

Physical examination

Physical examination revealed the following: height and weight, 150 cm and 42 kg, respectively; blood pressure, 139/69 mmHg; and pulse rate, 84 bpm. The abdomen was soft with tenderness in the upper part; no rebound tenderness, jaundice, or other abnormal signs were observed.

Laboratory examinations

Tumor indicators (Table 1) showed that carbohydrate antigen (CA19-9) was 233.70 U/mL, alpha-fetoprotein was 0.97 ng/mL, carcinoembryonic antigen (CEA) was 58.81 ng/mL, and cancer antigen was 125 4.45 U/mL.

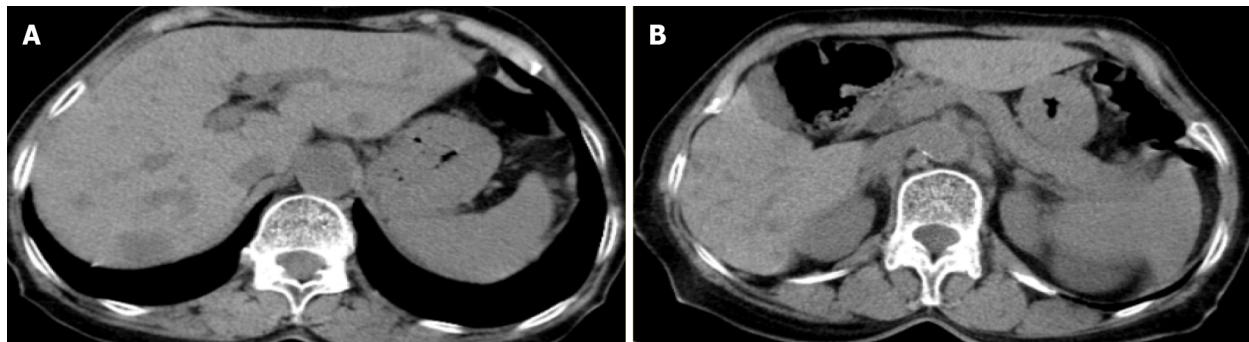
Imaging examinations

Imaging results from Jiaying No. 1 Hospital indicated multiple lesions in the liver and a tumor in the pancreatic tail (Figure 1).

Table 1 Variation of tumor markers

Date	CEA (ng/mL) normal range: 0-5.00	CA199 (U/mL) normal range: 0-37.00	CA125 (U/mL) normal range: 0-35.00	AFP (ng/mL) normal range: 0-20.00
3.30	58.81	233.70	4.45	0.97
5.8	48.69	133.80	9.24	3.18
5.24	38.16	245.10	5.15	1.01

AFP: Alpha-fetoprotein; CA: Carbohydrate antigen; CA125: Cancer antigen 125; CEA: Carcinoembryonic antigen.



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Figure 1 Computed tomography imaging of the liver, pancreas, and other abdominal organs. A: Multiple lesions in the liver; B: Tumor at the pancreatic tail with unclear boundaries.

FURTHER DIAGNOSTIC WORKUP

Several additional examinations were performed to confirm this diagnosis. Positron emission tomography-computed tomography (Figure 2) revealed irregular soft-tissue density at the pancreatic tail approximately 2.49 cm × 3.24 cm with an indistinct boundary. The tumor had an uneven mass density, with a plain computed tomography (CT) value of approximately 26 Hounsfield units and no widening of the pancreatic duct. Elevated metabolism of fluorodeoxyglucose (FDG), with a standardized uptake value (SUVmax) of 2.5, was noted. Diffuse thickening and turbidity were observed in the peritoneum, reticulum, and mesentery, with increased density and multiple nodules, the larger of which was approximately 2.17 cm. The FDG metabolism was unevenly elevated (SUVmax, 2.5). Multiple enlarged lymph nodes were detected in the retroperitoneal and pelvic mesangial area, of which the largest was about 1.87 cm × 1.38 cm; the FDG metabolism increased to a SUVmax of 3.9. Magnetic resonance imaging revealed a low signal at T1, a slightly high signal at T2, and limited diffusion on diffusion-weighted imaging. Overall, there were no obvious abnormalities in liver morphology or size, with smooth liver margins and no widening of the liver fissure. Multiple patchy low-density shadows with unclear boundaries were observed in the liver parenchyma, with a low signal on T1, a slightly high signal on T2, and a high signal on diffusion images as well as increased FDG metabolism (SUVmax, 2.6). The hilar region was well structured. No dilatation of the intra-or extrahepatic bile ducts was observed. Needle biopsy and immunohistochemistry results (Figure 3) suggested that the histological type was acinar cell carcinoma.

TREATMENT

Chemical and immunotherapies were considered the first-choice treatments considering that the tumor had metastasized to multiple organs. To enhance treatment strategy accuracy, the patient was enrolled in a gene sequencing project, the data of which showed that her tumor mutation load was low with microsatellite stability, which enabled a genetic analysis. Based on second-generation sequencing technology, four types of mutations (including point mutation, insertion-deletion of small fragments, copy number variation, and currently known fusion genes) of 1,016 genes related to tumorigenesis and development, were detected (Tables 2-4), including mutations in *KRAS*, *PIK3R2*, *TP53*, *TGFBR2*, and *CDKN2A*. *ROS1-CENPW* (intergenic) gene fusion has not been previously reported in the literature. The *ROS1-CENPW* fusion protein does not retain the intact kinase domain of *ROS1*, and its effect on gene function is unknown.

Table 2 Somatic mutation results

Gene	Transcript	Nucleobase alternation	Amino acid alternation	Functional domain	Mutation frequency
KRAS	NM_033360.2	c.34G>C	p.G12R	EX2	52.7%
PIK3R2	NM_005027.2	c.443C>T	p.P148L	EX4	18.0%
TP53	NM_000546.5	c.797G>T	p.G266V	EX8	15.1%
TGFBR2	NM_001024847.2	c.1528_1532delGAAAG	p.E510Hfs*29	EX7	15.0%
CDKN2A	NM_000077.4	c.35C>A	p.S12*	EX1	13.9%

Table 3 Gene copy coefficient results

Gene	Transcript	Mutation type	Functional domain	Copy coefficient
KRAS	NM_033360.2	Amplification	All exon	1.7

Table 4 Gene fusion results

Gene	Transcript	Mutation type	Functional domain	Mutation frequency
ROS1-CENPW (intergenic)	NM_002944.2; NM_001012507.2	Fusion	EX41:intergenic	21.6%

FINAL DIAGNOSIS

Pancreatic acinar cell carcinoma.

TREATMENT

To target this mutation, we selected crizotinib, a specific tyrosine kinase inhibitor (TKI), as the drug of choice for targeted therapy. Crizotinib was administered orally at a dose of 200 mg twice daily. AG chemotherapy (gemcitabine 1000 mg/m² plus albumin paclitaxel 125 mg/m²) was administered on the first and eighth days, followed by a week's rest.

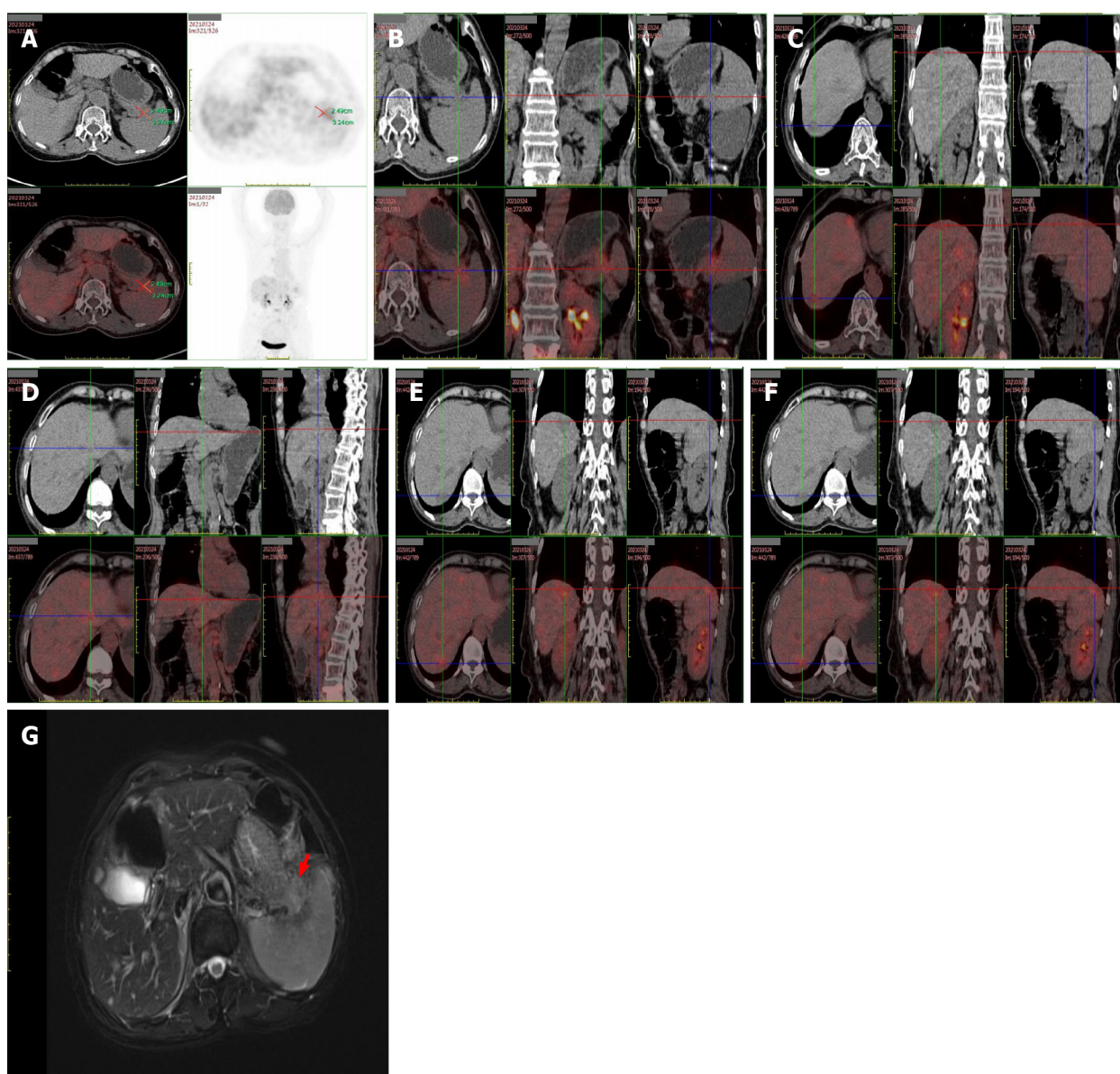
OUTCOME AND FOLLOW-UP

The patient cooperated without adverse reactions or intolerance; therefore, the treatment regimen remained unchanged, and she received regular treatment. Laboratory examination data (Table 1) showed that the CEA levels had declined by degrees. The CA19-9 levels remained stable and were not significantly elevated. Detailed data and other examination parameters are listed in Table 1. An enhanced CT scan (Figure 4) indicated that until the examination on June 21, the liver metastasis had diminished, and the pancreatic mass had shrunk.

DISCUSSION

Herein we report the case of a patient with pancreatic cancer harboring a specific fusion gene, the *ROS1-CENPW* mutation. *ROS1-CENPW* is a fusion gene that has not been previously used for diagnosing and treating pancreatic cancer. *ROS1* is a proto-oncogene with various physiological functions. Twenty-six genes have been found to fuse with *ROS1* and drive a variety of cancers in adult and pediatric patients when *ROS1* produces chimeric oncoproteins[10,11]. Different *N*-terminal fusion partners generate different cell signaling and oncogenic properties. *ROS1* fusion oncoproteins such as *SDC4-ROS1* and *CD74-ROS1* regulate mitogen-activated protein kinase signaling pathways[12]. The *CENPW* locus, a novel biomarker primarily expressed in hepatocellular and breast cancers, is closely associated with occurrence, development, and poor prognosis of cancer[13,14]. However, since the *ROS1-CENPW* fusion protein does not retain the complete kinase domain of *ROS1*, its effect on gene function remains unknown.

PACC is a rare malignant acinar-differentiated tumor with poor clinical prognosis and molecular heterogeneity[9,15]. Hypersecretion syndrome can result from the excessive release of lipases, and surgical resection remains the treatment of choice for PACC[16]. In this case, the patient missed the best time for surgical treatment due to her age and distant tumor metastasis. Fortunately, PACC often features multiple somatic gene mutations; therefore, mapping targeted treatment sites using genetic testing facilitates personalizing the treatment of locus genes[17]. Crizotinib, a specific TKI, is a



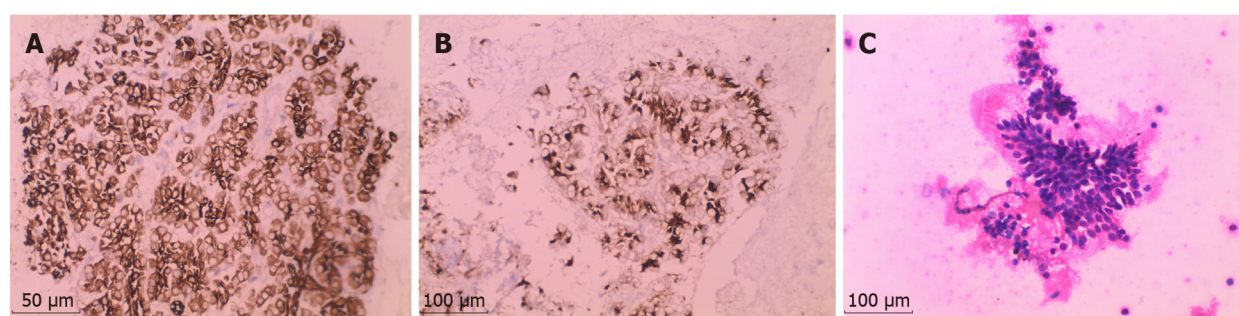
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Figure 2 Positron emission tomography-computed tomography images. A and B: Tumor at the pancreatic tail. Around the pancreatic tumor was fibrous and fat tissue with increased density and an unclear boundary shared with the gastric fundus. The tumor was invading the local hilum of the spleen; C-F: Multiple liver lesions with increased fluorodeoxyglucose metabolism; G: High-density T2-weighted magnetic resonance image.

competitive small-molecule inhibitor of ATP molecular implantation at the *ROS1* site[18]. Oral TKI resistance often develops[19]. However, it inhibits *ROS1*, *MET*, *ALK*, and other sites, is considered the gold standard for first-line treatment, and has been approved by the United States Food and Drug Administration (FDA) in the United States[20]. In addition to crizotinib, lorlatinib and entrectinib have been approved by the FDA for targeted therapy of *ROS1*, with an overall response rate of > 60% for all four targeted drugs[21].

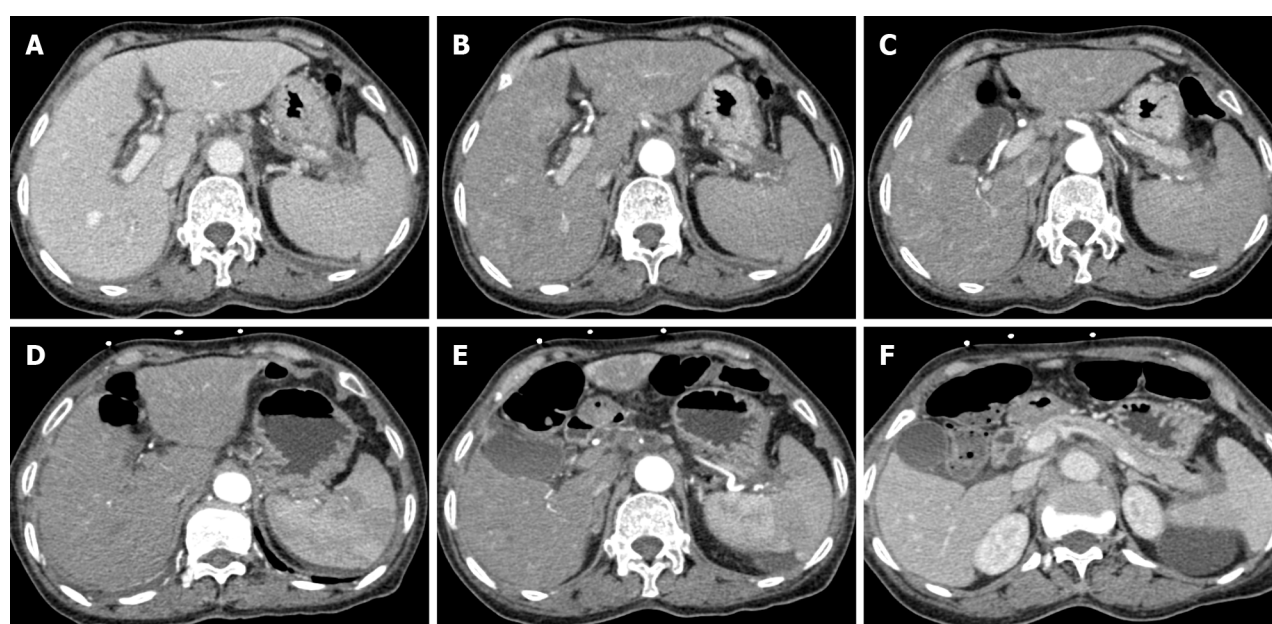
CONCLUSION

In summary, *ROS1*-*CENPW* is a novel fusion gene locus in PACC that has not been previously reported. We searched the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Reference Citation Analysis (<https://www.referencecitationanalysis.com/>), and MedlinePlus (<https://medlineplus.gov/>) databases using *ROS1*-*CENPW* as a keyword. However, no relevant reports have been published regarding this rare fusion gene. This is a unique finding. Gene sequencing was performed in patients with PACC. Both *ROS1* and *CENPW* have been reported only in breast cancer and hepatocellular carcinoma. However, neither has been reported for pancreatic-related cancers. However, effective targeting sites for the treatment of PACC are lacking. Thus, discovering the *ROS1*-*CENPW* complex may open new avenues for targeted therapy. In this case, the treatment regimen resulted in a favorable outcome. CEA levels decreased significantly, liver metastases decreased significantly, CA19-9 levels stabilized, and CT showed shrinkage of the pancreatic mass. In this case, the



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Figure 3 Biopsy images of acinar cell carcinoma. Microscopically, several clusters of nests, alveolar and papillary arrangement, fine nuclear chromatin, fine nucleoli, scattered cells, deviated nuclei, and extracellular particles are visible in the background suggestive of neoplastic lesions. A: Staining was positive for cytokeratin (original magnification 200); B: Staining was positive for epithelial membrane antigen 1 (original magnification 100); C: Staining was positive for hematoxylin and eosin (original magnification 100).



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Figure 4 Computed tomography images of the abdomen before vs after treatment. A-C: Pretreatment enhanced computed tomography images showing lesions in the liver and pancreas in the arterial and portal phases; D-F: Post-treatment images of the liver metastases and pancreatic tumor.

treatment plan of crizotinib plus AG chemotherapy achieved satisfactory therapeutic effects. Therefore, it may be a good treatment option for patients with PACC harboring the *ROS1-CENPW* fusion mutation. Owing to the possible specificity in individual cases, it is worth exploring whether the treatment plan of crizotinib plus AG chemotherapy is universally applicable for treating patients with PACC who are carrying the *ROS1-CENPW* fusion gene.

FOOTNOTES

Author contributions: Wang T analyzed the data and wrote the manuscript; Shen YY conducted data collection, analysis, and chart production; All authors have read and approved the final manuscript.

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REFERENCES

- Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet* 2020; **395**: 2008-2020 [PMID: 32593337 DOI: 10.1016/S0140-6736(20)30974-0]
- Yang H, Zhang W, Ding J, Hu J, Sun Y, Peng W, Chu Y, Xie L, Mei Z, Shao Z, Xiao Y. A novel genomic instability-derived lncRNA signature to predict prognosis and immune characteristics of pancreatic ductal adenocarcinoma. *Front Immunol* 2022; **13**: 970588 [PMID: 36148233 DOI: 10.3389/fimmu.2022.970588]
- Ho WJ, Jaffee EM, Zheng L. The tumour microenvironment in pancreatic cancer - clinical challenges and opportunities. *Nat Rev Clin Oncol* 2020; **17**: 527-540 [PMID: 32398706 DOI: 10.1038/s41571-020-0363-5]
- Nevala-Plagemann C, Hidalgo M, Garrido-Laguna I. From state-of-the-art treatments to novel therapies for advanced-stage pancreatic cancer. *Nat Rev Clin Oncol* 2020; **17**: 108-123 [PMID: 31705130 DOI: 10.1038/s41571-019-0281-6]
- Sarvepalli D, Rashid MU, Rahman AU, Ullah W, Hussain I, Hasan B, Jehanzeb S, Khan AK, Jain AG, Khetpal N, Ahmad S. Gemcitabine: A Review of Chemoresistance in Pancreatic Cancer. *Crit Rev Oncog* 2019; **24**: 199-212 [PMID: 31679214 DOI: 10.1615/CritRevOncog.2019031641]
- Casolino R, Braconi C, Malleo G, Paiella S, Bassi C, Milella M, Dreyer SB, Froeling FEM, Chang DK, Biankin AV, Golan T. Reshaping preoperative treatment of pancreatic cancer in the era of precision medicine. *Ann Oncol* 2021; **32**: 183-196 [PMID: 33248227 DOI: 10.1016/j.annonc.2020.11.013]
- Petersen GM. Familial pancreatic cancer. *Semin Oncol* 2016; **43**: 548-553 [PMID: 27899186 DOI: 10.1053/j.seminoncol.2016.09.002]
- Luo J. KRAS mutation in pancreatic cancer. *Semin Oncol* 2021; **48**: 10-18 [PMID: 33676749 DOI: 10.1053/j.seminoncol.2021.02.003]
- Wood LD, Klimstra DS. Pathology and genetics of pancreatic neoplasms with acinar differentiation. *Semin Diagn Pathol* 2014; **31**: 491-497 [PMID: 25441307 DOI: 10.1053/j.semdp.2014.08.003]
- Uguen A, De Braekeleer M. ROS1 fusions in cancer: a review. *Future Oncol* 2016; **12**: 1911-1928 [PMID: 27256160 DOI: 10.2217/fon-2016-0050]
- Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. ROS1-dependent cancers - biology, diagnostics and therapeutics. *Nat Rev Clin Oncol* 2021; **18**: 35-55 [PMID: 32760015 DOI: 10.1038/s41571-020-0408-9]
- Neel DS, Allegakoen DV, Olivas V, Mayekar MK, Hemmati G, Chatterjee N, Blakely CM, McCoach CE, Rotow JK, Le A, Karachaliou N, Rosell R, Riess JW, Nichols R, Doebele RC, Bivona TG. Differential Subcellular Localization Regulates Oncogenic Signaling by ROS1 Kinase Fusion Proteins. *Cancer Res* 2019; **79**: 546-556 [PMID: 30538120 DOI: 10.1158/0008-5472.CAN-18-1492]
- Zhou Y, Chai H, Guo L, Dai Z, Lai J, Duan J, Liu Y, Ding Q. Knockdown of CENPW Inhibits Hepatocellular Carcinoma Progression by Inactivating E2F Signaling. *Technol Cancer Res Treat* 2021; **20**: 15330338211007253 [PMID: 33973496 DOI: 10.1177/15330338211007253]
- Wang L, Wang H, Yang C, Wu Y, Lei G, Yu Y, Gao Y, Du J, Tong X, Zhou F, Li Y, Wang Y. Investigating CENPW as a Novel Biomarker Correlated With the Development and Poor Prognosis of Breast Carcinoma. *Front Genet* 2022; **13**: 900111 [PMID: 35783290 DOI: 10.3389/fgene.2022.900111]
- Thompson ED, Wood LD. Pancreatic Neoplasms With Acinar Differentiation: A Review of Pathologic and Molecular Features. *Arch Pathol Lab Med* 2020; **144**: 808-815 [PMID: 31869246 DOI: 10.5858/arpa.2019-0472-RA]
- Mustafa S, Hruban RH, Ali SZ. Acinar cell carcinoma of the pancreas: a clinicopathologic and cytomorphologic review. *J Am Soc Cytopathol* 2020; **9**: 586-595 [PMID: 32461075 DOI: 10.1016/j.jasc.2020.04.005]
- Al-Hader A, Al-Rohil RN, Han H, Von Hoff D. Pancreatic acinar cell carcinoma: A review on molecular profiling of patient tumors. *World J Gastroenterol* 2017; **23**: 7945-7951 [PMID: 29259370 DOI: 10.3748/wjg.v23.i45.7945]
- Heigener DF, Reck M. Crizotinib. *Recent Results Cancer Res* 2018; **211**: 57-65 [PMID: 30069759 DOI: 10.1007/978-3-319-91442-8_4]
- Roys A, Chang X, Liu Y, Xu X, Wu Y, Zuo D. Resistance mechanisms and potent-targeted therapies of ROS1-positive lung cancer. *Cancer Chemother Pharmacol* 2019; **84**: 679-688 [PMID: 31256210 DOI: 10.1007/s00280-019-03902-6]
- D'Angelo A, Sobhani N, Chapman R, Bagby S, Bortoletti C, Traversini M, Ferrari K, Voltolini L, Darlow J, Roviello G. Focus on ROS1-Positive Non-Small Cell Lung Cancer (NSCLC): Crizotinib, Resistance Mechanisms and the Newer Generation of Targeted Therapies. *Cancers (Basel)* 2020; **12** [PMID: 33172113 DOI: 10.3390/cancers12113293]
- Azelby CM, Sakamoto MR, Bowles DW. ROS1 Targeted Therapies: Current Status. *Curr Oncol Rep* 2021; **23**: 94 [PMID: 34125313 DOI: 10.1007/s11912-021-01078-y]



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