Evaluation of Metabolic Dysregulation, Endocrine Therapy Outcomes, and Tumor Biology in HER2-/HR+ Breast Cancer using a Multi-Omic, Real-World Analysis

J. Hundal[1], R.N. Plagens[2], A. Elliott[2], G. Sledge[2], C. Travaline[3], S. Graff[4], M. Lustberg[5], M. Vasekar[3], J.P. Leone[6*]

[1]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [2]Caris Life Sciences, Irving, TX, [3]Hershey Cancer Institute, Penn State, Hershey, PA, [4]Legorreta Cancer Center, Brown University, Providence, RI, [5]Yale Cancer Center, Yale University, New Haven, CT, [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, *corresponding author

Introduction

•Metabolic dysfunction, including hyperglycemia (HG) and type 2 diabetes (T2DM), is increasingly common in breast cancer (BC) patients

•Prior evidence suggests metabolic comorbidities may influence tumor biology, endocrine therapy response, and survival in hormone-receptor-positive (HR+) disease

•Knowledge gap: How HG/T2DM diagnosis (Dx) affects endocrine therapy (Tx) outcomes and multi-omic tumor characteristics in real-world HR+/HER2- BC

Objective

To integrate *real-world clinical outcomes* and *multi-omic tumor profiling* to evaluate the impact of HG/T2DM on endocrine Tx effectiveness and tumor molecular features

Methods

•Retrospective analysis of 2,074 HR+/HER2- BC patients starting first-line aromatase-inhibitor or fulvestrant (AI/Fulv) within 100 days of biopsy with profiling performed at Caris Life Sciences

•Cohorts defined using ICD-10 codes and treatment history of insulin, metformin, and/or GLP-1 receptor agonists from claims data:

(1) No HG/T2DM (without Ins/Met/GLP) (n=1119)

(2) HG/T2DM without Ins/Met/GLP (n=398)

(3) HG/T2DM with Ins/Met/GLP (n=557)

•Tumor profiling: NGS (whole-exome sequencing or 592-gene panel, whole-transcriptome RNA-seq), IHC

•Outcomes (inferred from claims):

• Overall survival (OS, start of AI/Fulv to last contact)

•Time on Tx (ToT, start of AI/Fulv to end of AI/Fulv)

•Statistics: Cox proportional hazards models, log-rank tests, Mann-Whitney U, and chi-square tests

Results

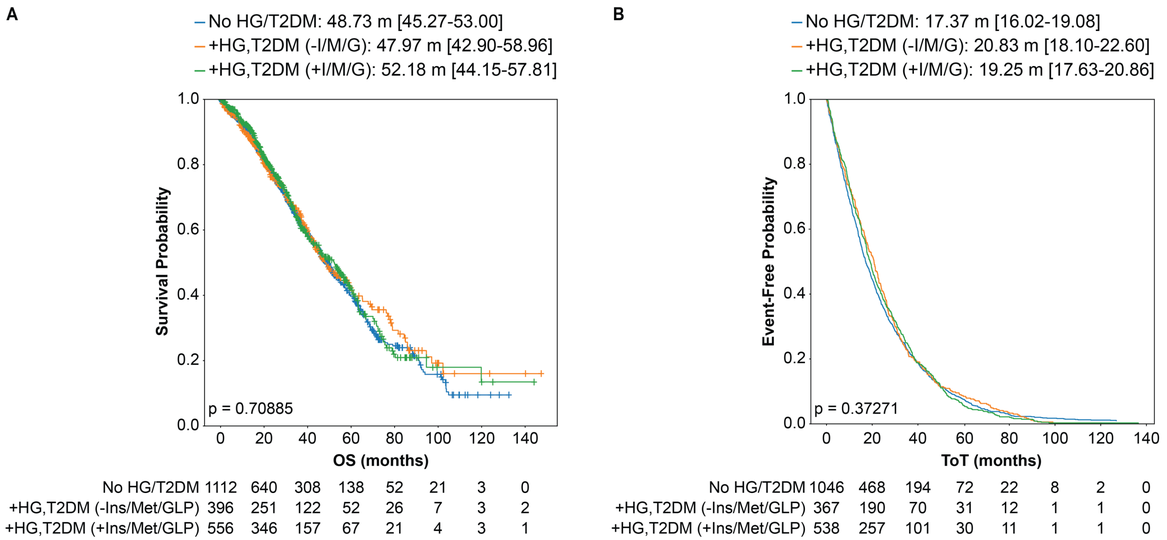


Figure 1. Outcomes between defined cohorts. Comparing OS **(A)** or ToT **(B)** between patients without history of HG or T2DM Dx or history of Ins, Met or GLP Tx to those with such Dx and/or Tx histories. Blue, cohort without Dx or Tx history; orange, cohort with Dx history but no Ins, Met, or GLP Tx history; green, cohort with HG and/or T2DM Dx and Ins, Met, and/or GLP Tx history

Table 1. Demographic and histological comparisons between cohorts without history of Ins/Met/GLP Treatments

Variable	Description	No HG/T2DM	+HG/T2DM	statistic	p-value
Age	Median age (range)	64.0 (23 - 90+)	70.0 (33 - 90+)	MWU	2.52E-17
Gender	Female	99.29% (1111/1119)	99.25% (395/398)	Fisher's Exact	1
	Male	0.71% (8/1119)	0.75% (3/398)		
Race*	White	62.91% (704/1119)	63.32% (252/398)	Chi-square	5.09E-09
	Unknown/Other	26.99% (302/1119)	15.83% (63/398)		
	Black or African American	7.95% (89/1119)	16.58% (66/398)		
	Asian or Pacific Islander	2.14% (24/1119)	4.27% (17/398)		
Ethnicity*	Not Hispanic or Latino	71.05% (795/1119)	80.9% (322/398)	Chi-square	3.23E-04
	Unknown/Other	22.97% (257/1119)	13.82% (55/398)		
	Hispanic or Latino	5.99% (67/1119)	5.28% (21/398)		
Histology	Ductal Carcinoma	47.9% (536/1119)	48.49% (193/398)	Fisher's Exact	0.095
	Carcinoma	24.04% (269/1119)	27.64% (110/398)		
	Adenocarcinoma	13.58% (152/1119)	10.3% (41/398)		
	Lobular Carcinoma	11.44% (128/1119)	10.05% (40/398)		
	Lobular and Ductal Carcinoma	0.8% (9/1119)	0.5% (2/398)		
	Other/Unclear	0.71% (8/1119)	0.5% (2/398)		
	Mucinous Adenocarcinoma	0.63% (7/1119)	0.5% (2/398)		
	Adenocarcinoma with Neuroendocrine Differentiation	0.36% (4/1119)	0.25% (1/398)		
	Non-Small Cell Carcinoma	0.18% (2/1119)	0.5% (2/398)		
	Papillary Carcinoma	0.18% (2/1119)	0.0% (0/398)		
	Micropapillary Adenocarcinoma	0.09% (1/1119)	0.0% (0/398)		
	Neuroendocrine Carcinoma	0.09% (1/1119)	0.0% (0/398)		
	Neoplasm	0.0% (0/1119)	0.75% (3/398)		
	Metaplastic Carcinoma	0.0% (0/1119)	0.25% (1/398)		
	Spindle Cell Carcinoma	0.0% (0/1119)	0.25% (1/398)		

**self-reported traits*

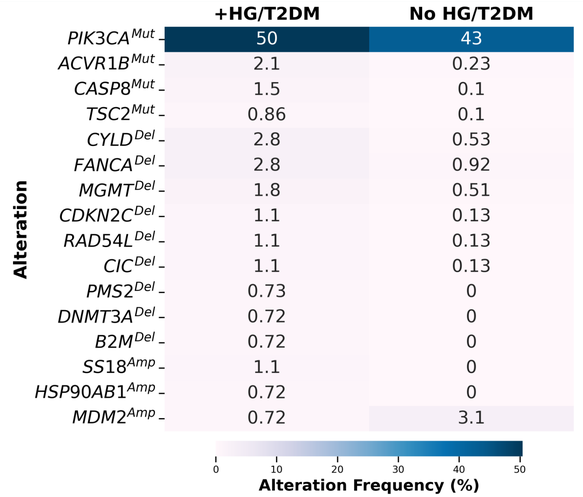


Figure 2. Alteration frequencies between patients with HG and/or T2DM vs patients without history of HG or T2DM. Comparing cohorts without history of Ins/Met/GLP Tx, genes with statistically significant differences ($p<0.05$) in alteration frequency between cohorts are shown. *Mut*, pathogenic or likely pathogenic mutation; *Del*, gene deletion; *Amp*, copy number amplification.

Conclusions

• HG/T2DM did *not* correlate with worse overall survival or shorter time on endocrine therapy

•Tumors from HG/T2DM pts demonstrate a slightly higher frequency of:

•*PIK3CA* mutations

•*HSP90AB1*, *SS18* amplifications

•*CYLD*, *B2M*, *CDKN2C* deletions

• Suggesting enhanced proliferative signaling and reduced immune activation

Future Directions

•Prospective studies integrating metabolic profiling and multi-omic tumor analysis

•Investigate the role of *PIK3CA*-driven signaling, immune dysregulation, and cell-cycle alterations

•Develop biomarker-driven, metabolically informed treatment algorithms