

FOLR1 Expression Defines Pan-Cancer Subgroup of Tumors with Specific Transcriptomic Profile

Andrew Ip¹, Ahmad Charifa², Sally Agersborg², Deena Graham¹, Donna McNamara¹, Merieme Klobocista¹, Andrew Pecora¹, Andre Goy¹, Maher Albitar¹, Martin Gutierrez¹
¹John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ ² Genomic Testing Cooperative, Lake Forest, CA



Background

- **Mirvetuximab soravtansine** is an antibody–drug conjugate approved for treating advanced platinum-resistant ovarian cancer.
- Its **efficacy is linked to high expression of folate receptor alpha (FR α)**, encoded by the FOLR1 gene.
- **Treatment eligibility** requires $\geq 75\%$ of tumor cells to be **FR α -positive by immunohistochemistry (IHC)**.
- This study defines the **FOLR1 RNA level** that corresponds to **very high FR α expression ($\geq 75\%$ by IHC)** in ovarian cancer.
- It compares the **transcriptomic profile of FOLR1-H (high expression)** cases to those with very low FR α expression (FOLR1-L).
- The study also examines the presence of a **similar FOLR1-H signature in other cancer types**.

Methods

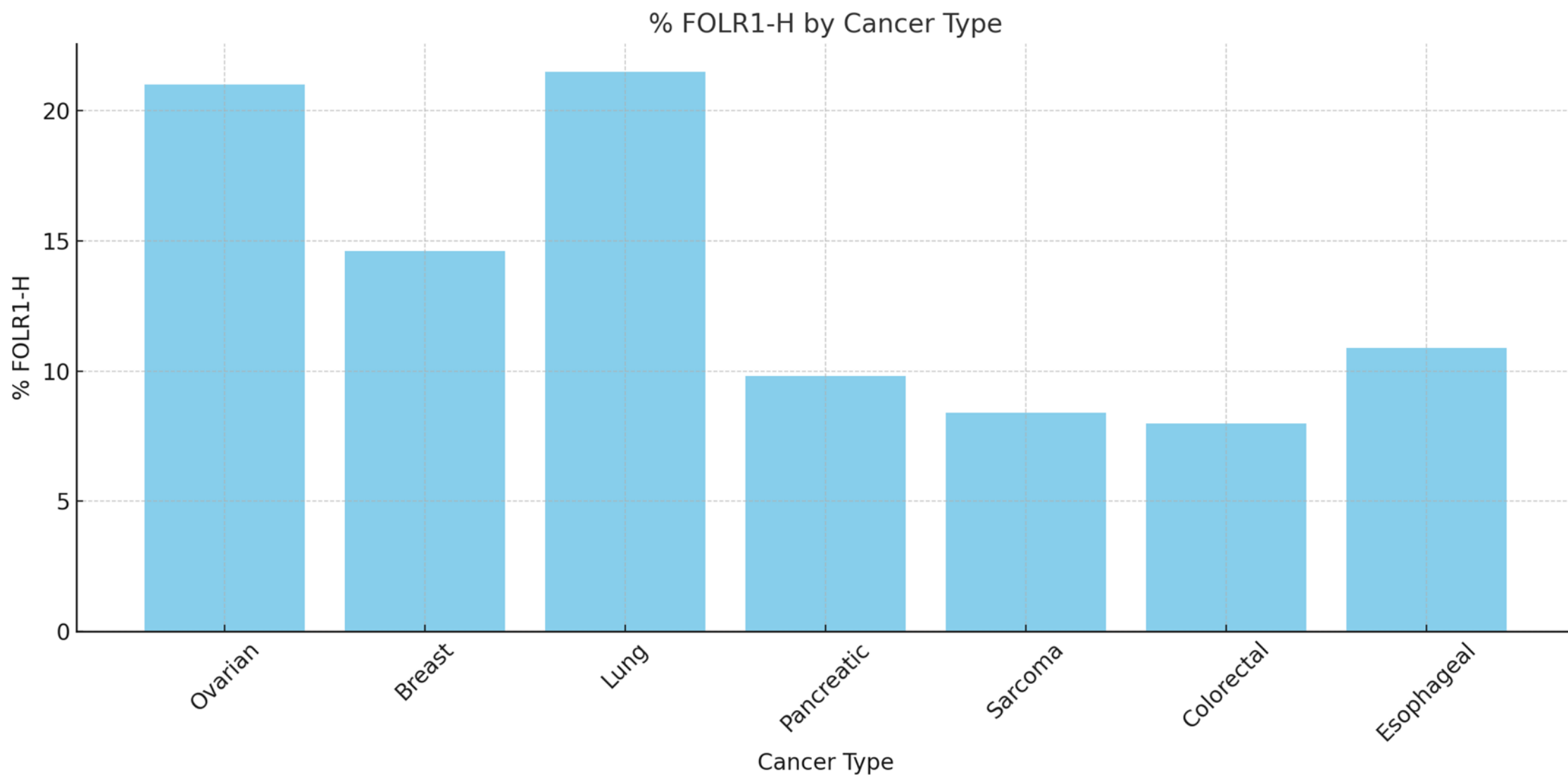
- **RNA was extracted** from **1,450 solid tumor FFPE** samples.
- **Targeted RNA sequencing** was performed using a panel of **1,600 genes**.
- **FR α protein expression** was evaluated in **49 ovarian cancer samples** using the **VENTANA FOLR1 RxDx IHC** assay.
- **RNA levels were correlated with IHC data** to determine high vs low FOLR1 RNA cases..

Results

Ovarian Cancer		Breast Cancer		Lung Cancer		Pancreatic Cancer		Sarcoma		Colorectal Cancer		Esophageal cancer	
Top highly expressed genes	-Log FDR	Top highly expressed genes	-Log FDR	Top highly expressed genes	-Log FDR	Top highly expressed genes	-Log FDR	Top highly expressed genes	-Log FDR	Top highly expressed genes	-Log FDR	Top highly expressed genes	-Log FDR
TROP2	Infinity	NTHL1	10	TROP2	Infinity	ACVRL1	6	NECTIN4	4	NECTIN4	9	ACVRL1	4
NECTIN4	Infinity	ACVRL1	9	NECTIN4	Infinity	ROR1	6	NTHL1	3	NTHL1	7	GALNT12	4
ROR1	Infinity	ROR1	8	ROR1	Infinity	AXIN2	5	SLC47A1	3	ACVRL1	7	NECTIN4	2
ROR2	Infinity	NECTIN4	5	ROR2	Infinity	NECTIN4	5	-	-	SLC47A1	5	-	-
ACVRL1	Infinity	ROR2	4	ACVRL1	Infinity	ROR2	4	-	-	ROR2	5	-	-
TROP2	Infinity	PRAME	3	NTHL1	Infinity	NTHL1	4	-	-	PRAME	4	-	-

Different cancer types of FOLR1-high showing **significant -Log₁₀FDR >2** (the logarithm (base 10) of the False Discovery Rate (FDR) as compared with FOLR1-Low subtype.

- **Cancers with high FOLR1 mRNA expression** represent a **distinct tumor subtype**.
- This subtype is characterized by **expression of embryonic cell surface markers: FOLR1, TROP2, NECTIN4, ROR1, ROR2**.
- The **pan-cancer overexpression** of these markers suggests a **shared underlying biology**.
- These tumors may **benefit from combination therapies** targeting multiple markers (e.g., **anti-FOLR1 + anti-TROP2 or anti-NECTIN4**).
- **Clinical trials exploring such combination treatments are justified.**



FOLR1-H was defined as **RNA expression ≥ 300 TPM**; correlating with $\geq 75\%$ of tumor cells to be FR α -positive IHC. **FOLR1-L** was defined as **RNA < 100 TPM**, correlating with very low FR α by IHC.