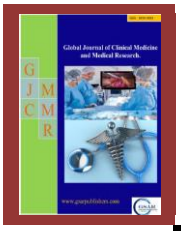

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High Tumor Mutational Burden and ARID1A Mutations in Pancreatic Ductal Adenocarcinoma: A Case Report on the Efficacy of Pembrolizumab and Chemotherapy Combination Therapy

By

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Abstract

Background: *Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with poor prognosis, characterized by late-stage diagnosis and limited treatment options. It is currently the 3rd leading cause of cancer-related deaths in the United States and it is projected to become the 2nd leading cause of cancer-related deaths by 2030. Standard treatment for advanced PDAC includes chemotherapy regimens such as FOLFIRINOX and Gemzar/Abraxane, for advanced PDAC, but its effectiveness is often modest and accompanied by significant toxicity. Recently, immune checkpoint inhibitors, particularly pembrolizumab, have shown promise in treating tumors with high tumor mutational burden (TMB), which is associated with increased neoantigen presentation and immune response. However, the role of TMB as a predictive biomarker for immunotherapy in PDAC remains under investigation.*

Case Report: *A 61-year-old male with a history of type 2 diabetes, hypertension, and hyperlipidemia was diagnosed with locally advanced PDAC. After initial chemotherapy with FOLFIRINOX and later with Gemzar/Abraxane, disease progression was noted. Genetic testing revealed a high TMB of 29 mutations/me mega base, prompting the addition of pembrolizumab to the treatment regimen.*

Subsequent imaging demonstrated a reduction in tumor size while serum CA 19-9 levels decreased from 654 to 29 U/mL. The patient tolerated the combination therapy well with no significant adverse effects.

Discussion: *PDAC's aggressive nature and low survival rates highlight the need for novel treatment strategies. While chemotherapy remains the cornerstone, immunotherapy with pembrolizumab has shown promise, particularly in tumors with high TMB. TMB correlates with better immune responses, including increased immune cell infiltration and upregulated T cell activity. The presence of ARID1A mutations, which contribute to genomic instability, further enhances the immunogenicity of TMB-high tumors, supporting the efficacy of immune checkpoint blockade. The usage of genetic markers in molding treatment strategies alongside conventional chemotherapy can be used to improve treatment outcomes and help guide personalized therapy.*

Introduction

Background

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy and the third leading cause of cancer-related deaths in the United States, with projections indicating it will become the second leading cause by 2030 [1]. The 5-year survival rate for PDAC remains dismal at approximately 11%, with survival for metastatic disease plummeting to around 3%. This poor prognosis is primarily due to late-stage diagnoses, as PDAC is often asymptomatic until it has already metastasized, complicating effective treatment options [2].

Standard treatment for advanced PDAC includes chemotherapy regimens such as FOLFIRINOX and Gemzar/Abraxane. While these therapies offer some benefit, they are associated with significant toxicity and typically provide only limited survival improvement. Genomic studies have shown that KRAS mutations are present in over 90% of PDAC cases, with the most common mutations occurring at codon 12 (KRAS G12D, G12V, and G12R) [3]. Emerging research has demonstrated that combining chemotherapy with MEK inhibitors may enhance survival outcomes in PDAC patients [4].

Considering chemotherapy's limitations, there has been an increasing interest in immunotherapy as an alternative approach. Pembrolizumab, a PD-1 immune checkpoint inhibitor, has shown promise in tumors with high tumor mutational burden, including some cases of PDAC. TMB, which quantifies the number of mutations within a tumor's DNA, serves as a key predictor for the response to immune

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checkpoint inhibitors [5]. Tumors with a high TMB are more likely to express neoantigens, abnormal proteins that can be recognized and targeted by the immune system [6].

Recent evidence suggests that even microsatellite stable (MSS) tumors, traditionally resistant to immunotherapy, may respond to immune checkpoint blockade when certain biomarkers, such as high TMB, are present [7]. The FDA has approved pembrolizumab for use in solid tumors with high TMB (>10 mut/Mb), further validating the importance of TMB as a predictive biomarker immunotherapy [8]. Understanding the genomic landscape of PDAC, particularly the role of KRAS mutations, is critical in developing personalized treatment strategies. Ongoing research into immunotherapy highlights the potential of these biomarkers to refine treatment approaches for PDAC patients.

Case Report

A 61-year-old male with a medical history of type 2 diabetes, hypertension, and hyperlipidemia presented to his primary care physician with persistent epigastric and left upper quadrant abdominal pain lasting 2–3 months. He was initially prescribed a proton pump inhibitor (PPI) and referred to a gastroenterologist for further evaluation.

On May 25, 2023, a CT scan revealed an 87 mm pancreatic mass, prompting additional investigation (Fig. 1). An esophagogastroduodenoscopy (EGD) and biopsy performed in June 2023 confirmed the diagnosis of pancreatic adenocarcinoma. The patient was referred to Surgical Oncology, where the recommendation was to proceed with chemotherapy. A baseline PET scan was obtained in August 2023 (Fig. 2), and the patient was started on first-line chemotherapy with FOLFIRINOX administered every two weeks.

A follow-up CT scan in November 2023 showed a partial response, with the pancreatic mass remaining stable. Based on this, the chemotherapy regimen was changed to gemcitabine (Gemzar) and nab-paclitaxel (Abraxane). In early January 2024, a rising CA 19-9 level prompted the addition of targeted therapy with oral MEK and BRAF inhibitors (Cotellic 20 mg twice daily and Braftovi 75 mg twice daily), initiated on January 15, 2024. However, due to gastrointestinal side effects, this regimen was discontinued on February 7, 2024.

A subsequent CT scan on February 20, 2024, showed disease progression, leading to the resumption of FOLFIRINOX therapy every two weeks. On April 29, 2024, CARIS blood testing revealed a high tumor mutational burden (TMB) of 29 mutations/megabase, prompting the addition of pembrolizumab to the treatment regimen (Fig. 3). Notably, oncogenic mutations in the KRAS gene are present in over 90% of pancreatic tumors, most commonly at codon 12 (KRAS G12D, G12V, and G12R) [9]. However, next-generation sequencing via CARIS confirmed the absence of KRAS mutations, indicating that the patient is KRAS wild-type (WT) (Fig. 4).

By August 15, 2024, the patient's CA 19-9 level had decreased from a peak of 654 U/mL to 80 U/mL. By October 2, 2024, levels had further declined to 29 U/mL (Fig. 5), and imaging showed a reduction in the size of the pancreatic mass, along with decreased periportal and retroperitoneal lymphadenopathy (Fig. 6a, 6b). Guardant 360 Liquid Biopsy was also sent out at this time to detect tumor mutational burden, found to be 3.5% TMB mut/Mb (Fig 7).

As of January 29, 2025, the patient had completed eight cycles of pembrolizumab, administered every three weeks, with good tolerance and no significant adverse effects. His abdominal pain had improved, and he remained under close monitoring for disease progression. However, by April 2025, a rise in CA 19-9 levels was observed (Fig. 8), prompting the reintroduction of chemotherapy alongside ongoing immunotherapy. The patient is currently tolerating this combined regimen well, and his tumor marker levels have since declined.

Discussion

PDAC remains one of the most aggressive malignancies, with low survival rates, primarily due to the advanced stage at diagnosis and widespread metastasis. The median survival for PDAC patients is approximately 8.6 months, and the 5-year survival rate is only 20% [2]. Chemotherapy, including regimens like FOLFIRINOX and Gemzar/Abraxane, remains the cornerstone of treatment, but these regimens often entail significant toxicity and limited survival benefits.

Immunotherapy, particularly pembrolizumab, has emerged as a potential treatment strategy by utilizing the body's immune system to target and destroy cancer cells. Pembrolizumab, a PD-1 immune checkpoint inhibitor, has demonstrated efficacy in tumors with high TMB, such as in this patient [8].

Despite the success of immune checkpoint medications in other tumor types such as renal cell carcinoma, pancreatic tumors are generally regarded as refractory to immunotherapy, and there has been very limited efficacy in checkpoint inhibitors on pancreatic adenocarcinoma [10].

Recent studies have explored the relationship between TMB and immune responses in PDAC. One study categorized PDAC tumors based on TMB levels (high, intermediate, and low) and found that TMB-high tumors exhibited enhanced immune cell infiltration, particularly T helper cells (CD4+ T cells) and dendritic cells, along with increased cytotoxic T cell (CD8+ T cell) activity. These tumors also demonstrated upregulated immune pathways involved in T cell activation, migration, and antigen presentation. In contrast, TMB-low tumors showed minimal immune response, with lower immune cell infiltration and reduced activation of immune pathways [11].

A significant proportion of TMB-high tumors also harbor mutations in the ARID1A gene, a chromatin remodeling protein that regulates gene expression and suppresses tumorigenesis [12]. ARID1A mutations are associated with genomic instability and defective DNA repair, leading to the accumulation of mutations and increased TMB [13]. This genomic instability fosters the generation of neoantigens,

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making the tumors more immunogenic and potentially responsive to immunotherapy [14]. The patient's ARID1A mutation frequency of 3.4% suggests the presence of this mutation, which likely contributes to his tumor's genomic instability and higher TMB, both of which may enhance its response to immune checkpoint inhibitors like pembrolizumab.

Studies have demonstrated that ARID1A-mutated cancers are more likely to respond to immune checkpoint blockade (ICB) therapies. In mouse models of ovarian cancer, ARID1A-deficient tumors responded significantly better to anti-PD-L1 treatment, resulting in improved survival. Clinical data in patients with ARID1A mutations in various cancer types have shown prolonged progression-free survival (PFS) after ICB therapy, further supporting the role of ARID1A mutations in enhancing immunotherapy efficacy [15].

Moreover, additional studies, such as those published in the *Journal for Immunotherapy of Cancer*, highlight the potential of combining TMB and other genetic markers, like copy number alterations (CNA) and MSI/MMR status, to predict response to immune checkpoint inhibitors. In gastrointestinal cancers, including PDAC, higher TMB correlates with better treatment outcomes, suggesting that TMB is a reliable biomarker for immunotherapy response [16].

Conclusion

In summary**,** pancreatic ductal adenocarcinoma (PDAC) remains one of the most challenging malignancies, with poor prognosis and limited treatment options due to its late-stage diagnosis and aggressive nature. While chemotherapy regimens like FOLFIRINOX and Gemzar/Abraxane are commonly used, they often provide modest survival benefits and come with significant side effects. The advent of immunotherapy, particularly the use of immune checkpoint inhibitors like pembrolizumab, offers promising new treatment strategies, especially for tumors with high tumor mutational burden (TMB).

This case illustrates the potential of combining chemotherapy with immunotherapy for the treatment of PDAC, particularly in patients with high TMB and ARID1A mutations. The promising clinical response in this patient supports the use of TMB as a predictive biomarker for immunotherapy in PDAC, emphasizing the importance of personalized treatment strategies. Ongoing studies into the molecular and immune profiles of PDAC, including the genetic landscape and immune response characteristics, will be crucial for refining therapeutic approaches. As we continue to uncover the genetic and immunological factors that drive PDAC progression, precision medicine will play a pivotal role in improving survival rates and quality of life for patients with this devastating disease.

Written informed Consent for Publication Statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Completed consent report can be made available to the Editor of the journal upon request.

Declaration of Competing Interest:

The authors of this manuscript have no conflicts of interest to declare.

Ethical statement:

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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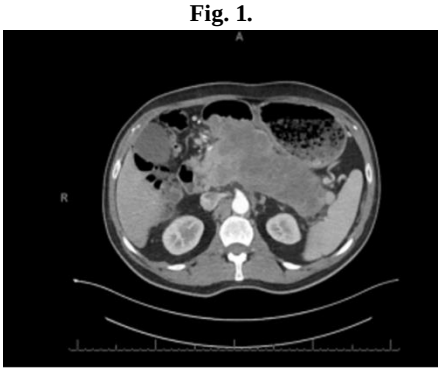
Author contributions:

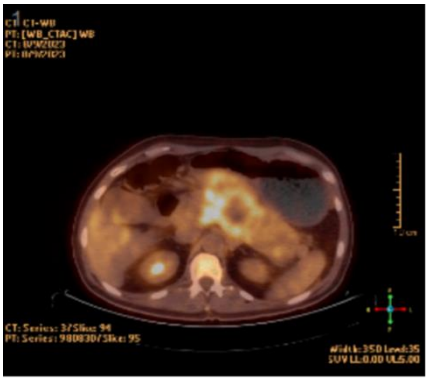
Bach Ardalan was directly involved in patient care. Bach Ardalan, Jose Azqueta, Rosali Gonzalez, Dora Machado were responsible for writing the manuscript and daily management of data collection. Bach Ardalan, Jose Azqueta, and Dora Machado were responsible for reviewing and editing the final draft for submission.

Fig. 1.



Initial CT scan of patient's large pancreatic mass conducted on 05/2023.

Fig 2.



Baseline PET/CT scan conducted on 08/2023.

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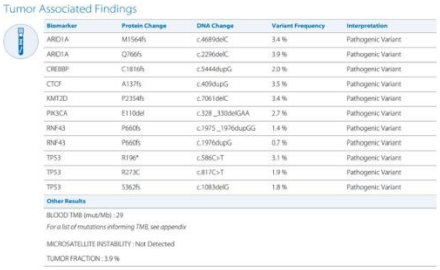
Fig 3.



Tumor Associated Findings

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
ARID1A	M1564fs	c.4689delC	3.4 %	Pathogenic Variant
ARID1A	Q766fs	c.2296delC	3.9 %	Pathogenic Variant
CREBBP	C1816fs	c.5444dupG	2.0 %	Pathogenic Variant
CTCF	A137fs	c.409dupG	3.5 %	Pathogenic Variant
KMT2D	P2354fs	c.7061delC	3.4 %	Pathogenic Variant
PIK3CA	E110del	c.328_330delGAA	2.7 %	Pathogenic Variant
RNF43	P660fs	c.1975_1976dupGG	1.4 %	Pathogenic Variant
RNF43	P660fs	c.1976dupG	0.7 %	Pathogenic Variant
TP53	R196*	c.586C>T	3.1 %	Pathogenic Variant
TP53	R273C	c.817C>T	1.9 %	Pathogenic Variant
TP53	536fs	c.1083delG	1.8 %	Pathogenic Variant

Other Results

BLOOD TMB (mut/Mb) : 29

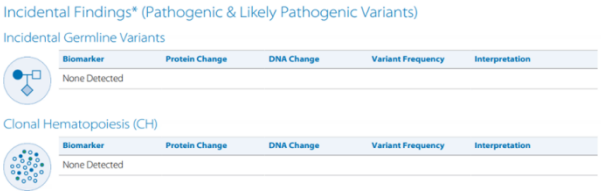
For a list of mutations informing TMB, see appendix

MICROSATELLITE INSTABILITY : Not Detected

TUMOR FRACTION : 3.9 %

Caris blood testing conducted on April 29, 2024, revealed a tumor mutational burden (TMB) of 29 mutations

Fig 4.



Incidental Findings* (Pathogenic & Likely Pathogenic Variants)

Incidental Germline Variants

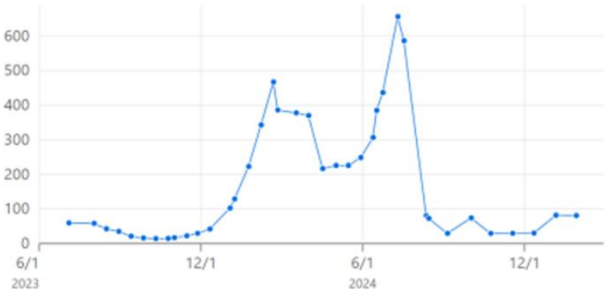
Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
None Detected				

Clonal Hematopoiesis (CH)

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
None Detected				

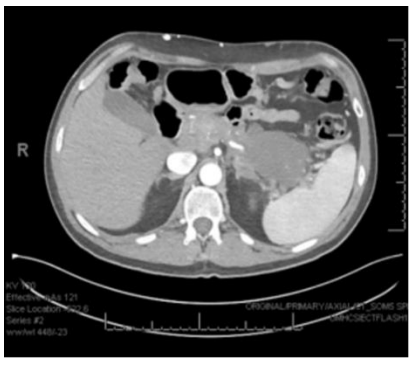
Caris report (solid tumor) confirming that he is KRAS wild-type (KRAS WT).

Fig 5.



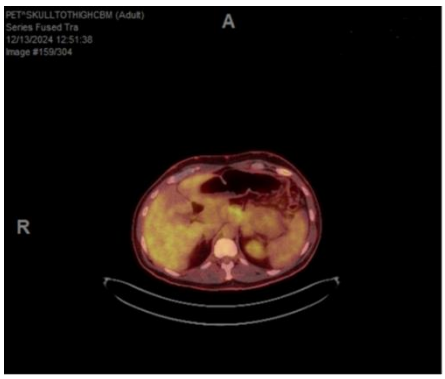
The patient's CA-19-9 levels were tracked throughout the course of treatment, this decline in CA-19-9 levels suggests a positive response to the treatment regimen.

Fig 6a.



Recent CT scan conducted on 12/16/24 demonstrating reduction in pancreatic mass size.

Fig 6b.



Recent PET scan conducted on 12/13/2024.

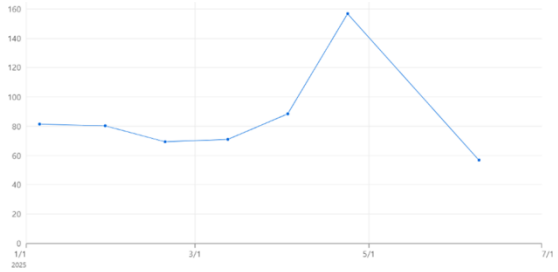
Fig 7.

Additional Biomarkers

Tumor Mutational Burden (TMB)	3.54 mut/Mb
MSI-High	NOT DETECTED
Tumor Fraction#	<0.3%

GUARDANT 360 liquid biopsy was performed on October 2, 2024, revealing a TMB of 3.5.

Fig 8.



The patients CA-19-9 levels show a rise around April 2025.

Figure Legend:

Figure 1: "Initial CT scan of patient's large pancreatic mass conducted on 05/2023."

Figure 2: "Baseline PET/CT scan conducted on 08/2023."

Figure 3: "Caris blood testing conducted on April 29, 2024, revealed a tumor mutational burden (TMB) of 29 mutations"

Figure 4: "Caris report (solid tumor) confirming that he is KRAS wild-type (KRAS WT)."

Figure 5: The patient's CA-19-9 levels were tracked throughout the course of treatment, this decline in CA-19-9 levels suggests a positive response to the treatment regimen.

Figure 6a: CT scan conducted on 12/2024 demonstrating reduction in pancreatic mass size.

Figure 6b: PET/CT scan performed 12/2024 showing decrease in FDG avidity of large pancreatic mass.

Figure 7: GUARDANT 360 liquid biopsy was performed on October 2, 2024, revealing a TMB of 3.5.

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Figure 8: The patients CA-19-9 levels show a rise around April 2025.

References:

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* 2024;74(1):12-49. doi:10.3322/caac.21820
2. Hidalgo M, Cascinu S, Kleeff J, et al. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology.* 2015;15(1):8-18. doi:10.1016/j.pan.2014.10.001
3. Ardalan B, Azqueta JI, England J, Sleeman D, Gonzalez R. Nab-paclitaxel and gemcitabine (modified) in combination with oral cobimetinib and encorafenib following FOLFIRINOX in patients with metastatic G12D and G12V pancreatic cancer. *J Clin Oncol.* 2024;42(16_suppl):e16330. doi:10.1200/JCO.2024.42.16_suppl.e16330
4. Ardalan B, Azqueta JI, England J, Sleeman D, Gonzalez R. Cobimetinib plus gemcitabine: An active combination in KRAS G12R-mutated pancreatic ductal adenocarcinoma patients in previously treated and failed multiple chemotherapies. *J Pancreatic Cancer.* 2021;7(1):65-70. doi:10.1089/pancan.2021.0006
5. Ott PA, Bang YJ, Piha-Paul SA, et al. T-cell–inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. *J Clin Oncol.* 2019;37.
6. Jardim DL, Goodman A, de Melo Gagliato D, Kurzrock R. The challenges of tumor mutational burden as an immunotherapy biomarker. *Cancer Cell.* 2020;38 (5): 624-633. doi:10.1016/j.ccell.2020.09.006
7. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med.* 2019;381(25):2500-2501. doi:10.1056/NEJMc1901901
8. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: Pembrolizumab for the treatment of tumor mutational burden-high solid tumors. *Clin Cancer Res.* 2021;27(17):4685-4689. doi:10.1158/1078-0432.CCR-21-0922
9. Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. *Nat Rev Dis Primers.* 2016;2:16022. doi:10.1038/nrdp.2016.22
10. Zheng Y, Liu H, Zhang L, Wang Y. Frontiers and future of immunotherapy for pancreatic cancer. *Front Immunol.* 2024;15:1383978. doi:10.3389/fimmu.2024.1383978
11. Jardim DL, Goodman A, de Melo Gagliato D, Kurzrock R. The challenges of tumor mutational burden as an immunotherapy biomarker. *Cancer Cell.*2021;39(2):154-173. doi:10.1016/j.ccell.2020.10.001
12. Karamitopoulou E, Andreou A, Wenning AS, Gloor B, Perren A. High tumor mutational burden (TMB) identifies a microsatellite stable pancreatic cancer subset with prolonged survival and strong anti-tumor immunity. *Eur J Cancer.* 2022;169:64-73. doi:10.1016/j.ejca.2022.03.033
13. Sha D, Jin Z, Budczies J, et al. Tumor mutational burden as a predictive biomarker in solid tumors. *Cancer Discov.* 2020;10(12):1808-1825. doi:10.1158/2159-8290.CD-20-052
14. Zheng Y, Liu H, Zhang L, Wang Y. Advances in immunotherapy for pancreatic cancer: Current status and future perspectives. *Front Oncol.* 2023;13:1136248. doi:10.3389/fonc.2023.1136248
15. Okamura R, Boichard A, Kato S, Sicklick JK, Kurzrock R. ARID1A alterations function as a biomarker for longer progression-free survival after anti-PD-1/PD-L1 immunotherapy. *J Clin Oncol.* 2020;38(15_suppl):12001. doi:10.1200/JCO.2020.38.15_suppl.12001
16. Lu Z, Chen H, Li S, et al. Tumor copy-number alterations predict response to immune checkpoint blockade in gastrointestinal cancer. *J Immunother Cancer.* 2020;8(2):e000374. doi:10.1136/jitc-2019-000374

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