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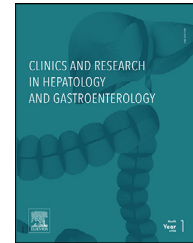


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ORIGINAL ARTICLE

Trop-2 is a ubiquitous and promising target in pancreatic adenocarcinoma



L. Mas^{a,b}, J. Cros^{c,d}, M. Svrcek^e, J.L. Van Laethem^f, J.F. Emile^g, V. Rebours^h, R. Nicolleⁱ, J.B. Bachet^{a,b,*}

^a Department of Hepato-Gastroenterology and Digestive Oncology, Pitié Salpêtrière Hospital, APHP, 47-83 Boulevard de l'Hôpital, Paris 75013, France

^b Sorbonne University, UPMC University, 15-21 Rue de l'École de Médecine, Paris 75006, France

^c Institut National de la Santé et de la Recherche Médicale, Centre de Recherche Biomédicale Bichat Beaujon (CRI)/INSERM U1149, Clichy, France

^d Department of Pathology, Beaujon Hospital, AP-HP, 100 Boulevard du Général Leclerc, Clichy 92110, France

^e Department of Pathology, Saint Antoine Hospital, APHP, 184 Rue du Faubourg Saint-Antoine, Paris 75012, France

^f Department of Gastroenterology and Gastrointestinal cancer Unit, Erasme Hospital, Université Libre de Bruxelles, Belgium

^g Department of pathology, Université Paris-Saclay, Université de Versailles SQY (UVSQ), EA4340-BECCOH, Assistance Publique-Hôpitaux de Paris (AP-HP), Ambroise-Paré Hospital, Smart Imaging, Boulogne, France

^h Department of Pancreatology, Beaujon Hospital, APHP, 100 Boulevard du Général Leclerc, Clichy 92110, France

ⁱ Université de Paris, Centre de Recherche sur l'Inflammation (CRI), INSERM U1149, CNRS ERL 8252, Paris F-75018, France

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Trop-2;
 Pancreatic ductal adenocarcinoma;
 PDAC;
 Antibody-drug conjugate

Abstract

Background: Trop-2 is overexpressed in tumor cells of various cancers, including pancreatic ductal adenocarcinoma (PDAC), and has emerged as a potent therapeutic target. We evaluated Trop-2 expression both at the transcriptomic and protein levels, and its correlation with tumor features and patients' outcomes in a large cohort of PDAC.

Methods: We included patients undergoing pancreatic resection for PDAC in 5 academic hospitals in France and Belgium. Transcriptomic profiles were obtained from FFPE tissue samples, with paired primary and metastatic lesions when available. Protein expression was evaluated by immunohistochemistry (IHC) using tissue micro-arrays.

Results: 495 patients (male 54%, median age 63 years) were included between 1996 and 2012. Trop-2 mRNA expression was significantly associated to tumor cellularity, but no association with survival nor with any clinical or pathological features was observed, with tumor cells showing an overall high expression among every subgroup. Trop-2 mRNA expression was maintained between primary and metastatic lesion in all 26 paired samples evaluated. In 50 tumors assessed by IHC, 30%, 68% and 2% harbored a high, medium, or low Trop-2 expression score, respectively. Trop-2

* Corresponding author at: Department of Hepato-Gastroenterology and Digestive Oncology, Pitié Salpêtrière Hospital, APHP, 47-83 Boulevard de l'Hôpital, Paris 75013, France.

E-mail address: jean-baptiste.bachet@aphp.fr (J.B. Bachet).

staining was significantly associated to mRNA expression, but not to survival or any pathological features.

Conclusions: Our results suggest Trop-2 overexpression as a ubiquitous marker of PDAC tumor cells and thus a promising therapeutic target to evaluate in these patients.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with a rising incidence in developed countries [1]. Despite significant advances in the management of these patients over the last decade, with new chemotherapy regimens in the adjuvant and metastatic settings [2–4], therapeutic options remain extremely limited. As a result, the prognosis of patients with PDAC remains particularly poor with a 5-year survival rate of less than 10% all stages combined [5]. Thus, the identification of new therapeutic targets is urgently needed to improve these patients' outcomes.

Trop-2 (trophoblast antigen 2) is a transmembrane glycoprotein encoded by the TACSTD2 (tumor-associated calcium signal transducer 2) gene, a member of the TACSTD gene family also comprising TACSTD1 (also known as EpCAM) which encodes epithelial cell adhesion molecule (EpCAM) [6,7]. Trop-2 primarily acts as an intracellular calcium signal transducer whose expression is detected in healthy epithelial cells of many organs [6,8,9]. It is also considered as a marker of stem cell populations in various human tissues such as prostate, lung or liver [10–12]. Trop-2 overexpression is detected in multiple epithelial cancers including lung, breast or gastro-intestinal tumors among others, and has been shown to drive cancer growth and metastasis through a complex signaling network [8,9,13,14]. Its overexpression has been shown as a prognostic marker consistently associated with poor overall survival (OS) and disease-free survival (DFS) across multiple tumor types [15].

Over the past few years, Trop-2 has also become an established therapeutic target in several cancer types with the development of Sacituzumab Govitecan (SG), an antibody-drug conjugate (ADC) composed of an antibody targeting Trop-2 coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker. SG notably demonstrated clinical efficacy for metastatic triple-negative breast cancer (TNBC) patients in the IMMU-132-01 phase I/II basket trial, resulting in an accelerated FDA approval in 2020 in this setting and further confirmed by the positive results of the phase III ASCENT trial [16–19]. The toxicity profile was manageable with neutropenia as the most common grade ≥ 3 adverse event (51%, febrile neutropenia 6%) followed by diarrhea (10%) and anemia (8%) [16]. Besides TNBC, SG demonstrated anti-tumor activity in several other cancer types such as urothelial carcinomas, for which an accelerated FDA approval was also delivered in 2021, metastatic hormone receptor positive/ human epidermal growth factor receptor 2- negative (HR+/HER2-) breast cancer, or small cell and non-small cell lung cancer (NSCLC) [20–25]. Datopotamab deruxtecan (Dato-DXd; DS-1062), another ADC composed of a humanized anti-Trop-2 monoclonal antibody attached to a topoisomerase I inhibitor (DXd) payload by a stable tetrapeptide-based linker, also showed promising activity in the TROPION-PanTumor01 phase I trial and is

currently being evaluated in phase III trials in HR+/HER2-breast cancer and NSCLC patients [26,27] (NCT04656652, NCT05104866).

In PDAC patients, Trop-2 overexpression assessed by immunohistochemistry (IHC) has been reported in more than half of cases and was associated with poorer outcomes [28,29]. A small cohort of PDAC patients (n=16) was included in the aforementioned IMMU-132-01 basket trial, for which treatment with SG led to disease stabilization in 7 patients (43%), although no complete or partial response was observed [30].

In this study, we evaluated the expression of Trop-2 in a large cohort of resected PDAC specimens both at the protein and transcriptomic level to investigate its involvement in PDAC and associations with patients' outcomes.

Patients and methods

Patients and data collection

The cohort comprised consecutive and unselected patients who underwent curative-intent surgery for PDAC at 5 academic hospitals in France and Belgium between 1996 and 2012, and for which archived tumor specimens were available. Patients who received preoperative chemotherapy or chemoradiotherapy, had macroscopically incomplete resection (R2), tumor histology other than ductal adenocarcinoma, or died of post operative complications within 30 days after surgery were excluded.

Each participating center maintains a prospective PDAC database, including patient demographics, clinical and pathological variables. These databases were reviewed to assess standardized clinicopathological variables for the entire cohort, including sex, age at diagnosis, tumor site, preoperative assessment of clinical disease stage, type of operative procedure, tumor stage according to the Union for International Cancer Control (UICC) TNM classification 8th edition, histologic grade, presence of lymphovascular invasion, perineural invasion, and relevant outcome parameters.

This study was approved by the appropriate institutional review boards at the participating hospitals (Ref 2010/01 NICB and 2014/59 NICB). All procedures were performed in accordance with relevant guidelines.

Sample processing and transcriptomic analysis

Representative formalin fixed and paraffin embedded (FFPE) tumor blocks were selected by specialized pathologists after examination of H&E-stained slides and two cores with diameters of 1.5 mm were extracted from tumor-enriched areas using an FFPE compatible protocol according to the manufacturer's instructions. Transcriptomic profiles were obtained either using FFPE-compatible microarray (n=144), RNA-sequencing (n=186) or both simultaneously (n=165). A linear model was applied in the 165 samples for which both

microarrays and RNAseq was applied to fit the expression of Trop-2 (Ensembl gene ID: ENSG00000184292) to obtain microarray-based measures of gene expression comparable to the RNAseq-based values. Paired metastatic lesions were analyzed using biopsy samples when available. DNA extraction and sequencing was performed in a subset of the study population as previously described [31].

Immunohistochemistry

Trop-2 protein expression was evaluated by IHC in a subset of the cohort study from one of the participating centers. Representative tumor-enriched areas were selected on H&E-stained slides and tumor cores from these areas were grouped together on tissue microarrays (TMA). Trop-2 protein expression was evaluated on TMA sections using IHC with Trop-2 directed monoclonal antibody (rabbit monoclonal, clone EPR20043, ab214488, Cambridge, UK) on routine automate (Benchmark Ultra – Ventana (Tuscon AZ, USA)).

Interpretation was carried out by a specialized pathologist (JC). Tumor cell membrane Trop-2 expression was categorized based on an IHC score (H-score) computed by multiplying the percentage of stained tumor cells with their intensity (0= no staining, 1= mild staining, 2= moderate staining, 3= strong staining). The following Trop-2 expression categories were used: H-score 0 to <100: Trop-2 low; H-score 100-200: Trop-2 medium; H-score >200 to 300: Trop-2 high.

Statistical analysis

Survival curves were estimated using the Kaplan-Meier method and compared with a log-rank test, and cox proportional hazard model was used to evaluate the association of survival outcomes with continuous variable. Associations between continuous and categorical variables were evaluated using non-parametric tests (Wilcoxon–Mann–Whitney or Kruskal–Wallis tests). P values of less than 0.05 were considered statistically significant. All analyses were performed using R software version 4.1.0.

Results

Patients

A total of 495 patients meeting the inclusion criteria and with sufficient quality RNA extraction were included in this study. Demographic and clinical characteristics of the population are summarized in Table 1. Median age was 63.1 years (range 34–84.6) and 54% were male.

OS was available for the entire cohort and DFS for 442 patients (89.3%). At a median follow-up of 66.1 months, median OS was 32.0 months (95% confidence interval (CI), 26.8 – 34.6 months) and median DFS was 14.2 months (95% CI, 12.5 – 16.6 months).

Trop-2 mRNA expression

The association of Trop-2 mRNA expression to OS was first evaluated using its continuous expression. Fig. 1A shows the univariate association of Trop-2 with OS, and the multivariate association including margin status, node invasion status, clinical center, and tumor size as stratification factors.

Table 1 Demographic and clinical characteristics of the cohort.

		Median (range)	
		N	%
Age (years)		63.1 (34 – 84.6)	
Sex	Male	269	54
	Female	226	46
Differentiationgrade	Well	194	39
	Moderate	193	39
	Poor	74	15
	Unknown	34	7
T stage	1	96	19
	2	232	47
	3	137	28
	Unknown	30	6
N stage	0	120	24
	1	235	48
	2	119	24
	Unknown	21	4
Margin status	R0	367	74
	R1	102	21
	unknown	26	5
VascularInvasion	Negative	137	28
	Positive	303	61
	unknown	55	11
NeuralInvasion	Negative	86	17
	Positive	352	71
	unknown	57	12

After splitting by median expression, OS of patients with low Trop-2 expression was compared to patients with high Trop-2 expression (Fig. 1B). A similar comparison was done between patients with expression values below first quartile or above third quartile (Fig. 1C). In all these comparisons, Trop-2 mRNA expression was not associated to OS. The same approach, using continuous Trop-2 expression, dichotomizing on median or comparing first and fourth quartile, showed no significant association of Trop-2 mRNA expression with DFS (Additional file 1, Fig. S1).

The expression of Trop-2 was then compared between stages (T1 vs T2 vs T3), tumor differentiation (well, moderate, and poorly differentiated), neural invasion status (positive vs negative), resection margin (R0 vs R1), and vascular invasion (positive vs negative). Trop-2 expression values were not significantly different in any of these subgroups, showing an overall high expression value (Additional file 2, Fig. S2).

To further compare the expression of Trop-2 between disease stages, we next collected the concomitant biopsies of 26 primary PDAC and their corresponding liver metastasis and generated the paired transcriptomic profiles. The paired primary-metastatic measure of Trop-2 expression showed no significant differences between disease stage (Fig. 2), demonstrating a maintenance of high Trop-2 expression during distant dissemination.

The mutational status of driver genes (*KRAS*, *TP53*, *SMAD4*) was available for 266 patients (54%). Wild-type *KRAS* and wild-type *TP53* tumors had a slightly lower Trop-2 mRNA expression while no association was observed with *SMAD4*

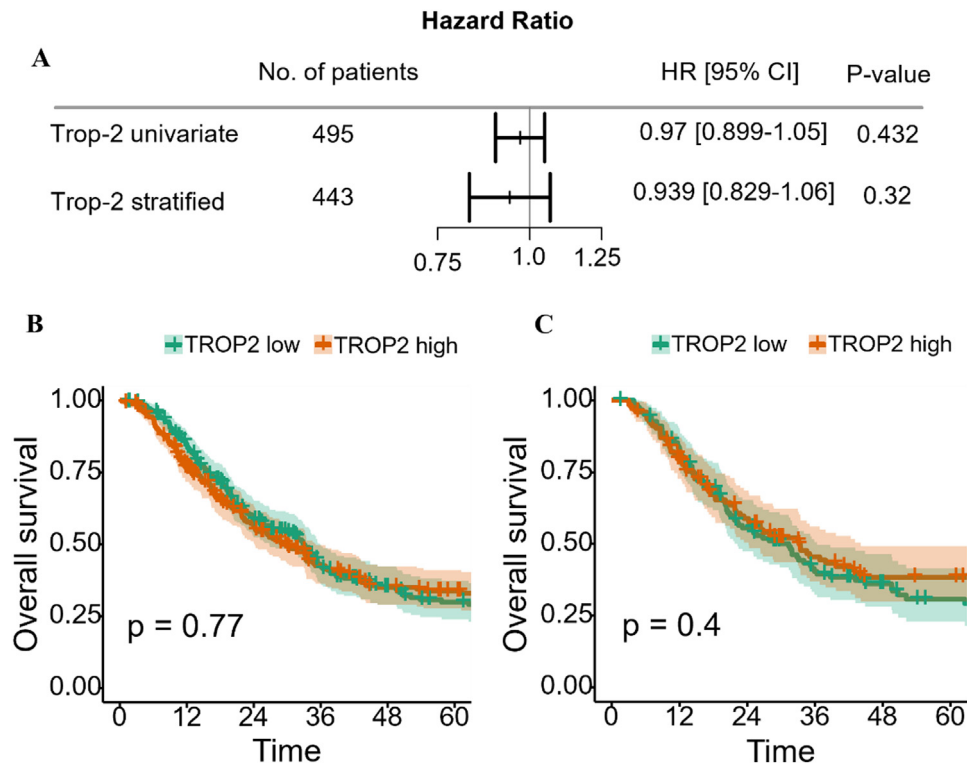


Fig. 1 Overall survival according to Trop-2 mRNA expression as a continuous variable (A), dichotomized on median expression (B) or comparing first and fourth quartile (C).

mutational status (Fig. 3). As the results suggested Trop-2 as a ubiquitous marker of PDAC tumor cells, the expression of Trop-2 was associated to variant allele frequency (VAF) of either *KRAS* or of the average VAF of all mutated genes for each patient, used as surrogates for tumor cellularity, showing a significant correlation in both cases (Additional file 3, Fig. S3).

Trop-2 protein expression by IHC

Trop-2 protein expression was evaluated by IHC in 50 patients. Overall, Trop-2 staining on tumor cells was predominantly membranous with fainter cytoplasmic expression (Fig. 4).

In the tumor, only tumor cells displayed a Trop-2 staining (i.e no stromal cells). When normal pancreatic tissue was

evaluable, Trop-2 staining was observed in normal ductal epithelial cells with lower intensity compared to tumor cells, while pancreatic islets showed no Trop-2 expression. Using H-score categorization, Trop-2 membranous expression was assessed as high, medium and low in 30%, 68%, and 2% of tumor samples, respectively. In all but 2 samples, 100% of tumor cells harbored at least low intensity Trop-2 staining.

Tumors with a high IHC score had a significantly higher Trop2-mRNA expression compared to low/medium tumors ($p=0.0064$). No association of Trop-2 IHC score (high vs medium/low) with OS (HR 1.456, 95%CI [0.6866 – 3.146]) (Additional file 4, Fig. S4) nor with any pathological features including nodal status, differentiation grade, vascular and perineural invasion, and margin status (Additional file 5, Table S1) was observed.

Trop-2 IHC categorization (low/medium vs high) was used to define a mRNA expression cut-off correlated to protein expression score in the subgroup of patients assessed by IHC. This cut-off was then applied to the entire cohort ($n=495$) to dichotomize low vs high Trop-2 mRNA expression, showing no association with OS (Additional file 6, Fig. S5).

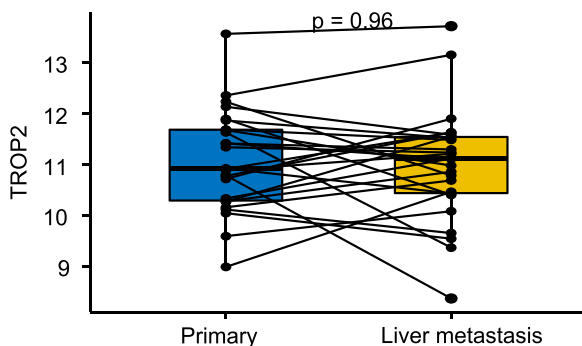


Fig. 2 Trop-2 mRNA expression in 26 paired primary tumor and liver metastasis.

Discussion

Trop-2 has become a tumor marker of great interest due to its recently demonstrated therapeutic implications in TNBC and several tumor types [16,21]. In this study, we evaluated Trop-2 expression both at the protein and transcriptomic levels in a large multicentric cohort of about 500 resected

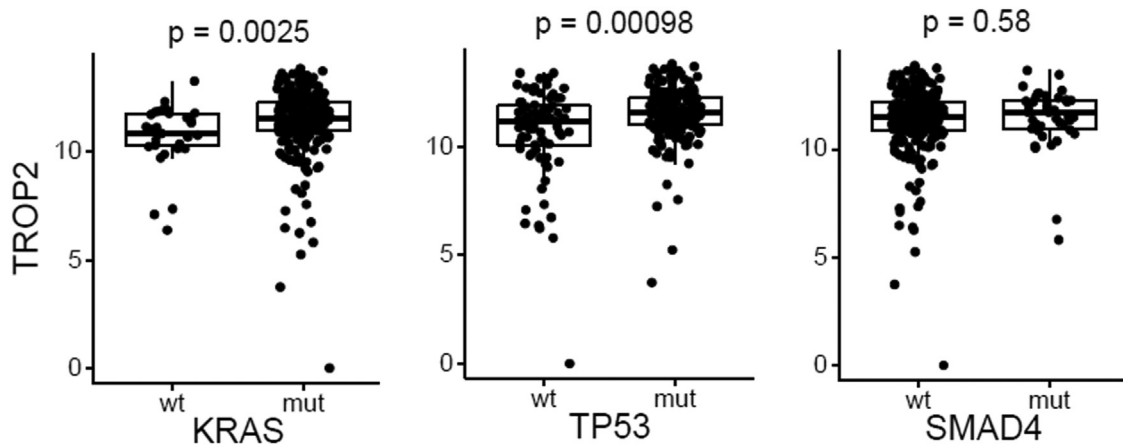


Fig. 3 Trop-2 mRNA expression according to *KRAS*, *TP53* and *SMAD4* mutational status (n=266).

PDAC tissues, demonstrating the overall high expression of Trop-2 in the vast majority of PDAC.

Previous studies in several tumor types collectively showed the association of Trop-2 protein overexpression assessed by IHC with worse survival outcomes and pathological features [15]. Of these, two specifically investigated PDAC tumors among which Trop-2 overexpression, defined as an intermediate or high IHC score, was reported in 55–60% of cases and associated with lower OS, DFS, and higher nodal invasion compared to samples with low or null expression [28,29].

Our IHC analysis showed conflicting results with a medium or high Trop-2 staining score observed in 98% of patients. To allow comparisons with recent high-quality studies, we chose to use the same grading system (H-score) used in the biomarker analysis of the phase III ASCENT trial [32], which differed from the one used in previous studies of PDAC. However, most samples in our cohort (96%) harbored a positive staining (weak or greater) in 100% of tumor cells which would have been categorized as an overexpression according to previous studies' classification. In the study by Mao et al.

[29], Trop-2 protein expression was assessed in tumor cells' cytoplasm and in the tumor stroma whereas in our work, as in most studies, IHC scoring was based on Trop-2 membranous staining which could explain the observed discrepancy. Such methodological issue was not present in the study by Fong et al. [28] which also assessed membranous staining in 197 patients, possibly pointing toward the smaller number of samples included in our IHC analysis (n=50), or the different antibodies used, as reasons for differing results. However, the staining pattern observed in tumor and healthy cells was in line with previous descriptions and the IHC score was significantly correlated with mRNA expression, demonstrating the consistency of our results. Moreover, the rabbit monoclonal antibody used in this work (clone EPR20043, ab214488, Cambridge, UK) has been evaluated and proven as a valid option in several recent studies in glioblastoma, lung or skin cancer [33–35]. Therefore, further studies will be needed to clarify Trop-2 protein expression pattern in PDAC.

The prognostic value of Trop-2 overexpression in previous studies was demonstrated comparing tumors with no/low to those with medium/high Trop-2 expression, a comparison that was not feasible in this work as almost all samples harbored medium or high Trop-2 IHC score [15]. When comparing samples with medium or high Trop-2 expression, no association neither with OS nor with pathological features was observed. While most studies only categorized Trop-2 expression in a dichotomous manner (no/low vs medium/high), a few did compare medium to high Trop-2 expression showing, in line with our results, similar survival outcomes [32,36].

Also at the transcriptomic level, no association of Trop-2 mRNA expression with OS nor DFS was observed in our cohort, either considering its continuous expression or different low versus high Trop-2 categories. Moreover, Trop-2 mRNA expression was maintained between paired primary and metastatic lesions and no association was evidenced with any clinical or pathological features, showing a consistently high expression value across all subgroups. Its expression was significantly correlated only to tumor cellularity as evaluated by either *KRAS* or all mutations VAF.

Altogether, these results strongly suggest Trop-2 overexpression, both at the protein and transcriptomic level, as a

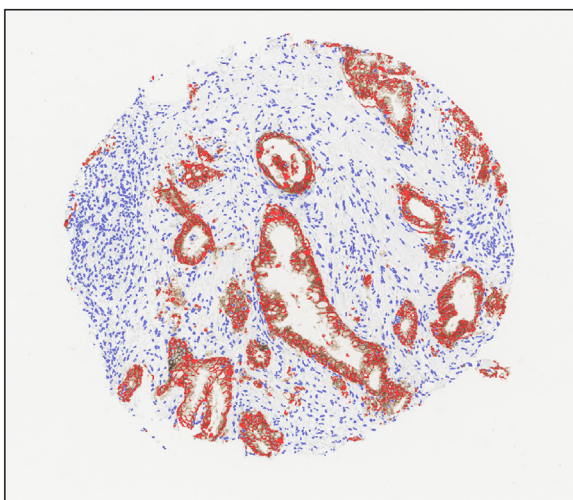


Fig. 4 Immunohistochemistry using Trop-2 directed antibody showing positive staining of all PDAC tumor cells.

ubiquitous marker of PDAC tumor cells. However, *KRAS* and *TP53* mutations were associated with slightly higher Trop-2 mRNA expression values, suggesting that, despite an overall high expression, distinct tumor biology across PDAC subgroups might be associated to tenuous variations in Trop-2 mRNA expression. The association of low Trop-2 mRNA expression and wild-type status of *KRAS* and *TP53* may also reflect the increased probability of not detecting a mutation in samples with low cellularity.

In contrast with previous studies demonstrating the prognostic value of Trop-2 protein overexpression by comparing tumors with low/null vs medium/high staining, we showed no association with survival when comparing low/medium vs high Trop-2 expression in this study. This can support the hypothesis that among Trop-2 expressing PDAC, the degree of overexpression is of limited clinical relevance.

Even though the predictive value of Trop-2 expression level for the efficacy of targeted agents remains to be comprehensively assessed, the biomarker analysis of the phase III ASCENT trial recently suggested an association of Trop-2 IHC score with SG' efficacy in TNBC. Among patients treated with SG, those with a low IHC score (18%) tended to have lower PFS and OS (2.7 and 9.3 months, respectively) compared to medium (5.6 and 14.9 months, respectively) and high (6.9 and 14.2 months, respectively) Trop-2 subgroups [32]. Thus, our results showing a medium/high Trop-2 expression in almost all PDAC cases argue for an in-depth clinical evaluation of Trop-2 targeted therapeutic options in PDAC patients.

Beyond ADCs, other Trop-2 targeted strategies are being investigated which could further extend the possibilities for improving patients' outcomes. Among these, Trop-2 has demonstrated potential for cancer detection and monitoring as an immunoPET target [37], while Cubas et al. [38] reported a strong immune activation and infiltration in PDAC murine models after treatment with virus-like particles incorporating murine Trop-2, suggesting a potential for combining Trop-2 targeted therapies with immunotherapeutic approaches.

The strength of this study lies both in the combined transcriptomic and protein analysis, the large number of patients analyzed for Trop-2 mRNA expression, and the paired evaluation of primary and metastatic lesions in a subset of patients which suggest, as no difference was observed according to disease stage, that our results are likely to be extrapolated to the population of metastatic PDAC patients. On the other hand, the lack of IHC evaluation in the entire cohort limits the interpretation of the protein analysis. Moreover, the different antibodies used for IHC analysis may have made it difficult to compare this study with previous ones, but the correlation with mRNA reinforces the value of our results.

Conclusion

In this study, we assessed Trop-2 expression both at the transcriptomic and protein level in a large cohort of PDAC patients, showing an overall high expression in the vast majority of cases. No significant association with tumor

features or survival outcomes was observed comparing different levels of Trop-2 overexpression. Altogether, our results suggest Trop-2 overexpression as a ubiquitous marker of PDAC tumor cells and thus a promising therapeutic target to evaluate in these patients.

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Declaration of Competing Interest

The authors declare no competing interests in relation to the work described at the exception of the research grant from Daiichi-Sankyo.

CRedit authorship contribution statement

L. Mas: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **J. Cros:** Conceptualization, Resources, Data curation, Writing – original draft, Writing – review & editing. **M. Svrcek:** Conceptualization, Resources, Writing – review & editing. **J.L. Van Laethem:** Conceptualization, Resources, Writing – review & editing. **J.F. Emile:** Conceptualization, Resources, Writing – review & editing. **V. Rebours:** Conceptualization, Resources, Writing – review & editing. **R. Nicolle:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **J.B. Bachet:** Conceptualization, Resources, Data curation, Writing – original draft, Writing – review & editing.

Acknowledgments

Ethics approval and consent to participate:

This study was approved by the appropriate regional institutional review board (Comité de Protection de Personnes Ile de France IV, N° IRB 00003835, Ref 2010/01 NICB and 2014/59 NICB).

According to French ethical law, patient active consent is not required for this type of retrospective non interventional study (Jarde law 2012). Instead the law requires that patients are informed by postal mail of the study and can ask to be withdrawn from it. We complied with French ethical standards as guaranteed by the IRB approval (Comité de Protection de Personnes Ile de France IV, N° IRB 00003835, Ref 2010/01 NICB and 2014/59 NICB).

Availability of data and materials

Data are available from the corresponding author (Prof Jean-Baptiste Bachet, Email: jean-baptiste.bachet@aphp.fr) upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clinre.2023.102108](https://doi.org/10.1016/j.clinre.2023.102108).

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