

Camrelizumab Combined with Gemcitabine and Albumin-Bound Paclitaxel in Pancreatic Cancer Patients with Liver Metastases: A Prospective, Pilot Trial

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant tumors, with approximately 80% of PDAC patients having locally advanced or metastatic disease at diagnosis. The liver is a predominant site of metastasis and is linked to a particularly poor prognosis. Here, we explored camrelizumab (an anti-programmed cell death-1 antibody) combined with albumin-bound paclitaxel and gemcitabine (AG) in patients with PDAC and liver metastases (PCLM).

Methods: In this pilot trial (ChiCTR2000038587), patients received camrelizumab (200 mg on day 1) plus gemcitabine (1000 mg/m² on days 1 and 8) and albumin-bound paclitaxel (125 mg/m² on days 1 and 8) every 21-day cycle until disease progression, intolerable toxicity, or death. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety. Exploratory analyses evaluated potential biomarkers associated with survival.

Results: From October 2018 to October 2023, 17 patients were enrolled. The median OS was 14.0 months (95% confidence interval [CI], 10.0–24.0) and the median PFS was 6.4 months (95% CI, 5.2–10.2). Five patients achieved an objective response (29.4%), with a DCR of 64.7%. Fewer liver metastasis lesions, higher white blood cell-to-lymphocyte ratio, and lower neutrophil-to-lymphocyte ratio were associated with improved PFS and OS ($P < 0.05$). Grade 3 treatment-related adverse events (TRAEs) included platelet count decreased (2 [11.8%]) and neutrophil count decreased (1 [5.9%]). No grade 4 or 5 TRAEs occurred.

Conclusion: Camrelizumab combined with AG demonstrates promising antitumor activity in patients with PCLM, with an acceptable safety profile.

Keywords: camrelizumab, chemotherapy, pancreatic ductal adenocarcinoma, liver metastases

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and lethal malignancy, which is the fourth leading cause of cancer-related death in 2021 and is projected to be second by 2030.^{1,2} It is associated with a poor 5-year survival rate of 9% in China³ and 13.3% in Western countries.⁴ The lethality of PDAC is centered on several factors, including its asymptomatic presentation at the early stages, compounded by the paucity of diagnostic biomarkers, and the difficult-to-access anatomical location of the pancreas prevents routine office-based screening.⁵ Approximately 80% of patients with PDAC are diagnosed with locally advanced or metastatic disease at the onset.⁶ Metastatic spread commonly occurs to the

liver and is the primary cause of death for patients with PDAC. At diagnosis,⁷ more than half of patients have liver metastasis, and around 70% of the patients whose primary tumor is removed relapse with liver metastasis within 2 years of surgery.⁸ The current first-line treatment options for metastatic PDAC, including PDAC patients with liver metastases (PCLM), included FOLFIRINOX (calcium folinate, fluorouracil, irinotecan, and oxaliplatin) and gemcitabine-based combinations, such as gemcitabine plus albumin-bound paclitaxel (AG).^{9–11} Nevertheless, their efficacy was very limited, with reported median OS of approximately 11.1 months for FOLFIRINOX and 6.8 months for gemcitabine plus albumin-bound paclitaxel.^{9,10} Therefore, there remains an urgent need for more effective regimens in PCLM.

Although immune checkpoint inhibitors (ICIs) have demonstrated significant efficacy in multiple solid tumor types, PDAC has long been considered a malignancy that is recalcitrant to immunotherapy.¹² This resistance might be attributed to the heterogeneity of the PDAC tumour microenvironment (TME), characterized in part by the presence of cancer-associated fibroblast (CAF) that may have an immunosuppressive effect.¹³ Consequently, the effectiveness of ICIs as single-agent therapy in metastatic PDAC remains limited.^{14,15} Preclinical evidence has suggested that certain chemotherapeutic agents, such as nab-paclitaxel, can attenuate the immunosuppressive effects of CAFs and the surrounding desmoplastic stroma.^{16,17} This has fueled interest in combining chemotherapy with immunotherapy for PDAC. Early clinical findings are encouraging. A phase Ib/II study indicated that pembrolizumab plus AG as a first-line treatment for patients with metastatic PDAC was safe and tolerable.¹⁸ Similarly, the larger randomized CCTG PA.7 Phase II trial evaluated the addition of durvalumab (anti-programmed cell death-1 [PD-1]) and tremelimumab (anti-CTLA-4) to AG, showing no significant benefit in the overall population but revealing potential survival advantages in patients with *KRAS* wildtype tumors.¹⁹ Despite these signals of activity, the number of clinical studies exploring ICI–chemotherapy combinations in PDAC remains limited, and evidence in the subset of patients with PCLM is particularly scarce.

Camrelizumab is a humanized anti-PD-1 antibody approved in China for multiple malignancies,^{20–22} and its combination with chemotherapy has shown promising efficacy in several solid tumors, such as biliary tract cancer²³ and non-small cell lung cancer.²⁴ However, its combination with chemotherapy has not yet been investigated in patients with PCLM. Therefore, we conducted this pilot trial to evaluate the efficacy and safety of camrelizumab plus AG in patients with PCLM.

Methods

Study Design and Patients

This prospective, single-arm, single-center pilot study was conducted at Sir Run Run Shaw Hospital in China. Eligible patients were aged ≥ 18 years, had pathologically (obtained by puncture or exploratory biopsy) confirmed PCLM, no previous systematic treatment, at least one measurable disease per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), a Child-Pugh liver function score of A or B, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and a life expectancy of ≥ 3 months. Patients were excluded if they had metastases to organs other than the liver or if they had non-ductal adenocarcinoma histology.

The study was approved by the ethics committee of Sir Run Run Shaw Hospital, and written informed consent was obtained from all participants. This study is registered at ChiCTR.org.cn (ChiCTR2000038587).

Procedures

All patients (within 3 days after diagnosis) received camrelizumab (200 mg on day 1) plus gemcitabine (1000 mg/m² on days 1 and 8) and albumin-bound paclitaxel (125 mg/m² on days 1 and 8) in a 21-day cycle, until disease progression, unacceptable toxicity, or death. Dose modifications of chemotherapy were permitted for adverse events (AEs).

Tumor assessments were performed using computed tomography (CT) every 3 cycles per the investigators, according to the RECIST v1.1. Safety was evaluated based on AEs and laboratory abnormalities. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and European Society for Medical Oncology (ESMO) Clinical Practice Guidelines on the management of toxicities from immunotherapy.¹¹

Additionally, peripheral blood data of white blood cell-to-lymphocyte ratio (WLR), neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and lactate dehydrogenase (LDH), as well

as data of immunohistochemistry (IHC) and next-generation sequencing (NGS), were collected at baseline. Tumor mutation burden (TMB) was estimated by counting the coding somatic mutations per megabase of the sequence examined in each patient, and TMB-high was defined as ≥ 10 mut/Mb. The microsatellite instability (MSI) status was inferred based on the MANTIS score. Programmed cell death-ligand 1 (PD-L1) expression was interpreted as a combined positive score (CPS), which was defined as the number of PD-L1-positive cells divided by the total number of tumor cells, and then multiplied by 100.

Endpoints

The primary endpoint was OS (defined as time from initial diagnosis until death from any cause). Second endpoints were progression-free survival (PFS, defined as the time from diagnosis to disease progression or death due to any cause), investigator-assessed objective response rate (ORR, defined as the proportion of patients with a complete response [CR] or partial response [PR]), disease control rate (DCR, defined as the proportion of patients with CR or PR, or stable disease [SD]), and safety. Exploratory endpoints encompassed the correlations between liver metastases (the number and size), blood-based inflammatory indices (WLR, NLR, PLR, LMR, and LDH levels), or immune-related biomarkers (PD-L1 expression, TMB, MSI status) and survival.

Statistical Analysis

Baseline characteristics and safety were summarized by descriptive statistics. Results for the ORR and DCR were expressed as frequencies and percentages, and the exact two-sided 95% confidence intervals (CIs) were calculated by using the Clopper-Pearson method. PFS and OS were estimated using the Kaplan-Meier method, with their 95% CIs estimated using the Brookmeyer-Crowley method. The Log rank test and Cox proportional hazard model were used to compare between groups. Univariate and multivariate regression analyses were used to estimate the relationship between exploratory endpoints and survival.

All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, United States), SAS version 9.4 (SAS Institute, Cary, NC, United States), and R version 3.3.0 (The R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

From October 2018 to October 2023, 53 patients with PCLM were assessed for eligibility. Of these patients, 36 were excluded, including 23 who declined to receive treatment, 1 who received FOLFIRINOX, 6 who were treated with AG plus erlotinib concurrently received targeted therapy (3 anlotinib, 2 fuzuloparib, and 1 apatinib), and 6 who received AG chemotherapy alone without immunotherapy. Finally, a total of 17 patients who received camrelizumab plus AG were enrolled.

Baseline characteristics are summarized in Table 1. Seven (41.2%) patients were male, with a mean $\pm$ SD age of 66.8 ± 8.42 . The majority of patients had an ECOG performance status score of 1 (64.7%), Child-Pugh class A (82.4%), and stage cN0 (52.9%), with all patients having cM1 (100.0%). Nine patients had ≤ 3 metastatic liver lesions, and more than half (52.9%) had liver metastases lesions of > 19 mm.

Table 1 Baseline Characteristics

Characteristics	Patients (n=17)
Age (years), mean $\pm$ SD	66.8 $\pm$ 8.42
Sex, n (%)	
Male	7 (41.2)
Female	10 (58.8)

(Continued)

Table 1 (Continued).

Characteristics	Patients (n=17)
ECOG performance status, n (%)	
0	1 (5.9)
1	11 (64.7)
2	5 (29.4)
Child-Pugh class, n (%)	
A	14 (82.4)
B	3 (17.6)
T stage, n (%)	
2	7 (41.2)
3	3 (17.6)
4	7 (41.2)
N stage, n (%)	
0	9 (52.9)
1	3 (17.6)
2	5 (29.4)
M stage, n (%)	
1	17 (100.0)
Size of liver metastasis lesions (mm), n (%)	
≤19	8 (47.1)
>19	9 (52.9)
Number of liver metastasis lesions, n (%)	
≤3	9 (52.9)
>3	8 (47.1)

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

Efficacy

As of data cutoff on August 30, 2023, the median duration of follow-up was 16.0 months (range, 5.1–33.0). Fifteen of 17 patients had died, and the median OS was 14.0 months (95% CI, 10.0–24.0). Two patients were still alive, with an estimated OS of at least 33 months and 32.9 months, respectively. The median PFS was 6.4 months (95% CI, 5.2–10.2; [Figure 1](#)).

Regarding the overall response, 5 achieved PR, 6 had SD, and 4 were PD. The ORR and DCR were 29.4% (95% CI, 13.3–53.1) and 64.7% (95% CI, 41.3–82.7), respectively.

Safety

Treatment-related AEs (TRAEs) are summarized in [Table 2](#). TRAEs of any grade occurred in 11 (64.7%) patients. The most common TRAEs of any grade were liver dysfunction, represented by elevation of alanine aminotransferase or aspartate aminotransferase (9 [52.9%]), platelet count decreased (8 [47.1%]), decreased white blood cell (8 [47.1%]), and neutrophil count decreased (5 [29.4%]). Three patients experienced grade 3 TRAEs, including platelet count decreased (2 [11.8%]) and neutrophil count decreased (1 [5.9%]). No grade 4 or 5 TRAEs occurred. One patient discontinued camrelizumab due to grade 2 immune-related hepatitis.

Association Between Exploratory Endpoints and Survival

Patients with ≤3 liver metastasis lesions had significantly longer median OS (18.4 months [95% CI, 16.3–21.7] vs 9.3 month [95% CI, 7.0–15.2], $P=0.004$) and PFS (12.4 months [95% CI, 6.4–14.2] vs 4.0 month [95% CI, 3.1–7.5], $P=0.017$) than those with >3 liver metastasis lesions. No significant differences in OS or PFS were observed when stratified by the size of liver metastases ([Figure 2](#)).

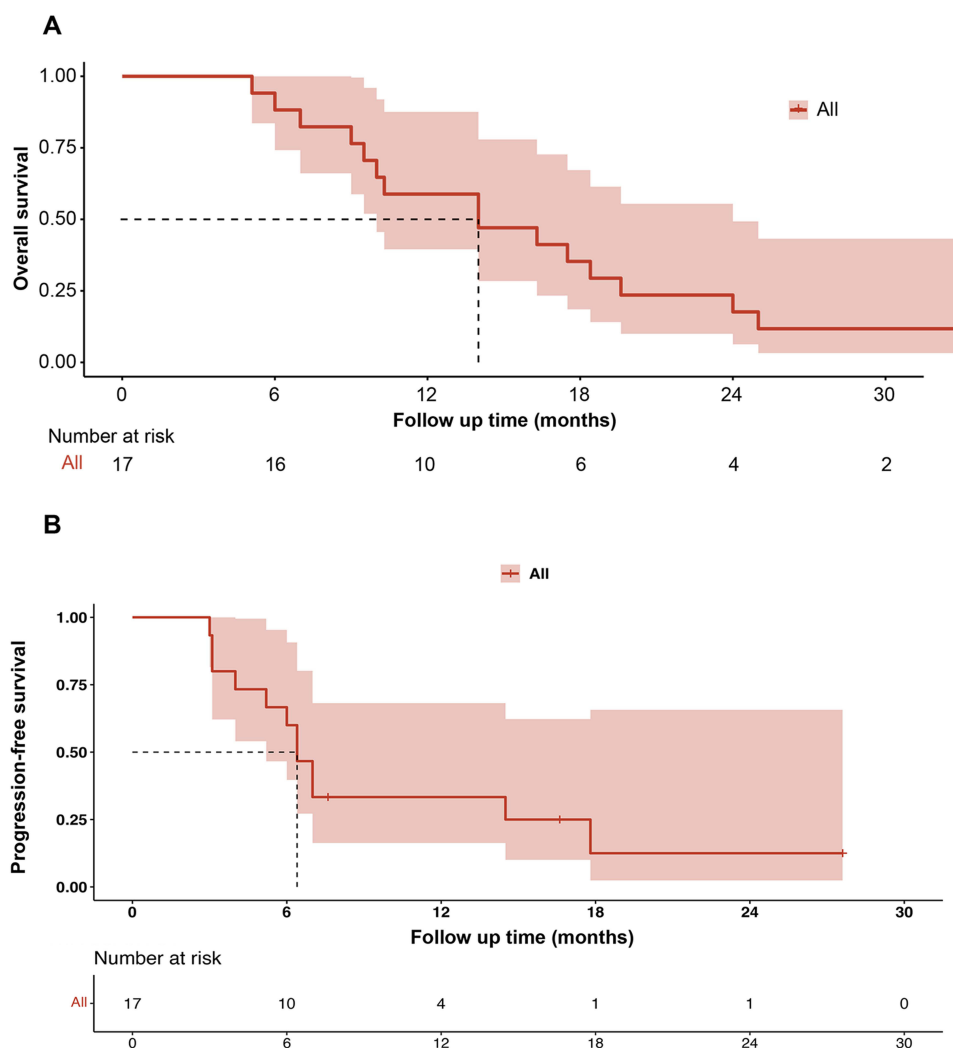


Figure 1 Overall survival (A) and progression-free survival (B).

Patients with higher WLR and lower NLR had significantly longer OS and PFS (all $P < 0.05$). A lower LDH level was only associated with longer OS ($P < 0.05$; Figure 3). No significant association was observed between PLR/LMR and survival (all $P > 0.05$).

Five (29.4%) of 17 patients had available IHC and NGS data. Of them, only 1 had PD-L1-positive (63 years, hepatic oligometastases with vascular involvement), who achieved a PFS of 7 months and an OS of 17.5 months after receiving 9

Table 2 Treatment-Related Adverse Events

Event, n (%)	Patients (n=17)		
	Any Grade	Grade 3	Grade 4
Liver dysfunction	9 (52.9)	0	0
Platelet count decreased	8 (47.1)	2 (11.8)	0
White blood cell decreased	8 (47.1)	0	0
Neutrophil count decreased	5 (29.4)	1 (5.9)	0
Gastrointestinal reaction	3 (17.6)	0	0
Kidney dysfunction	3 (17.6)	0	0
Allergy	1 (5.9)	0	0

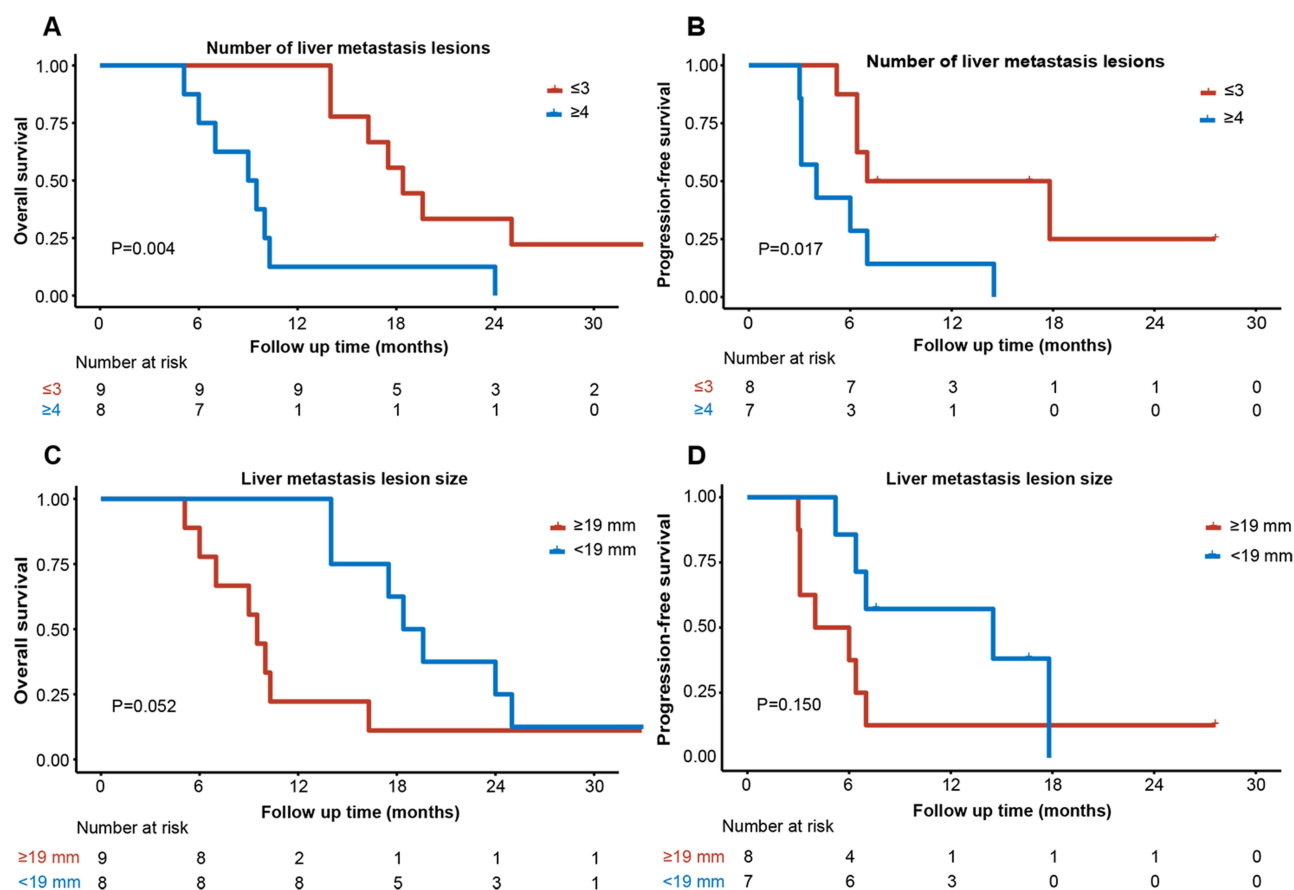


Figure 2 Overall survival and progression-free survival in subgroups by number of liver metastasis lesions (**A** and **B**) or liver metastasis lesion size (**C** and **D**).

cycles of the combination regimen. One patient had TMB-high (80 years, tumor located in the pancreatic tail with diffuse liver metastases) and achieved a PFS of 3.1 months and OS of 10.3 months after 1 cycle of AG and 5 cycles of camrelizumab. All 5 patients were microsatellite stable (MSS; Table 3).

Discussion

In this pilot study, camrelizumab in combination with AG demonstrated encouraging clinical benefits with a median OS of 14.0 months, PFS of 6.4 months, and an ORR of 29.4% in patients with PCLM. The regimen was generally well tolerated, with no grade 4–5 TRAEs observed. These findings provide preliminary evidence supporting the feasibility of integrating ICIs with AG in this particularly aggressive disease subset.

Historically, both FOLFIRINOX and AG are recommended as standard first-line regimens for metastatic PDAC. Although several studies have shown broadly comparable OS, PFS, and ORR between the two regimens (evidence from retrospective studies), differences in patient selection and toxicity profiles represent key considerations for treatment decisions.^{25,26} The slightly longer OS observed with FOLFIRINOX in a systematic review is likely attributable to the fact that patients receiving this regimen are generally younger and have better baseline performance status;^{25,27} but, retrospective studies adjusting for ECOG performance status have reported comparable or even marginally longer OS with AG.^{28,29} Importantly, AG has consistently demonstrated a more favorable tolerability profile, with lower rates of grade 3–4 neutropenia and febrile neutropenia compared with FOLFIRINOX.²⁵ In addition, the MPACT trial demonstrated that dose modifications in the AG regimen can effectively mitigate toxicity without compromising efficacy.³⁰ Overall, to achieve a favorable benefit-to-risk profile, we selected the AG regimen as the first-line treatment for patients with PCLM in this study.

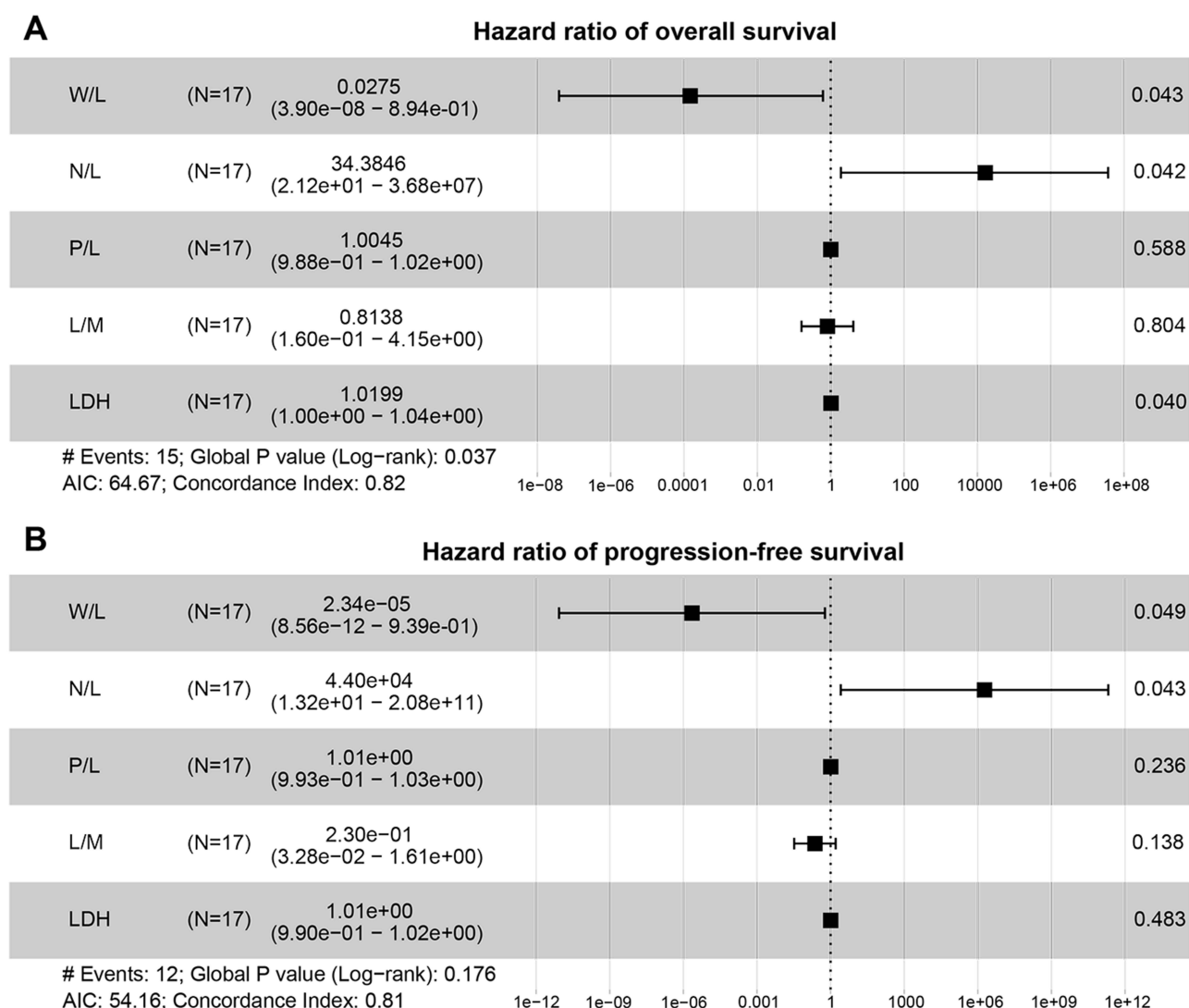


Figure 3 The association of blood indicators with overall survival (A) and progression-free survival (B). “#” indicates the statistical significance of the overall model comprising all five variables. For panel A, the global P value from the Log rank test was 0.037, indicating statistically significant predictive ability for overall survival, whereas the concordance index (0.82) demonstrated excellent discriminative performance of the model. For panel B, the global log-rank P value was 0.176, showing no statistically significant predictive ability for progression-free survival, while the concordance index (0.81) similarly indicated excellent model discrimination.

Abbreviations: AIC, Akaike information criterion; W/L, white blood cell-to-lymphocyte ratio; N/L, neutrophil-to-lymphocyte ratio; P/L, platelet-lymphocyte ratio; L/M, lymphocyte-monocyte ratio; LDH, lactate dehydrogenase.

In our study, camrelizumab combined with AG yielded a median OS of 14.0 months, a median PFS of 6.4 months, and an ORR of 29.4%, which compares favorably with the historical benchmark of AG alone (OS 8.5 months, PFS 5.5 months, ORR 23%).¹⁰ To further improve survival outcomes, ICIs have attracted considerable attention in PDAC, given

Table 3 PD-L1 Expression, TMB, MSI Status, and Survival in Patients with Available Data

No.	PD-L1 Expression	TMB	MSI Status	PFS (Months)	OS (Months)
1	Negative	Low	MSS	4	9
2	Negative	Low	MSS	14.5	24
3	Positive	Low	MSS	7	17.5
4	Negative	Low	MSS	7	9.5
5	Negative	High	MSS	3.1	10.3

Abbreviations: PD-L1, programmed cell death-ligand 1; TMB, tumor mutation burden; MSI, microsatellite instability; PFS, progression-free survival; OS, overall survival; MSS, microsatellite-stable.

their demonstrated efficacy in multiple solid tumors.^{31,32} However, their effectiveness in PDAC has remained limited, with modest response rates and short survival durations reported in multiple studies. The KEYNOTE-158 study reported that only of the pancreatic cancer cohort achieved an ORR of 18.2%, with a median PFS of 2.1 months and median OS of 4.0 months.¹⁵ Similarly, durvalumab monotherapy following prior fluoropyrimidine- or gemcitabine-based therapy resulted in median OS of 3.6 and 3.1 months, respectively.¹⁴ In contrast, early-phase studies combining ICIs with AG have demonstrated improved outcomes in metastatic PDAC. In a Phase I trial, pembrolizumab plus AG achieved a median OS of 15.0 months and median PFS of 9.1 months,¹⁸ while the CCTG PA.7 phase II trial reported a median OS of 9.8 months, median PFS of 5.5 months, and ORR of 30.3% for durvalumab plus AG with tremelimumab.¹⁹ The PRINCE trial, evaluating sotigalimab (a CD40 agonist) or nivolumab in combination with AG, reported a 1-year OS rate of 57.7% for the nivolumab plus chemotherapy arm.³³ Compared with these studies, our trial suggests that camrelizumab plus AG provides outcomes at least comparable to other ICI-based combinations, notably enrolling patients with less favorable baseline characteristics in this study (including a relatively high proportion of patients with ECOG performance scores of 1–2 and multiple liver metastases, reflecting a greater tumor burden).

The safety profile of camrelizumab plus AG chemotherapy in our study was acceptable, with most TRAEs being grade 1–2 and manageable. Three patients experienced grade 3 TRAEs, which is lower compared to previous studies of ICI plus AG (grade 3–4, 55.6%–84%).^{18,19,33,34} No grade 4–5 events occurred, and treatment discontinuation due to TRAEs was rare, occurring in 1 patient (5.9%) due to grade 2 immune-related hepatitis. Therapy for this patient was interrupted following communication among the investigator, patient, and family; then, this patient underwent close clinical monitoring.

Liver is the most common metastatic site in PDAC and portends a particularly poor prognosis, with a historical median OS below 6 months.⁷ Importantly, the number of liver metastases has repeatedly been demonstrated as a key prognostic factor. Retrospective analyses by Hackert et al reported 5-year OS rates of ~8%–10% in patients with PDAC undergoing synchronous resection of primary and ≤ 3 hepatic lesions.³⁵ Consistently, a multicenter study with 417 patients found that oligometastatic cases (≤ 3 lesions) had a median OS of 13.1 months versus 8.2 months in polymetastatic presentations (> 3).³⁶ In line with this, our study confirmed that patients with ≤ 3 liver metastases achieved significantly longer OS and PFS compared with those having > 3 lesions. Regarding lesion size, a previous study showed that small liver metastatic lesions (< 1500 μm in diameter) comprised more CD8-positive T cells, which were located at the tumor center, while large ones (> 1500 μm) comprised fewer CD8-positive T cells, which were mainly located at the invasion front.³⁷ However, our cohort did not show any significant correlation between lesion size and survival outcomes, which may be attributable to limited sample size and event numbers. In addition, although current international and Chinese guidelines do not recommend surgery for metastatic PDAC,⁷ patients with ≤ 3 liver metastases (oligometastases) may benefit from resection in certain cases.³⁸ In our study, one female patient with pancreatic body cancer and liver oligometastases underwent radical surgery due to colon obstruction (colorectal space-occupying lesions). The primary tumor and liver metastases were carefully resected, and the invaded colon was removed and reconstructed. After surgery, she received 4 cycles of AG and achieved a survival of 30 months.

We also performed exploratory subgroup analyses to identify potential biomarkers associated with response to camrelizumab plus AG. Inflammatory markers have been suggested as a predictor for immunotherapy.^{39–42} Previous studies reported that baseline NLR, PLR, LMR, and LDH levels were associated with tumor response and survival for patients with pancreatic cancer.^{39,43,44} In our subgroups, we observed that higher WLR and lower NLR were correlated with longer OS and PFS, and lower LDH was associated with OS. Qiu et al similarly reported that patients with lower LDH had superior PFS and OS, but in their analysis, NLR was not significantly correlated with survival.³⁹ However, the reported associations between inflammatory markers and survival in pancreatic cancer remain inconsistent across studies. These discrepancies may be explained by the relatively small sample sizes (often fewer than 100 patients), differences in baseline patient characteristics, heterogeneity in treatment regimens, variation in cutoff values used for inflammatory indices, and differences in study design and statistical methodology.^{39,43,44} Established immunotherapy biomarkers, including PD-L1 expression, TMB, and microsatellite instability/deficient mismatch repair (MSI/dMMR) status, have shown predictive value in various solid tumors.^{45,46} PD-L1 expression on tumor cells can suppress CD8⁺ T cell activity and has been associated with worse survival in certain cancers,⁴⁷ while TMB-high tumors generate more neoantigens,

enhancing immunogenicity and response to ICIs.⁴⁸ MSI-H/dMMR tumors also exhibit increased sensitivity to ICIs, though their prevalence in PDAC is low (<2%).^{49,50} In our study, PD-L1 data were available for five patients, with only one patient positive; TMB was high in one patient, and all were microsatellite-stable. Notably, these two patients experienced moderate clinical benefit (PFS 3.1–7 months; OS 10.3–17.5 months), suggesting potential utility of these biomarkers. Overall, while our sample is limited, these exploratory analyses indicate that inflammatory and genomic biomarkers may help predict ICI response in PDAC with liver metastases, warranting validation in larger cohorts.

This study has several limitations. Firstly, this was a single-arm, single-center trial. Secondly, the number of patients enrolled was small. Therefore, selection bias and statistical bias could exist. Thirdly, the exploratory subgroup analyses, including assessments of inflammatory markers, PD-L1 expression, TMB, and MSI status, were conducted in only a few patients, preventing definitive conclusions regarding predictive biomarkers. Finally, the short follow-up duration for some patients may have underestimated long-term outcomes. Future studies should increase the sample size, incorporate randomized controlled designs with appropriate control groups, extend follow-up, and evaluate immune-related markers to further explore the efficacy of camrelizumab combined with AG in this patient population.

Conclusion

In conclusion, camrelizumab combined with AG shows promising antitumor activity in patients with PCLM, with an acceptable safety profile. These findings initially support further prospective studies and the exploration of biomarker-driven strategies to improve efficacy in this patient population.

Abbreviations

PDAC, Pancreatic ductal adenocarcinoma; AG, albumin-bound paclitaxel and gemcitabine; PCLM, PDAC and liver metastases; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; CI, confidence interval; ICIs, immune checkpoint inhibitors; TME, tumour microenvironment; CAF, cancer-associated fibroblast; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ECOG, Eastern Cooperative Oncology Group; AEs, adverse events; CT, computed tomography; ESMO, European Society for Medical Oncology; WLR, white blood cell-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; LDH, lactate dehydrogenase; IHC, immunohistochemistry; NGS, next-generation sequencing; TMB, Tumor mutation burden; MSI, microsatellite instability; CPS, combined positive score; CR, complete response; PR, partial response.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author, Xiaolong Liu, on reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and was approved by the ethics committee of Sir Run Run Shaw Hospital. Written informed consent was obtained from each patient.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *Ca a Cancer J Clin*. 2021;71(1):7–33. doi:10.3322/caac.21654
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913–2921. doi:10.1158/0008-5472.CAN-14-0155
3. Zheng RS, Sun KX, Zhang SW, et al. Report of cancer epidemiology in China, 2015. *Zhonghua zhong liu za zhi*. 2019;41(1):19–28. doi:10.3760/cma.j.issn.0253-3766.2019.01.005
4. National Cancer Institute. Cancer Stat Facts: pancreatic Cancer. Available from: <https://seer.cancer.gov/statfacts/html/pancreas.html>. Accessed August 13, 2025.
5. Halbrook CJ, Lyssiotis CA, Pasca Di Magliano M, Maitra A. Pancreatic cancer: advances and challenges. *Cell*. 2023;186(8):1729–1754. doi:10.1016/j.cell.2023.02.014
6. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet*. 2020;395(10242):2008–2020. doi:10.1016/S0140-6736(20)30974-0
7. Liu Z, Gou A, Wu X. Liver metastasis of pancreatic cancer: the new choice at the crossroads. *Hepatobiliary Surg Nutrition*. 2023;12(1):88–91. doi:10.21037/hbsn-22-489
8. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *New Engl J Med*. 2018;379(25):2395–2406. doi:10.1056/NEJMoa1809775
9. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New Engl J Med*. 2011;364(19):1817–1825. doi:10.1056/NEJMoa1011923
10. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *New Engl J Med*. 2013;369(18):1691–1703. doi:10.1056/NEJMoa1304369
11. Singh RR, O'Reilly EM. New treatment strategies for metastatic pancreatic ductal adenocarcinoma. *Drugs*. 2020;80(7):647–669. doi:10.1007/s40265-020-01304-0
12. Hu ZI, O'Reilly EM. Therapeutic developments in pancreatic cancer. *Nat Rev Gastroenterol Hepatol*. 2024;21(1):7–24. doi:10.1038/s41575-023-00840-w
13. Grünwald BT, Devisme A, Andrieux G, et al. Spatially confined sub-tumor microenvironments in pancreatic cancer. *Cell*. 2021;184(22):5577–5592.e5518. doi:10.1016/j.cell.2021.09.022
14. O'Reilly EM, Oh DY, Dhani N, et al. Durvalumab with or without tremelimumab for patients with metastatic pancreatic ductal adenocarcinoma: a Phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5(10):1431–1438. doi:10.1001/jamaoncol.2019.1588
15. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the Phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1–10. doi:10.1200/JCO.19.02105
16. Alvarez R, Musteanu M, Garcia-Garcia E, et al. Stromal disrupting effects of nab-paclitaxel in pancreatic cancer. *Br J Cancer*. 2013;109(4):926–933. doi:10.1038/bjc.2013.415
17. Ford K, Hanley CJ, Mellone M, et al. NOX4 inhibition potentiates immunotherapy by overcoming cancer-associated fibroblast-mediated CD8 T-cell exclusion from tumors. *Cancer Res*. 2020;80(9):1846–1860. doi:10.1158/0008-5472.CAN-19-3158
18. Weiss GJ, Blaydorn L, Beck J, et al. Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma. *Invest New Drugs*. 2018;36(1):96–102. doi:10.1007/s10637-017-0525-1
19. Renouf DJ, Loree JM, Knox JJ, et al. The CCTG PA.7 phase II trial of gemcitabine and nab-paclitaxel with or without durvalumab and tremelimumab as initial therapy in metastatic pancreatic ductal adenocarcinoma. *Nat Commun*. 2022;13(1):5020. doi:10.1038/s41467-022-32591-8
20. Huang J, Xu B, Mo H, et al. Safety, activity, and biomarkers of SHR-1210, an Anti-PD-1 antibody, for patients with advanced esophageal carcinoma. *Clin Cancer Res*. 2018;24(6):1296–1304. doi:10.1158/1078-0432.CCR-17-2439
21. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naïve patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, Phase 3 trial. *Lancet Respir Med*. 2021;9(3):305–314. doi:10.1016/S2213-2600(20)30365-9
22. Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(4):571–580. doi:10.1016/S1470-2045(20)30011-5
23. Chen X, Wu X, Wu H, et al. Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. *J ImmunoTher Cancer*. 2020;8(2):e001240. doi:10.1136/jitc-2020-001240
24. Ren S, Chen J, Xu X, et al. Camrelizumab plus carboplatin and paclitaxel as first-line treatment for advanced squamous NSCLC (CameL-Sq): a Phase 3 trial. *J Thoracic Oncol*. 2022;17(4):544–557. doi:10.1016/j.jtho.2021.11.018
25. Chiorean EG, Cheung WY, Giordano G, Kim G, Al-Batran SE. Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in advanced pancreatic cancer: a systematic review. *Therapeut Adv Med Oncol*. 2019;11:1758835919850367. doi:10.1177/1758835919850367
26. Santucci J, Tacey M, Thomson B, et al. Impact of first-line FOLFIRINOX versus Gemcitabine/Nab-Paclitaxel chemotherapy on survival in advanced pancreatic cancer: evidence from the prospective international multicentre PURPLE pancreatic cancer registry. *European J Cancer*. 2022;174:102–112. doi:10.1016/j.ejca.2022.06.042
27. Foley K, Kim V, Jaffee E, Zheng L. Current progress in immunotherapy for pancreatic cancer. *Cancer Lett*. 2016;381(1):244–251. doi:10.1016/j.canlet.2015.12.020
28. Cartwright TH, Parisi M, Espirito JL, et al. Clinical outcomes with first-line chemotherapy in a large retrospective study of patients with metastatic pancreatic cancer treated in a US community oncology setting. *Drugs - Real World Outcomes*. 2018;5(3):149–159. doi:10.1007/s40801-018-0137-x
29. Kim S, Signorovitch JE, Yang H, et al. Comparative effectiveness of nab-paclitaxel plus gemcitabine vs FOLFIRINOX in metastatic pancreatic cancer: a retrospective nationwide chart review in the United States. *Adv Ther*. 2018;35(10):1564–1577. doi:10.1007/s12325-018-0784-z

30. Scheithauer W, Ramanathan RK, Moore M, et al. Dose modification and efficacy of nab-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: Phase III MPACT trial. *J Gastrointestinal Oncol.* 2016;7(3):469–478. doi:10.21037/jgo.2016.01.03
31. Muller M, Haghnejad V, Schaefer M, et al. The immune landscape of human pancreatic ductal carcinoma: key players, clinical implications, and challenges. *Cancers.* 2022;14(4):995. doi:10.3390/cancers14040995
32. Wandmacher AM, Letsch A, Sebens S. Challenges and future perspectives of immunotherapy in pancreatic cancer. *Cancers.* 2021;13(16):4235. doi:10.3390/cancers13164235
33. Padrón LJ, Maurer DM, O'Hara MH, et al. Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial. *Nat Med.* 2022;28(6):1167–1177. doi:10.1038/s41591-022-01829-9
34. Cheng D, Hu J, Wu X, et al. PD-1 blockade combined with gemcitabine plus nab-paclitaxel is superior to chemotherapy alone in the management of unresectable stage III/IV pancreatic cancer: a retrospective real-world study. *Front Oncol.* 2023;13:1281545. doi:10.3389/fonc.2023.1281545
35. Hackert T, Niesen W, Hinz U, et al. Radical surgery of oligometastatic pancreatic cancer. *European J Surg Oncol.* 2017;43(2):358–363. doi:10.1016/j.ejso.2016.10.023
36. Takeda T, Sasaki T, Okamoto T, et al. Outcomes of pancreatic cancer with liver oligometastasis. *J Hepato-Biliary-Pancreatic Sci.* 2023;30(2):229–239. doi:10.1002/jhbp.1184
37. Beckinger S, Daunke T, Aldag L, et al. Hepatic myofibroblasts exert immunosuppressive effects independent of the immune checkpoint regulator PD-L1 in liver metastasis of pancreatic ductal adenocarcinoma. *Front Oncol.* 2023;13:1160824. doi:10.3389/fonc.2023.1160824
38. Yang J, Zhang J, Lui W, et al. Patients with hepatic oligometastatic pancreatic body/tail ductal adenocarcinoma may benefit from synchronous resection. *HPB.* 2020;22(1):91–101. doi:10.1016/j.hpb.2019.05.015
39. Qiu X, Shi Z, Tong F, et al. Biomarkers for predicting tumor response to PD-1 inhibitors in patients with advanced pancreatic cancer. *Hum Vaccines Immunother.* 2023;19(1):2178791. doi:10.1080/21645515.2023.2178791
40. Gu A, Li J, Qiu S, et al. Pancreatic cancer environment: from patient-derived models to single-cell omics. *Mol Omics.* 2024;20(4):220–233. doi:10.1039/D3MO00250K
41. Huang M, Gong G, Deng Y, et al. Crosstalk between cancer cells and the nervous system. *Med Adv.* 2023;1(3):173–189. doi:10.1002/med4.27
42. Uehara M, Domoto T, Takenaka S, et al. Glycogen synthase kinase 3 β : the nexus of chemoresistance, invasive capacity, and cancer stemness in pancreatic cancer. *Cancer Drug Resistance.* 2024;7:4. doi:10.20517/cdr.2023.84
43. Wang Q, Tong F, Qiao L, et al. Hypofractionated radiotherapy plus PD-1 antibody and SOX chemotherapy as second-line therapy in metastatic pancreatic cancer: a single-arm, phase II clinical trial. *Cancer Immunol Immunother.* 2024;73(10):201. doi:10.1007/s00262-024-03744-z
44. Maloney S, Pavlakis N, Itchins M, et al. The prognostic and predictive role of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) as biomarkers in resected pancreatic cancer. *J Clin Med.* 2023;12(5):1989. doi:10.3390/jcm12051989
45. Tian L, Ma J, Ma L, et al. PD-1/PD-L1 expression profiles within intrahepatic cholangiocarcinoma predict clinical outcome. *World J Surg Oncol.* 2020;18(1):303. doi:10.1186/s12957-020-02082-5
46. Lawlor RT, Mattiolo P, Maffiini A, et al. Tumor mutational burden as a potential biomarker for immunotherapy in pancreatic cancer: systematic review and still-open questions. *Cancers.* 2021;13(13):3119. doi:10.3390/cancers13133119
47. Deng M, Li SH, Fu X, et al. Relationship between PD-L1 expression, CD8+ T-cell infiltration and prognosis in intrahepatic cholangiocarcinoma patients. *Can Cell Int.* 2021;21(1):371. doi:10.1186/s12935-021-02081-w
48. Marcus L, Fashoyin-Aje LA, Donoghue M, et al. 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-21-0327
49. Salem ME, Puccini A, Grothey A, et al. Landscape of tumor mutation load, mismatch repair deficiency, and PD-L1 expression in a large patient cohort of gastrointestinal cancers. *Mol Cancer Res.* 2018;16(5):805–812. doi:10.1158/1541-7786.MCR-17-0735
50. Cortes-Ciriano I, Lee S, Park WY, Kim TM, Park PJ. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017;8(1):15180. doi:10.1038/ncomms15180

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