HER2 in uterine carcinosarcoma: Testing platforms and implications for targeted therapy

Navin Maredia, MD[1], Sharon Wu, PhD[2], Alex Farrell, PhD[2], Matthew Oberley,[2,] MD, PhD, Lauren Thomaier, MD[1], Nathaniel Jones, MD[3], Thomas Herzog, MD[4], Premal Thaker, MD[5], Matthew Powell, MD[5], Tenley Klc, MD[1], Britt Erickson, MD[1]

[1] University of Minnesota, Division of Gynecologic Oncology, Minneapolis, MN; [2] Caris Life Sciences; [3] Mitchell Cancer Institute, University of South Alabama; [4]University of Cincinnati Cancer Institute, University of Cincinnati, [5] Washington University School of Medicine

Background:

- Uterine carcinosarcomas (UCS) are rare, aggressive tumors with high recurrence and 5-year survival of only 18-39%.[1,2]
- HER2 is an emerging prognostic and therapeutic target in uterine cancer including UCS but optimal HER2 testing has not yet been established.

Objective:

- To determine HER2 prevalence in UCS and the concordance of chromogenic in situ hybridization (CISH), immunohistochemistry (IHC), and next generation sequencing (NGS) platforms to aid in the development of UCS specific testing guidelines
- To evaluate the rate of downstream mutations and immune biomarkers that may affect response to HER2 directed therapy.

Methods:

- 875 UCS tumor samples from the CARIS registry (primary 81.4%; metastatic 17.1%; unknown 1.5%) were analyzed using NGS
- A subset of tumors with HER2 positivity were tested with IHC and/or CISH
- *ERBB2* amplification by NGS used a copy number cut-off ≥6.
- PD-L1 expression was analyzed by IHC (SP142: positive cut-off ≥1%)
- Tumor mutational burden (TMB) was measured by counting all somatic mutations found per tumor (TMB-H: ≥10 mt/MB).
- Microsatellite instability (MSI) was tested by fragment analysis (FA), IHC, and NGS.

There is HIGH CONCORDANCE between CISH and IHC in determining HER2 positivity in uterine carcinosarcoma

Results:

- Rate of HER2 positivity was 3.4% (28/820) by NGS (Figure 1)
- Concordance between CISH and NGS (N = 127) was 90.6% (sensitivity 100% and specificity 89.3%) and 100% between CISH and IHC (Table 1).
- Common gene alterations in CISH HER2+ UCS tumors that may implicate resistance to HER2 targeted therapy included mutations in FBXW7 (22.2%), PIK3CA (33.3%), PIK3R1 (18.5%), PTEN (3.7%) and KRAS (3.7%) and amplification of KRAS (11.1%) (Table 2).
- CISH+ HER2+ UCS tumors had low immunotherapy biomarker prevalence (0% MSI-H, 0% TMB high, 7.7% PD-L1+) (Table 2).

Conclusions:

- Increased HER2 positivity was detected via CISH testing compared to IHC and NGS, which may reflect the heterogeneity of HER2 amplification due to mixed histology between the sarcoma and carcinoma portion of the tumor
- High concordance rates were observed between CISH and IHC as well as CISH and NGS. These testing platforms need to be validated by response to HER2 targeted therapies in order to develop UCS specific testing guidelines.

Figure 1: HER2/ERBB2 Positivity/Amplification in Uterine Carcinosarcoma by Technology

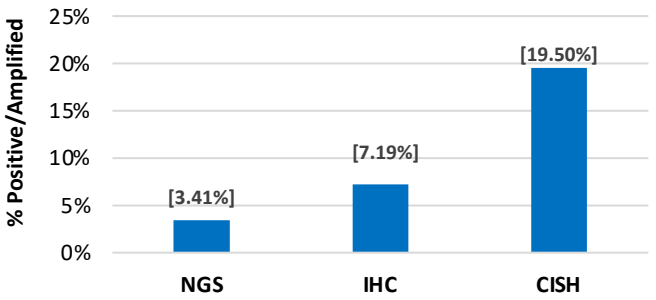

Table 1. Concordance analysis comparing CISH/ IHC and NGS testing for HER2/ERBB2

Comparison	Concordance, N/Total (%)	Sensitivity, N/Total (%)	Specificity, N/Total (%)
CISH and IHC	105/105 (100)	9/9 (100)	96/96 (100)
CISH/IHC and NGS	115/127 (90.6)	15/15 (100)	100/112 (89.3)

Table 2. Top alterations and immuno-oncology (IO) therapy-related biomarkers in HER2+ (by CISH/IHC) uterine carcinosarcoma tumors

Alteration	Biomarker	Pos/Total (%Altered)
Mutation	TP53	27/27 (100)
	PIK3CA	9/27 (33.3)
	FBXW7	6/27 (22.2)
	PIK3R1	5/27 (18.5)
	PTEN	1/27 (3.70)
Amplification	KRAS	3/27 (11.1)
IO therapy-related Biomarkers	PD-L1 (SP142)	2/26 (7.69)
	dMMR/MSI-H	0/27 (0)
	TMB-H	0/27 (0)

References:

1. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: A review of the literature. Gynecol Oncol. 2015;137(3):581-588
2. Schwab CL, English DP, Black J, et al. Neratinib shows efficacy in the treatment of HER2 amplified carcinosarcoma in vitro and in vivo. Gynecol Oncol. 2015;139(1):112-117.