Lesion-resolved multimodal profiling of PRRT resistance in metastatic well-differentiated neuroendocrine tumors

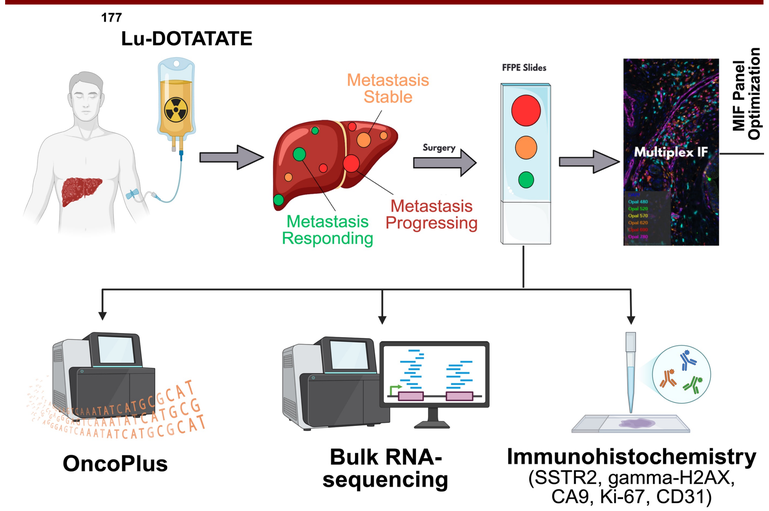
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Background – Why do some metastases escape PRRT?

^{177}Lu-DOTATATE prolongs PFS in SSTR2^{+} Neuroendocrine Tumors (NETs), but response rates remain suboptimal and patients progress within 2-3 years. Here, we explore lesion-resolved multimodal profiling from small bowel and pancreatic NET metastases to uncover mechanistic explanations for PRRT resistance.

Methodology – 13 patients · 58 lesions · 5 data layers



SSTR2 Immunohistochemistry – SSTR2 is retained

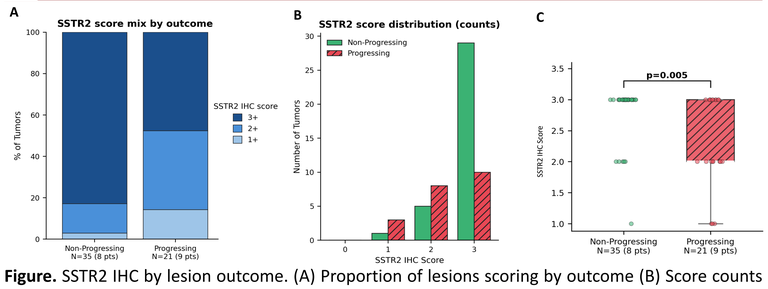


Figure. SSTR2 IHC by lesion outcome. (A) Proportion of lesions scoring by outcome (B) Score counts (C) SSTR2 score in non-progressing (N = 35, n = 8) vs progressing (N = 21, n = 9) lesions, two-sided Mann–Whitney p = 0.005 (post-PRRT lesions only, p = 0.007).

OncoPlus DNA Sequencing and IHC – No tumor-intrinsic drivers

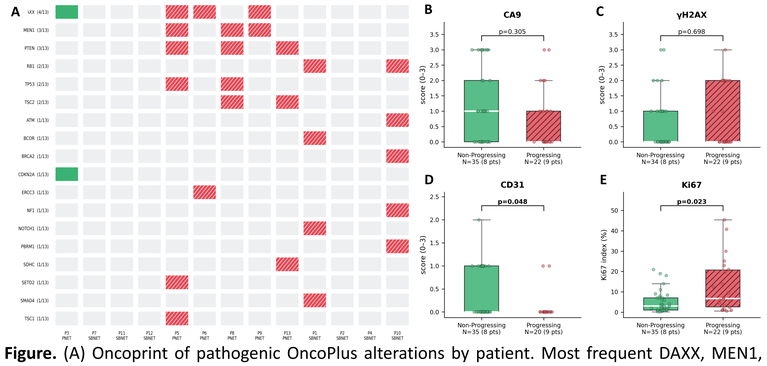


Figure. (A) Oncoprint of pathogenic OncoPlus alterations by patient. Most frequent DAXX, MEN1, and PTEN. (B) CA9 (p = 0.305), (C) γH2AX (p = 0.698) and (D) CD31 (p = 0.048) IHC scores (0–3) and (E) Ki-67 index (p = 0.023), non-progressing vs progressing lesions across all 58 lesions.

Bulk RNA-Seq – Each tumor subtype has distinct transcriptional pathways



PNET · 9 lesions

- Non-progressing keep β-cell (IAPP, NKX6-1) and vascular/ECM programs
- 33/35 endothelial genes higher

SBNET · 14 lesions

- Progressing gain G2M/E2F proliferation
- PROM1↑ SOX8↓: less differentiated

Figure. Bulk RNA-seq, 23 liver metastases (11 patients). Top 10 genes per direction; green = higher in non-progressing, red = higher in progressing (limma-voom, FDR < 0.05, |FC| > 1.5).

Multiplex IF – Progressing lesions hold more CD8^{+} T cells, not fewer

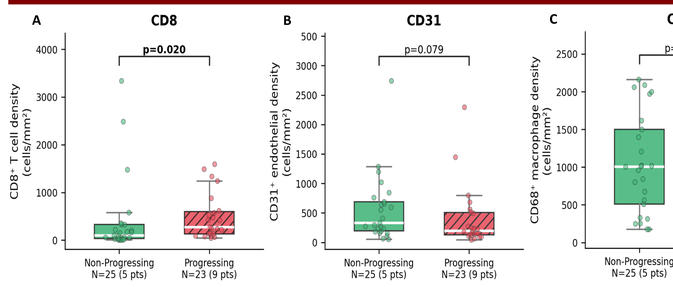


Figure. 6-plex mIF, 48 post-PRRT lesions (25 non-progressing, 5 patients; 23 progressing, 9 patients); medians NP → P. Strongest in SBNET (453 vs 60/mm², p = 0.012); held in liver metastases (p = 0.019).

Multiplex IF – CD8^{+} T cells lose their clusters and sit closer to suppressive cells

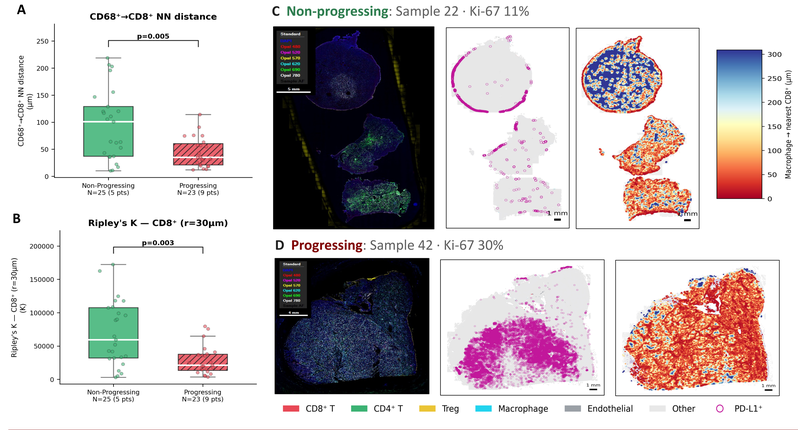


Figure. (A) Median macrophage-to-nearest-CD8^{+} distance and (B) Ripley's K for CD8^{+} at r = 30 µm per lesion, non-progressing (N = 25) vs progressing (N = 23). (C–D) Whole-slide multispectral image, phenotype map with PD-L1^{+} cells outlined, and macrophages colored by distance to the nearest CD8^{+} (blue far, red close).

Multiplex IF – Progressing lesions have a PD-L1-enriched niche

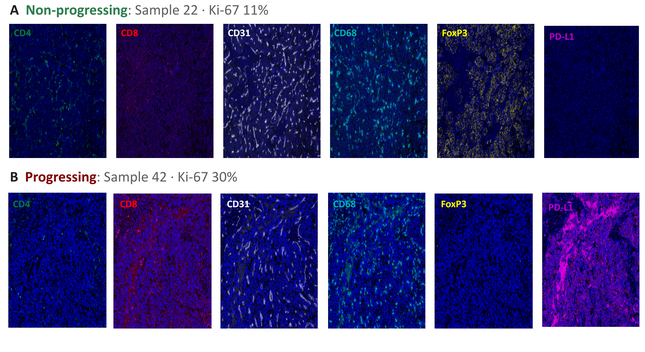


Figure. Representative mIF of post-PRRT PNET liver metastases: (A) non-progressing, Sample 22 (Ki-67 11%); (B) progressing, Sample 42 (Ki-67 30%). CD4, CD8, CD31, CD68, FoxP3, PD-L1 (C-D) PD-L1 quantification

Heterogeneity – Same patient, different immune ecosystems

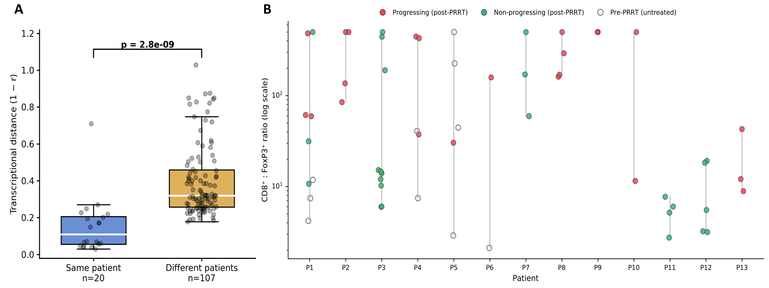
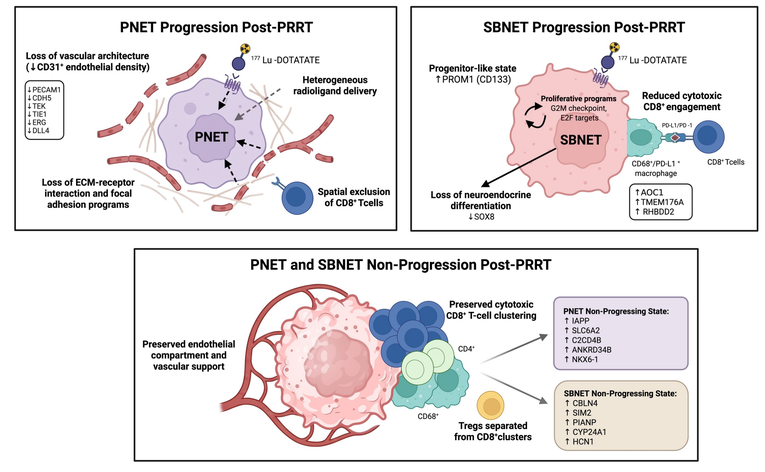


Figure. (A) Pairwise transcriptional distance (1 − Pearson r) between lesions from the same patient (20 pairs) vs different patients of the same subtype (107 pairs); Mann–Whitney p = 2.8 × 10^{-9}. (B) CD8^{+}:FoxP3^{+} ratio for each lesion (log scale), grouped by patient

Conclusion – Proposed mechanisms of resistance



Future Directions – Clinical relevance of our findings

Our finding	Strategy to test	Example agents or tools	Current evidence
SSTR2 retained in progressing lesions	More potent SSTR-targeted radioligands after ^{177}Lu failure	**^{212}Pb-DOTAMTATE ^{225}Ac-DOTATATE (RYZ101)**	ALPHAMEDIX-02: ORR 34.6% (9/26) after prior PRRT; ACTION-1 phase 3
PD-L1^{+}, T-cell-rich but disorganized progressing lesions	Add PD-1/PD-L1 blockade to PRRT	**Nivolumab Pembrolizumab Atezolizumab**	Alone, ORR 3.7% in NETs (KEYNOTE-158); ^{177}Lu-DOTATATE + nivolumab tolerable (phase I, lung NETs)
Vascular and ECM programs lost in progressing PNET	Vascular priming before or with PRRT to aid delivery and T-cell access	**Cabozantinib Sunitinib Bevacizumab**	Cabozantinib approved in pNET/epNET (CABINET); atezolizumab + bevacizumab ORR 15–20%; sequencing with PRRT untested

Acknowledgments

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