Exploring molecular profiles of **uterine** carcinosarcoma with alterations in the chromatin remodeling pathway

AM Wilhite[1], S Wu[2], J Xiu[2], RP Rocconi[1], BK Erickson[3], T Klc[3], J Lesnock[4], J Brown[5], T Herzog[6], R Holloway[7], WM Korn[2], M Powell[8], N Jones[1]

[1]University of South Alabama, Mobile, AL [2]Caris Life Sciences, Phoenix, AZ [3] University of Minnesota, Minneapolis, MN [4] Magee-Women's Hospital of UPMC, Pittsburgh, PA [5] Atrium Health, Charlotte, NC [6] University of Cincinnati, Cincinnati, OH [7] Advent Health Cancer Institute, Orlando, FL [8]Washington University, St. Louis, MO

2021 ASCO ANNUAL MEETING

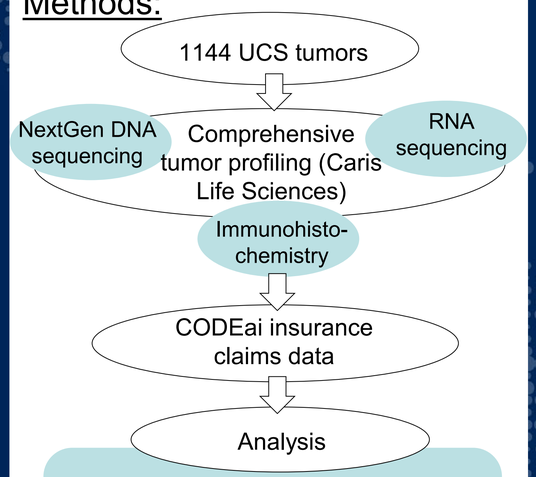
Background:

- Uterine carcinosarcomas (UCS) are rare tumors that account for less than 5% of all uterine malignancies and are high risk variant of endometrial adenocarcinoma
- Despite the identification of several clinicopathologic prognostic factors, more research is needed to determine the molecular features responsible for the aggressive behavior of this disease and identify therapeutic targets

Objective:

Compare molecular profiles of KMT2C mutated and wild type uterine carcinosarcoma tumors and explore treatment outcomes

Methods:



- Statistical significance determined by chi-square and Wilcoxon rank sum test.
- p values adjusted for multiple comparisons (q) to be <0.05
- Survival calculated using CodeAI data

Figure 1: Flowchart describing methods

Results:

Figure 2: Pathogenic KMT2C mutations, a gene in the chromatin remodeling pathway, were associated with improved median survival in UCS

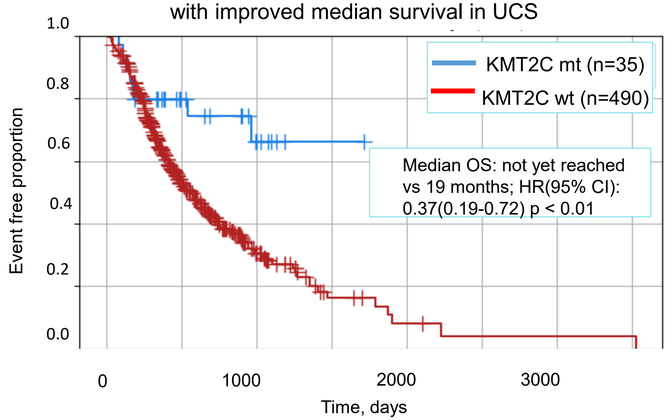


Figure 3. KMT2C mutated tumors had higher rates of IO therapy response markers.

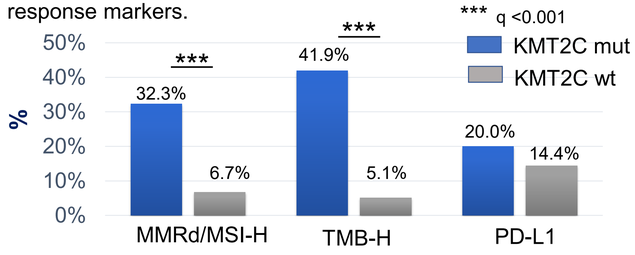


Table 1: KMT2C mutated tumors have distinct molecular profiles compared to wildtype tumors

	Molecular Alteration	KMT2C MT	KMT2C WT	Q value
Gene	JAK1	35.4%	3.6%	<0.001
	KMT2D	32.1%	6.9%	0.022
	POLE	25.8%	1.0%	<0.001
	DICER1	19.4%	2.0%	0.017
	ATM	16.1%	1.0%	0.015
	MAP3K1	13.8%	0.6%	0.032
Pathway	Chromatin Remodeling	100.0%	28.2%	<0.001
	WNT	38.7%	11.6%	0.012
	Base/ Nucleotide Excision Repair	29.0%	4.5%	<0.01
	HR Pathway	25.8%	6.1%	0.023
	DNA Damage Sensors	22.5%	3.9%	0.017
	Fanconi Anemia	12.9%	1.2%	0.039

Table 2: Sub-analysis of MMR proficient and microsatellite stable (MSS) tumors based on KMT2C: KMT2C mutated MSS tumors more commonly had JAK1 and POLE mutations, and mutations in the chromatin remodeling pathway.

	Molecular Alteration	KMT2C MT (%)	KMT2C WT (%)	Adjusted p-value
Pathway Gene	JAK1	23.8	0.86	<0.01
	POLE	23.8	1.07	<0.01
	Chromatin Remodeling	100	23.4	<0.001

Figure 4: MSS tumors with KMT2C mutations continued to show a higher likelihood of high TMB, but PD-L1 (SP142, cut-off ≥1, 1%) expression was similar.

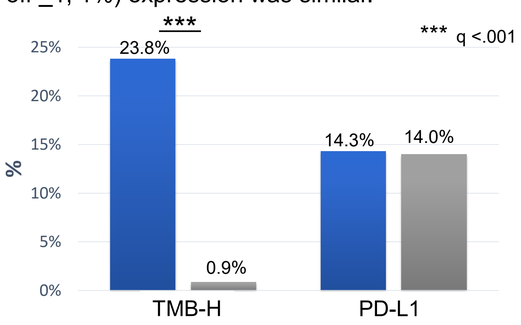
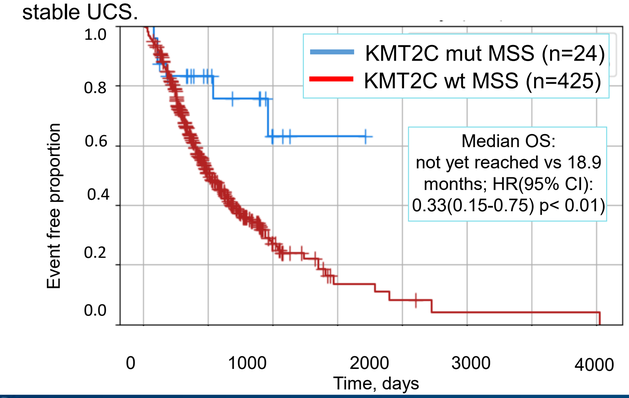


Figure 5: Pathogenic KMT2C mutations were associated with improved median survival in MMR proficient and microsatellite stable UCS.



KEY FINDINGS:

- Mutations in KMT2C correlate with improved OS in UCS
- KMT2C-mut tumors have distinct molecular profiles from WT
- Exhibit greater immunogenicity, with more frequent MSI-H and TMB-H
- **This suggests a potential role for Immune-oncology (IO) therapy.**