Liquid biopsy to track plasma kallikrein-activated TGF-β associates with resistance to combined immunotherapy and radiotherapy in metastatic pancreatic cancer

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BACKGROUND

- Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest malignancies with poor response to immune checkpoint inhibitors (ICIs)
- A major barrier to an effective anti-tumor immunity is the immunosuppressive tumor microenvironment (TME), in which transforming growth factor-beta (TGF-β) plays a central role
- TGF-β is produced as a latent complex with latency-associated protein (LAP) and requires proteolytic cleavage for activation
- Plasma kallikrein (PLK)-mediated cleavage of LAP releases bioactive TGF-β enabling receptor engagement and signaling
- Biomarkers reflecting this TGF-β activation in the TME may provide insights into treatment response

- Here, we evaluated a serological biomarker of PLK-activated TGF-β (TGF-β-LAP) in patients with treatment-refractory metastatic PDAC receiving stereotactic body radiotherapy (SBRT) combined with ICIs in the CheckPAC trial

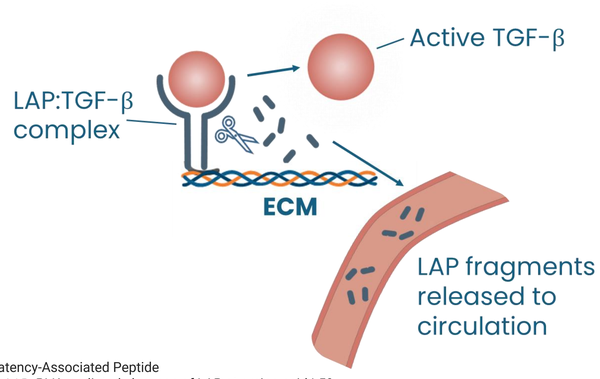
METHODS

Phase II trial
Treatment refractory, Metastatic PDAC
N=84

Arm A: SBRT 15 Gy + Nivolumab
N = 41

Arm B: SBRT 15 Gy + Nivolumab + Ipilimumab
N = 43

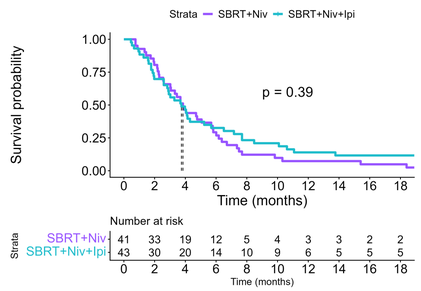
SBRT: Stereotactic body radiotherapy



LAP: Latency-Associated Peptide
TGF-β-LAP: PLK-mediated cleavage of LAP at amino acid L59

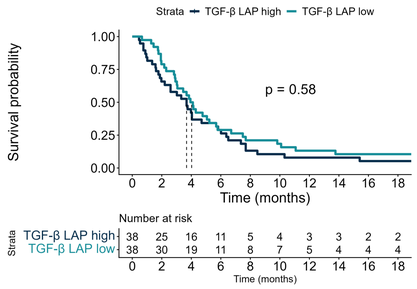
RESULTS

Baseline - Treatment arm



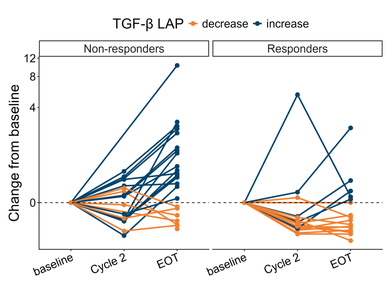
Similar OS outcome in both arms

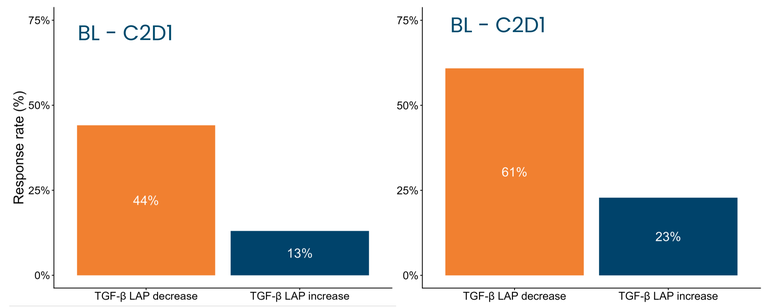
Baseline - TGF-β LAP



Baseline TGF-beta LAP did not associate with OS

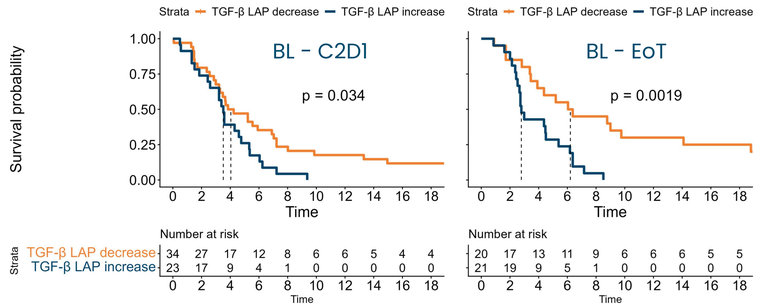
TGF-β LAP change predicts treatment response (ORR)





Patients with progressive disease increase in TGF-β-LAP during treatment as early as cycle 2 (p=0.02), whereas all patients with partial or complete response had stable or declining TGF-β-LAP levels at cycle 2

TGF-β LAP change predicts overall survival outcome



Cox regression analysis for risk of death (OS)

TGF-β-LAP	HR (95% CI)	p value
increase vs. decrease (BL - C2D1)	1.84 (1.04-3.26)	0.035
increase vs. decrease (BL - EoT)	3.13 (1.48-6.64)	0.003

BL: Baseline; C2D1: Cycle 2, Day 1; EoT: End of Treatment; HR: Hazard Ratio; CI: Confidence Interval.

TGF-β-LAP increase from baseline to C2D1 and EoT associates with shorter OS

CONCLUSION

- Changes in circulating TGF-β-LAP associate with clinical outcomes in patients with metastatic PDAC that are treated with SBRT and ICIs whereas pre-treatment levels were not.
- Early increases (C2D1) in TGF-β-LAP identify patients with treatment resistance, supporting the use as a pharmacodynamic biomarker of immune suppression and (lack of) therapeutic response.
- These findings warrant further investigation of TGF-β-LAP as a biomarker for patient stratification and monitoring in immunotherapy-based treatment strategies and in trials targeting the TGF-β pathway

TGF-β LAP

Biological Relevance:
Reflects protease-mediated activation of latent TGF-β in tissue to capture locally occurring TGF-β signaling in a liquid biopsy

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