Abstract # 112

Pan-cancer association between increased iron utilization and poor prognosis highlights potential of transferrin receptor-targeting therapies in multiple tumor types

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BACKGROUND

The cell-surface transferrin receptor TFR1 imports iron-bound transferrin into cells via clathrin-mediated endocytosis.

Tumors require constitutive iron import to drive proliferation, and several studies establish TFR1 as a target able to facilitate intracellular delivery of cytotoxic therapeutic molecules.

Our own work previously revealed association between high expression of *TFRC*, the gene encoding TFR1, and high risk for poor outcome in diffuse large B-cell lymphoma (DLBCL). We showed therapeutic targeting of TFR1 in DLBCL results in significant anti-tumor benefit. Systematic analysis of *TFRC* expression as a prognostic marker across tumor types, however, has not been investigated.

METHODS

- Tissue samples underwent comprehensive molecular profiling at Caris Life Sciences. Analyses included next generation sequencing of DNA (592 Gene Panel, NextSeq, or whole exome sequencing, NovaSeq), RNA (NovaSeq, whole transcriptome sequencing, WTS) and immunohistochemistry.
- Overall survival (OS) was calculated from date of tissue collection to last contact from insurance claims data and employed Kaplan-Meier analysis by Wilcoxon statistics, with p<0.05 defined as significant.
- A Consensus Molecular Subtype (CMS) calling algorithm was developed using mRNA levels (transcripts per million; TPM).

RESULTS

In an all-tumor cohort (n= 93248), patients with higher TFRC expression (cutoff = median) had significantly worse OS. This was statistically significant in 23 individual tumor types (blue box). Drilling down further, TFRC adverse prognostic value was mainly driven by cohorts with larger number of samples in the database such as breast, NSCLC and CRC cancer types. Surprisingly, TFRC overexpression correlated with improved outcome in vulvar squamous cell carcinoma (VSCC).

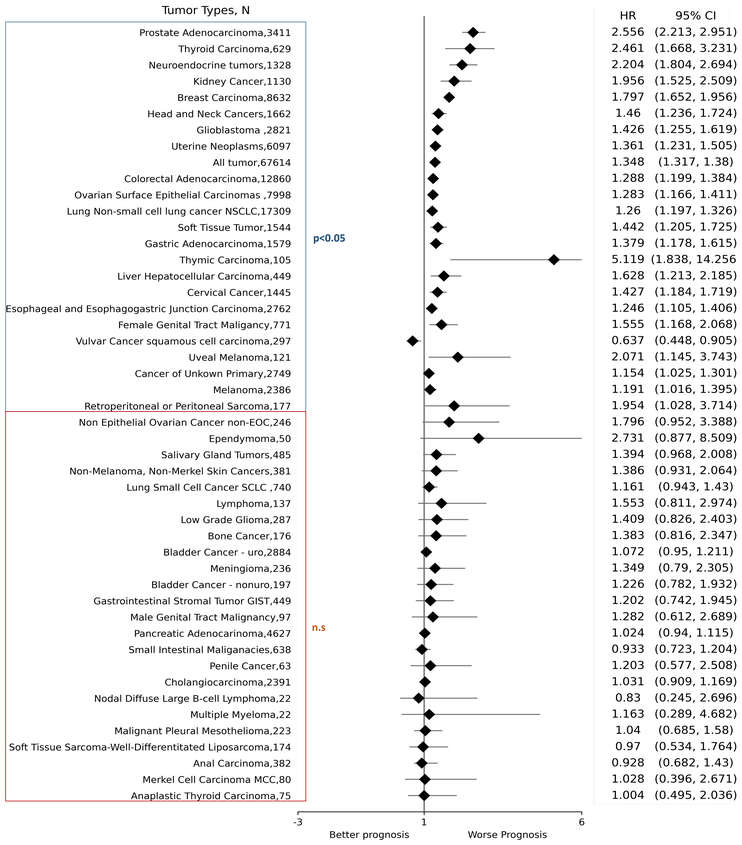
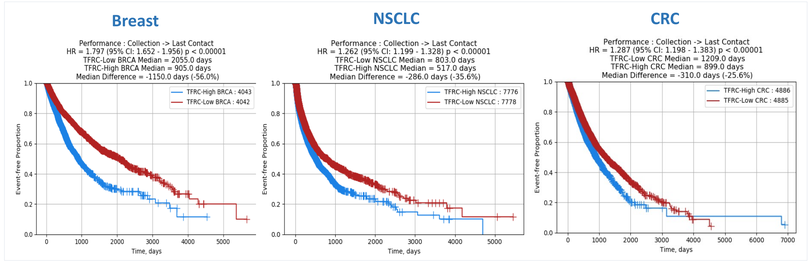


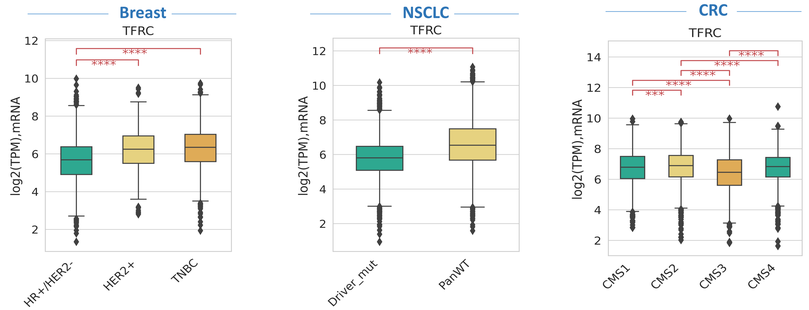
Figure 1. Prognostic value of TFRC expression in various of tumor types (blue box, p<0.05, red box, not significant).

Take home point: *TFRC* expression is prognostic across multiple tumor types

- TFRC was found to be most prognostic in breast cancer with median OS 1139 days in pts with high vs 3230 days in pts with low TFRC (HR= 2.556, 95% CI [2.213-2.951], p <0.00001).



- mRNA level of TFRC correlated with different molecular subtypes in breast cancer, with the most significant enrichment in TNBC; In NSCLC, TFRC were expressed less in tumors with well annotated driver alterations (mutation of EGFR, ALK, ROS1, KRAS; fusion of NTRK1/2/3, NRG1, RET). Interesting, in CRC, TFRC was the highest in CMS2 subtype (canonical), followed by CMS4 (mesenchymal), CMS1 (immune) and the lowest in CMS3 (metabolic) subtype.



DISCUSSION

- Our study is the first to combine modern molecular profiling with a large cohort of clinical tissue samples to reveal a prognostic role for *TFRC* expression in a variety of solid tumor types.
- We found *TFRC* overexpression to be prognostic in a large proportion of histologies, though surprisingly associated with improved OS in VSCC.
- A number of TFR1-targeting therapeutic agents are currently at various states of pre-clinical and clinical development and warrant further investigation in disease cohorts identified from our study.