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Original Research

Extent and clinical significance of the therapy-relevant tight junction protein Claudin 18.2 in pancreatic ductal adenocarcinoma - real-world evidence

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ABSTRACT

Purpose: Pancreatic ductal adenocarcinoma (PDAC) is associated with poor prognosis, wherefore targeted therapies have experienced increasing interest. Zolbetuximab is a novel targeted therapy under investigation in patients with PDAC and targets Claudin 18.2 (CLDN18.2), which is a component of tight junctions and is of significance in various solid tumors. As its role in PDAC is not definitively elucidated, this study aims to clarify the significance of CLDN18.2 expression in PDAC in a real-world setting.
Methods: All patients ($n = 309$) were recruited at one of the PANCALYZE study centers and received pancreatic resection with curative intention. Paraffin samples were analyzed using an antibody against CLDN18.2, which is known to be comparable to the antibody used by the SPOTLIGHT and GLOW studies.
Results: 94 PDACs are positive for CLDN18.2 (30.4 %). Positive CLDN 18.2 expression was associated with significantly better cancer differentiation ($p < 0.001$). Patients with positive CLDN18.2 expression showed significantly better overall survival when compared to patients with negative expression (median OS: 30 versus 18 months, $p = 0.003$). Additionally, in multivariable analyses, CLDN18.2 expression was identified as an independent factor for better survival in patients with PDAC (HR = 0.686, 95 %CI = 0.492–0.956, $p = 0.026$).
Conclusion: Significant improvement in survival could be demonstrated by adding Zolbetuximab to known chemotherapy regimes in patients with gastro-esophageal junction adenocarcinoma with at least 75 % CLDN18.2 positive cancer cells. Our findings demonstrate, that 30.4 % of the included patients with PDAC would potentially be eligible for therapy with Zolbetuximab in a real-world patient cohort. Results of trials targeting Claudin 18.2 are pending in patients with PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) accounts for 85 % of all pancreatic malignancies and remains one of the leading causes of cancer-related deaths around the world in both men and women [1]. Overall, 5-year survival rates range around 5–13 % and both mortality and incidence of PDAC have been noted to be increasing over the past decades, demonstrating the need for the development of effective targeted therapies [1,2]. Current treatment regimens for the metastatic disease include combination chemotherapy such as nab-Paclitaxel plus Gemcitabine and 5-fluorouracil/leucovorin with irinotecan and oxaliplatin (FOLFIRINOX) which have increased overall survival [3–5]. Various targeted therapies are also currently under investigation, using common genomic mutations to improve prognosis and survival [5]. Exemplary, Erlotinib, an inhibitor of EGFR tyrosine kinase is the first approved targeted therapy. However, it improved survival in a phase III

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trial that compared Gemcitabine therapy with Gemcitabine and Erlotinib only by approximately 10 days [4,5]. It is clear, that new treatment targets are needed to finally reach a breakthrough in systemic therapy for patients with PDAC. A newer investigated drug is Zolbetuximab, a selective monoclonal antibody to Claudin 18.2 (CLDN 18.2), which has shown efficiency in terms of longer progression-free survival and overall survival in patients with esophageal, gastric, and gastric-esophageal junction cancers [6–8]. Here, patients treated with Zolbetuximab showed significantly better survival, if the mentioned antibody was added to already established treatment options like CAPOX, mFOLFOX6, or EOX in multicenter, randomized, double-blind phase II or III trials [6–8]. The mentioned studies have shown, that targeting CLDN 18.2 could improve patient survival if at least 75 %, or 40 % in the FAST trial, of the tumor cells show a moderate-to-strong staining intensity in immunohistochemical stainings in paraffin-embedded tumor tissue [6–8]. The antibody is now being investigated in a phase II trial in patients with metastatic PDAC (NCT03816163).

Claudins are one of the two major components of tight junctions that are responsible for the formation of a barrier to regulate paracellular ion transport [9–11]. There are currently 27 known claudin proteins that exhibit expression patterns in tumors specific to their origins [12]. Claudin 18.2 is physiologically expressed only in the gastric mucosa [13]. However, Claudin 18.2 is frequently expressed in adenocarcinomas of different origins, namely gastric, esophageal, pancreatic, and ovarian adenocarcinomas [14]. While Claudin 18.2 overexpression is more frequent in metastatic gastric adenocarcinoma, no significant correlation could be found between Claudin 18.2 expression and patient survival [15,16]. *Wöll* et al. investigated CLDN 18.2 expression frequency in PDAC and its metastases. Here, approximately 60 % of the primary tumors and lymph nodes as well as distant metastases of PDAC showed Claudin 18.2 expression. Furthermore, higher Claudin 18.2 expression could be detected in lymph node-positive tumors [17].

This study aimed to assess the frequency of patients eligible for potential treatment with Zolbetuximab in a real-world patient cohort using the immunohistochemical CLDN 18.2 inclusion criteria of the SPOTLIGHT and GLOW study.

Materials and methods

Patients and tumor samples

All patients included in this study were diagnosed and received treatment at one of the mentioned PANCALYZE study centers. Patients received resections with curative intention between 2012 and 2020. We excluded patients with a survival period of less than 30 postoperative days or if insufficient tumor sample quality was obtained. In conformity with the PANCALYZE study protocol, samples were collected prospectively and analyzed retrospectively [18]. Written informed consent was obtained from each patient and data as well as the respective tumor samples were transferred to the study center (University Hospital of Cologne). The study received approval from the Ethics Committee of the University Hospital of Cologne (ethics committee number: 16–230). The conduction of the study followed the Declaration of Helsinki.

An experienced pathologist evaluated the samples regarding tissue quality. To assess tumor stage values, the 7th edition of the Union for International Cancer Control was followed. Tumor borders were marked and two tissue cylinders of 1.2-milimeters each were punched out with a semi-automated precision instrument. After transfer of these cylinders to a paraffin-embedded tissue microarray, slices of 4 μm of the microarray were obtained and further experiments were conducted using these slices.

Immunohistochemistry

Immunohistochemical stainings were conducted using the automatic staining system Leica BOND-MAX with Leica Bond Polymer Refine Detection Kit (Leica Biosystems, Wetzlar, Germany). The mouse monoclonal antibodies Claudin 18.2 were used according to the manufacturers (LS-B16145, LSBio, Shirley, MA, USA, 1:200, EDTA; Ventana CLDN18 (43–14A) Assay, Roche, Basel, Switzerland).

The analyses were performed by two experienced pathologists (A.Q. and S.L). CLDN18.2 stainings were assessed for their intensity of staining (weak = 1+, moderate = 2+, strong = 3+) and percentage of stained tumor cells compared to non-stained tumor cells of each section. Tissue samples were classified as either positive or negative for CLDN18.2. Samples with staining of ≥ 75 % of tumor cells and staining intensities of ≥ 2+ were defined as positive, aligning with grading criteria in previous studies [6,7,19].

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 29.0.1.1, Armonk, USA). P-values below 0.05 were regarded as statistically significant. Survival analyses were conducted using Kaplan-Meier curves and log-rank tests. Qualitative values were evaluated with the chi-square test and interdependencies between clinicopathologic values and overall survival were calculated with univariable and multivariable Cox regression analyses. The multivariable Cox regression analysis only included clinicopathological values that exhibited P-values of below 0.2 in the univariable Cox regression analysis.

Results

In total 309 patients with pancreatic ductal adenocarcinoma were included in this study. Of these patients 148 were male (47.9 %) and 210 patients were older than 64 years (68.0 %). 4.9 % ($n = 15$) of the total study cohort received neoadjuvant therapy before pancreatic resection in curative intention. The majority of our study cohort was diagnosed pathologically with lymph node metastases (72.2 %, $n = 223$). We performed immunohistochemical stainings for Claudin 18.2 with the antibody from LSBio. Our study cohort was divided into tumors with negative Claudin 18.2 staining ($n = 215$, 69.6 %) and positive Claudin 18.2 staining ($n = 94$, 30.4 %, Fig. 1A). Since recent phase III trials used the VENTANA assay, we also performed immunohistochemical stainings with this antibody in a random subgroup of 62 patients. Here, a positive staining with the VENTANA assay correlated with a positive staining with the LSBio antibody ($p < 0.001$, Supp. Table 1). Following this, we compared the classically assessed clinicopathological values of these two subgroups. Here, a positive Claudin 18.2 expression could be detected significantly less frequently following neoadjuvant therapy ($p = 0.040$). Furthermore, patients with positive Claudin 18.2 expression showed significantly better cancer differentiation ($p < 0.001$) (Table 1).

Previous studies showed inconsistent results regarding the influence of Claudin 18.2 on patients' survival in PDAC [9,20]. Therefore, we performed survival analyses comparing the overall survival of patients with negative and positive Claudin 18.2 expression. Hither, patients with positive Claudin 18.2 expression showed significantly better overall survival compared to patients with negative expression (median OS: 30 versus 18 months, $p = 0.003$, Fig. 1B).

Moreover, univariable and multivariable Cox regression analyses were conducted to assess possible interdependencies between clinicopathological values and the patients' overall survival. (y)pT-, and (y)pN-stage could be described as significant, independent factors for worse patient survival ((y)pT: HR = 1.321, 95 % CI = 1.030–1.694, $p = 0.029$; (y)pN: HR = 2.611, 95 % CI = 1.734–3.930, $p < 0.001$). Besides, positive Claudin 18.2 expression proved to be an independent factor for a favorable survival of patients with PDAC (Claudin 18.2: HR = 0.686, 95 % CI = 0.492–0.956, $p = 0.026$) (Table 2).

Summarizing the result above, patients with positive Claudin 18.2 expression showed a significant better overall survival compared to patients with negative expression. Additionally, Claudin 18.2 could be described as an independent factor for favorable survival in patients

Table 1
General clinicopathological values of the total study population and patients with negative or positive Claudin 18.2 expression. Bold print marks p-values below 0.05.

Characteristic	Total	Claudin 18.2		
	n (%)	negative n (%)	positive n (%)	p-value
No. of patients	309 (100)	215 (100)	94 (100)	
Sex				0.625
Male	148 (47.9)	101 (47.0)	47 (50.0)	
Female	161 (52.1)	114 (53.0)	47 (50.0)	
Age				0.975
< 65	99 (32.0)	69 (32.1)	30 (31.9)	
≥ 65	210 (68.0)	146 (67.9)	64 (68.1)	
Median overall survival (months)	17.0 (2.0–98.0)	15.0 (2.0–98.0)	21.0 (2.0–71.0)	
Neoadjuvant therapy				**0.040**
No	294 (95.1)	201 (93.5)	93 (98.9)	
Yes	15 (4.9)	14 (6.5)	1 (1.1)	
(y)pT				0.680
1	21 (6.8)	16 (7.4)	5 (5.3)	
2	119 (38.5)	83 (38.6)	36 (38.3)	
3	162 (52.4)	110 (51.2)	52 (55.3)	
4	7 (2.3)	6 (2.8)	1 (1.1)	
(y)pN				0.551
0	86 (27.8)	62 (29.1)	24 (25.5)	
1	223 (72.2)	153 (70.9)	70 (74.5)	
R				0.511
0	201 (65.0)	136 (63.3)	65 (69.1)	
1	107 (34.6)	78 (36.3)	29 (30.9)	
2	1 (0.3)	1 (0.5)	0 (0.0)	
L				0.625
0	121 (39.2)	86 (40.0)	35 (37.2)	
1	187 (60.5)	128 (59.5)	59 (62.8)	
unknown	1 (0.3)	1 (0.5)	0 (0.0)	
V				0.119
0	210 (68.0)	138 (64.2)	72 (76.6)	
1	95 (30.7)	73 (34.0)	22 (23.4)	
unknown	4 (1.3)	4 (1.8)	0 (0.0)	
Pn				0.218
0	72 (23.3)	46 (21.4)	26 (27.7)	
1	225 (72.8)	161 (74.9)	64 (68.1)	
unknown	12 (3.3.9)	8 (3.7)	4 (4.2)	
G				**< 0.001**
1	7 (2.3)	3 (1.4)	4 (4.2)	
2	149 (48.2)	87 (40.5)	62 (66.0)	
3	134 (43.4)	108 (50.2)	26 (27.7)	
4	3 (0.9)	3 (1.4)	0 (0.0)	
not applicable/unknown	16 (5.1)	14 (6.5)	2 (2.1)	

with PDAC.

Discussion

This retrospective cohort study was conducted as part of the PANCALYZE study and investigated the role of Claudin 18.2 in pancreatic ductal adenocarcinoma. A total of 309 patients were included and immunohistochemical stainings of the tumor samples for Claudin 18.2 were performed. Positive Claudin 18.2 expression was associated with better cancer differentiation ($p < 0.001$). This is in line with the literature [21]. Claudin 18.2 positivity was found in 30.4 % of the investigated 309 tumor samples in the here described study. Previous studies, which investigated the expression of Claudin 18.2 in PDAC showed higher expression rates [14,21,22]. However, other studies showed expression rates, that align with our study [9,20]. These differences could be explained by the use of various antibodies and cut-off values for CLDN18.2 positivity. To identify CLDN18.2 expression in patients, we used the mouse monoclonal antibody anti-Claudin 18.2 by LSBio. Meanwhile, the phase III trials GLOW and SPOTLIGHT, which investigated Zolbetuximab in combination with CAPOX or mFOLFOX6 in gastric and gastro-esophageal carcinomas, identified positive Claudin 18.2 expression solely using the VENTANA CLDN18 (43–14A) Assay [6,7]. A recent global ring study found high concordance among the VENTANA and LSBio antibodies regarding the accuracy, precision, sensitivity, and specificity rates, therefore confirming analytical comparability between the two antibodies [11]. To further confirm the similarity between the staining results of the two antibodies, we conducted stainings of the tumor samples with both the VENTANA CLDN18 (43–14A) Assay and the LSBio anti-Claudin 18.2 antibody on a random subgroup of 62 patients, which showed a significant correlation in staining classifications. All in all, analytical comparability of the LSBio antibody with the in clinical trials used VENTANA assay can be assumed, which has played an established role in Claudin 18.2 detection. Notably, the studies mentioned above of Claudin 18.2 expression levels in patients with PDAC did not use the VENTANA CLDN18 Assay or LSBio antibody but used distinct antibodies by Abcam and Invitrogen which were not explored in the previously mentioned ring study regarding their reliability [9,11,20,22]. Moreover, different findings between Claudin 18.2 overexpression and patient survival could be explained by a common problem of analyses of immunohistochemical stainings. Various cut-offs for the definition of positive Claudin 18.2 stainings were used in previous studies investigating Claudin 18.2 positivity in PDAC (≥ 75 % of tumor cells and staining intensities of ≥ 2+, staining intensity solely, and median H-Score) [9,20,22]. Nevertheless, we used the definition (positive staining in ≥75 % of tumor cells and staining intensities of ≥ 2+), which is used in phase III trials evaluating the newly introduced antibody Zolbetuximab in combination with established therapy options [6,7]. In addition, the FAST trial used CLAUDETECT™ as a different detection method as well as a different cut-off for Claudin 18.2 positivity with ≥ 40 % [23]. A lower cut-off value could enable Zolbetuximab as a potential treatment option in a wider patient group. However, this could lead to a higher false-positive rate, leading to a lower clinical efficiency rate. These patients would receive Zolbetuximab with the potential occurrence of side effects without clinical benefit. This hypothesis is supported by the results of the FAST trial. Here, no survival benefit could be detected in patients with 40–69 % Claudin 18.2 positive tumor cells in contrast to patients with ≥ 70 % positive tumor cells [23]. Therefore, a further evaluation of the ideal cut-off in patients with PDAC is warranted. We conducted survival analyses with a cut-off of ≥ 40 % for Claudin 18.2 positivity. Here, similar results of the performed survival analyses occurred as stated above with a cut-off of ≥ 75 %.

But not only differences in the frequency of Claudin 18.2 expression could be detected. Also, the reported correlation between survival and Claudin 18.2 differs in the literature. Our findings revealed that positive expression of Claudin 18.2 was associated with better overall survival (median OS: 30 versus 18 months, $p = 0.003$). We also found that Claudin 18.2 was an independent factor for favorable prognosis in patients with PDAC (HR = 0.686, 95 % CI = 0.492–0.956, $p = 0.026$). Supporting our findings, Kayikcioglu et al. report a significant correlation between patients with high Claudin 18.2 expression and better overall survival in a patient cohort of sixty-eight patients [20]. On the contrary, high Claudin 18.2 expression was correlated with lymph node and distant metastases as well as poor patient survival [22]. Additionally, a third retrospective study with 130 included patients reported no correlation between Claudin 18.2 expression levels and patient survival [9].

Furthermore, the patient numbers between these studies differed greatly. Our study cohort included a considerable number of patients ($n = 309$), which surpasses the sample sizes of previously referenced studies and thereby enhances the overall strength of the here reported study.

Interestingly, Claudin 18.2 positivity was found significantly less frequently following neoadjuvant therapy ($p = 0.040$). Previous studies did not include information about potential neoadjuvant treatment of the included patients with PDAC [9,20,22]. In esophageal

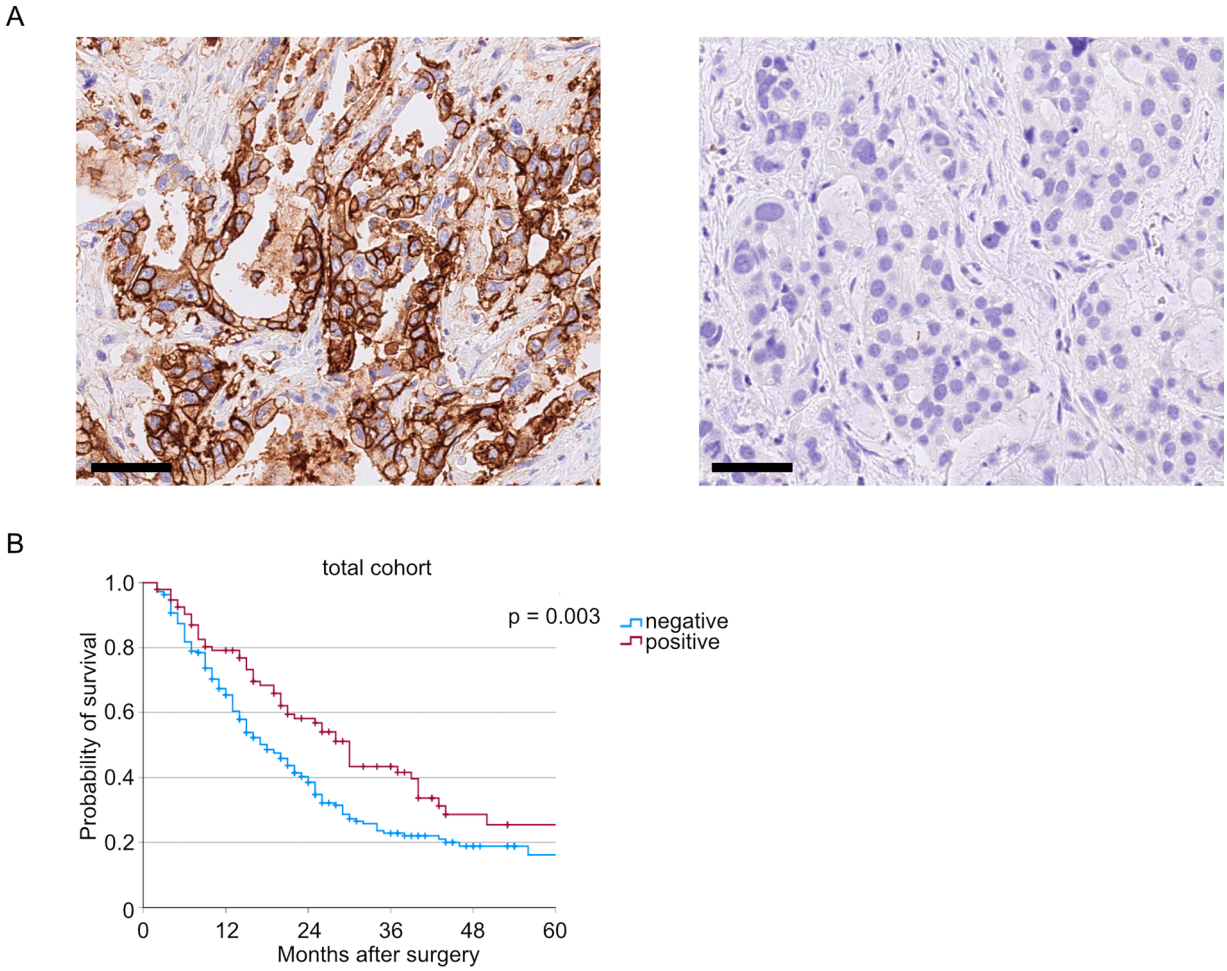

Fig. 1. (A) Exemplary pictures of tumors with positive (left) and negative (right) Claudin 18.2 expression. (B) Kaplan-Meier curve for overall survival depending on Claudin 18.2 expression levels of the total cohort (n(negative) = 215, n(positive) = 94, $p = 0.003$). Sidebar: 50 µm.

Table 2
Multivariable Cox regression analyses of the total study cohort. Bold print marks *p*-values below 0.05.

Characteristic	Borders	Hazard Ratio	95 % confidence interval	*p* - value
(y)pT	≥ 2 vs 1	1.321	1.030 - 1.694	**0.029**
(y)pN	≥ 1 vs 0	2.611	1.734 - 3.930	**< 0.001**
R	1 vs 0	1.172	0.880 - 1.561	0.277
L	1 vs 0	0.692	0.489 - 0.980	**0.038**
Pn	≥ 1 vs 0	1.093	0.740 - 1.615	0.655
G	≥ 2 vs 1	1.203	0.940 - 1.539	0.142
Claudin 18.2	positive vs negative	0.686	0.492 - 0.956	**0.026**

adenocarcinoma, no impact of neoadjuvant therapy on Claudin 18.2 could be observed [24]. However, only 15 patients (4.9 %) of the included patients in our study received neoadjuvant therapy prior to resection. Taking into account, that the recommendation of neoadjuvant therapy for patients with locally advanced PDAC was formulated in international guidelines only a few years ago [25], further studies are needed to evaluate the possible alteration of Claudin 18.2 expression due to neoadjuvant therapy and its implication for patients' survival.

Phase III trials in patients with Claudin 18.2-positive gastric and gastro-esophageal junction cancer met their primary endpoints to reduce progression-free survival by approximately two months [6,7]. Moreover, a recent meta-analysis could confirm the clinical benefit of Zolbetuximab administered in combination with established systemic treatment options for these patients. Furthermore, adverse events occurred significantly more often while administering Zolbetuximab in combination therapy regimes. Nevertheless, these adverse events were manageable [26]. As targeting Claudin 18.2 with Zolbetuximab revealed a great clinical benefit in the mentioned patient group, various treatment options, like other monoclonal antibodies or chimeric antigen receptor T cell therapy (CAR T cell), are currently under investigation in various tumor entities [27]. Results of clinical trials in patients with PDAC are still pending. However, as our findings showed that 30 % of all resected patients with PDAC showed a Claudin 18.2 overexpression, a big subgroup of patients with PDAC would be eligible for treatment with Zolbetuximab. Preclinical studies showed promising results. Zolbetuximab bound to Claudin 18.2 expressing pancreatic cancer cells ex vivo and induced cytotoxicity [28]. Interestingly, Gemcitabine, a widely used

cytostatic drug in patients with PDAC, induced Claudin 18.2 expression in cultured pancreatic cancer cells [28,29]. Moreover, Zolbetuximab decreased tumor growth, metastasis development, and prolonged survival in a subcutaneous primary tumor mouse model as well as in a lung metastasis mouse model, which tracked metastasis development following intravenous injection of pancreatic cancer cells [28].

Our results suggest that Claudin 18.2 positivity as defined in clinical trials evaluating Zolbetuximab as a potential targeted treatment option could be observed in 30.4 % of our large real-world patient cohort consisting of mainly Caucasian patients. Future prospective, randomized studies to evaluate the potential treatment benefit for this patient cohort are pending.

Conclusions

This research aimed to assess the occurrence of therapeutical relevant overexpression of Claudin 18.2 in pancreatic ductal adenocarcinoma as defined by previous clinical trials in other malignancies. A total of 309 patients were enrolled in the study. Notably, our analysis revealed that elevated Claudin 18.2 levels were found in 30.4 % of the included patients. Additionally, CLDN 18.2 positivity served as an independent predictor for a more favorable prognosis.

These findings underscore the potential utility of incorporating Claudin 18.2 antibodies, like Zolbetuximab, as potential treatment options in clinical practice, pending further prospective studies in patients with PDAC.

Funding

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Cologne (protocol code 16–230, 19th of September 2016).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable.

CRediT authorship contribution statement

Su Ir Lyu: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Caroline Fretter:** Writing – review & editing, Data curation. **Adrian Georg Simon:** Writing – review & editing, Investigation. **Sarah-Michele Spielmann:** Writing – review & editing, Investigation. **Alexander I. Damanakis:** Writing – original draft, Investigation, Data curation. **Yue Zhao:** Writing – review & editing, Methodology. **Christiane J. Bruns:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization. **Thomas Schmidt:** Writing – review & editing, Supervision, Project administration, Investigation. **Felix C. Popp:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Dirk Waldschmidt:** Writing – review & editing, Supervision. **Alexander Quaas:** Writing – original draft, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Karl Knipper:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2024.102044.

References

[1] M. Ilic, I. Ilic, Epidemiology of pancreatic cancer, World J. Gastroenterol. 22 (44) (2016) 9694–9705.
[2] H. Sarfraz, A. Saha, K. Jhaveri, D.W. Kim, Review of current systemic therapy and novel systemic therapy for pancreatic ductal adenocarcinoma, Curr. Oncol. 30 (6) (2023) 5322–5336.
[3] D.D. Von Hoff, T. Ervin, F.P. Arena, E.G. Chiorean, J. Infante, M. Moore, et al., Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine, N. Engl. J. Med. 369 (18) (2013) 1691–1703.
[4] M.J. Moore, D. Goldstein, J. Hamm, A. Figer, J.R. Hecht, S. Gallinger, et al., Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group, J. Clin. Oncol. 25 (15) (2007) 1960–1966.
[5] Y.T. Fang, W.W. Yang, Y.R. Niu, Y.K. Sun, Recent advances in targeted therapy for pancreatic adenocarcinoma, World J. Gastrointest. Oncol. 15 (4) (2023) 571–595.
[6] M.A. Shah, K. Shitara, J.A. Ajani, Y.J. Bang, P. Enzinger, D. Ilson, et al., Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial, Nat. Med. 29 (8) (2023) 2133–2141.
[7] K. Shitara, F. Lordick, Y.-J. Bang, P. Enzinger, D. Ilson, M.A. Shah, et al., Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial, Lancet 401 (10389) (2023) 1655–1668.
[8] U. Sahin, Ö. Türeci, G. Manikhas, F. Lordick, A. Rusyn, I. Vynnychenko, et al., FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma, Ann. Oncol. 32 (5) (2021) 609–619.
[9] S. Park, K. Shin, I.H. Kim, T. Hong, Y. Kim, J. Suh, et al., Clinicopathological features and prognosis of resected pancreatic ductal adenocarcinoma patients with Claudin-18 overexpression, J. Clin. Med. 12 (16) (2023).
[10] S. Angelow, R. Ahlstrom, A.S. Yu, Biology of claudins, Am. J. Physiol. Renal. Physiol. 295 (4) (2008) F867–F876.
[11] B. Jasani, P. Taniere, H.-U. Schildhaus, K. Blighe, S. Parry, D. Wilkinson, et al., Global ring study to investigate the comparability of total assay performance of commercial Claudin 18 antibodies for evaluation in gastric cancer, Lab. Investig. 104 (1) (2024) 100284.
[12] D. Kyuno, A. Takasawa, K. Takasawa, Y. Ono, T. Aoyama, K. Magara, et al., Claudin-18.2 as a therapeutic target in cancers: cumulative findings from basic research and clinical trials, Tissue Barriers 10 (1) (2022) 1967080.
[13] T. Niimi, K. Nagashima, J.M. Ward, P. Minoo, D.B. Zimonjic, N.C. Popescu, et al., claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing, Mol. Cell Biol. 21 (21) (2001) 7380–7390.
[14] U. Sahin, M. Koslowski, K. Dhaene, D. Usener, G. Brandenburg, G. Seitz, et al., Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development, Clin. Cancer Res. 14 (23) (2008) 7624–7634.
[15] H.D. Kim, E. Choi, J. Shin, I.S. Lee, C.S. Ko, M.H. Ryu, et al., Clinicopathologic features and prognostic value of claudin 18.2 overexpression in patients with resectable gastric cancer, Sci. Rep. 13 (1) (2023) 20047.

[16] E. Kayikcioglu, R.O. Yüceer, B. Cetin, K. Yüceer, N. Karahan, Prognostic value of claudin 18.2 expression in gastric adenocarcinoma, World J. Gastrointest. Oncol. 15 (2) (2023) 343–351.
[17] S. Wöll, A.M. Schlitter, K. Dhaene, M. Roller, I. Esposito, U. Sahin, et al., Claudin 18.2 is a target for IMAB362 antibody in pancreatic neoplasms, Int. J. Cancer 134 (3) (2014) 731–739.
[18] F.C. Popp, M.C. Popp, Y. Zhao, C. Betzler, S. Kropf, B. Garlipp, et al., Protocol of the PANCALYZE trial: a multicenter, prospective study investigating the tumor biomarkers CXCR4, SMAD4, SOX9 and IFIT3 in patients with resected pancreatic adenocarcinoma to predict the pattern of recurrence of the disease, BMC Cancer 17 (1) (2017) 229.
[19] V. Angerilli, F. Ghelardi, F. Nappo, F. Grillo, P. Parente, S. Lonardi, et al., Claudin-18.2 testing and its impact in the therapeutic management of patients with gastric and gastroesophageal adenocarcinomas: a literature review with expert opinion, Pathol. - Res. Pract. 254 (2024) 155145.
[20] E. Kayikcioglu, R.O. Yuceer, The role of claudin 18.2 and HER-2 in pancreatic cancer outcomes, Medicine (Baltimore) 102 (6) (2023) e32882.
[21] Z.E. Karanjawala, P.B. Illei, R. Ashfaq, J.R. Infante, K. Murphy, A. Pandey, et al., New markers of pancreatic cancer identified through differential gene expression analyses: claudin 18 and annexin A8, Am. J. Surg. Pathol. 32 (2) (2008) 188–196.
[22] X. Wang, C.S. Zhang, X.Y. Dong, Y. Hu, B.J. Duan, J. Bai, et al., Claudin 18.2 is a potential therapeutic target for zolbetuximab in pancreatic ductal adenocarcinoma, World J. Gastrointest. Oncol. 14 (7) (2022) 1252–1264.
[23] U. Sahin, O. Tureci, G. Manikhas, F. Lordick, A. Rusyn, I. Vynnychenko, et al., FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma, Ann. Oncol. 32 (5) (2021) 609–619.
[24] V. Moentenich, F. Gebauer, E. Comut, A. Tuchscherer, C. Bruns, W. Schroeder, et al., Claudin 18.2 expression in esophageal adenocarcinoma and its potential impact on future treatment strategies, Oncol. Lett. 19 (6) (2020) 3665–3670.
[25] T. Conroy, P. Pfeiffer, V. Vilgrain, A. Lamarca, T. Seufferlein, E.M. O'Reilly, et al., Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, Ann. Oncol. 34 (11) (2023) 987–1002.
[26] Z. Liang, L. Liu, W. Li, H. Lai, L. Li, J. Wu, et al., Efficacy and safety of zolbetuximab for first-line treatment of advanced Claudin 18. 2-positive gastric or gastro-esophageal junction adenocarcinoma: a systematic review and meta-analysis of randomized controlled trials, Front. Oncol. 13 (2023) 1258347.
[27] Y. Kubota, K. Shitara, Zolbetuximab for Claudin18.2-positive gastric or gastroesophageal junction cancer, Ther. Adv. Med. Oncol. 16 (2024) 17588359231217967.
[28] Ö. Tureci, R. Mitnacht-Kraus, S. Woll, T. Yamada, U. Sahin, Characterization of zolbetuximab in pancreatic cancer models, Oncoimmunology 8 (1) (2019) e1523096.
[29] H. Ueno, T. Kosuge, Y. Matsuyama, J. Yamamoto, A. Nakao, S. Egawa, et al., A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer, Br. J. Cancer 101 (6) (2009) 908–915.