HER2 in Uterine Serous Carcinoma: Testing platforms and implications for targeted therapy

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Background:

- Uterine serous carcinoma (USC) is a rare, aggressive, poor prognostic subtype of endometrial cancer.
- HER2 is an emerging prognostic and therapeutic target in USC.
- Optimal testing platforms in uterine cancer have not been established.

Objective:

- Describe the rate of HER2 positivity in uterine serous carcinoma by in situ hybridization (ISH) and immunohistochemistry (IHC) and to assess the concordance of these testing platforms.
- Determine the rate of potential downstream mutations that may affect response to HER2 directed therapy.

Methods:

- 2,192 primary and recurrent USC tumors analyzed using next generation sequencing (NextSeq, 592 Genes and WES, NovSEQ), a subset of tumors were tested by immunohistochemistry (IHC; 4B5, Ventana) and chromogenic in situ hybridization (CISH; INFORM DUAL HER2 ISH Assay, Ventana) (Caris Life Sciences, Phoenix, AZ).
- HER2 positivity was determined based on 2007 and 2018 ASCO/CAP HER2 breast cancer guidelines.
- PD-L1 expression was tested by IHC using SP142 (Spring Biosciences) (positive cut-off ≥1, 1%). Microsatellite instability (MSI) was tested by fragment analysis, IHC, and NGS. Tumor mutational burden (TMB) was measured by totaling somatic mutations per tumor (TMB-high cut-off ≥ 10 mutations per Mb).
- Statistical significance was determined using chi-square.

There is HIGH CONCORDANCE between CISH and IHC in determining HER2 positivity in Uterine Serous Carcinoma

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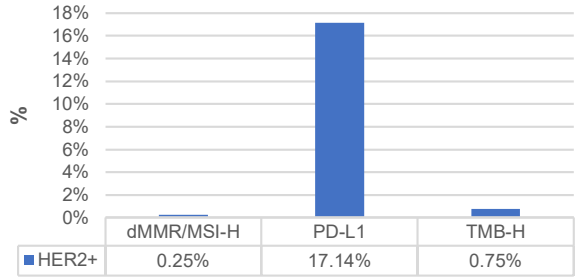
Results:

- HER2 positivity rates were comparable using the 2018 and 2007 breast cancer guidelines (19.5% vs 17.5%; *p*=0.25).
- The concordance between IHC and CISH was 98.9%, based on 2018 guidelines. 16% of tumors were IHC+/CISH+, 0.4% were IHC+/CISH-, and 0.8% were IHC-/CISH+ (Table 1)
- ERBB2 amplification (≥ 6 copies) was identified in 10.5% of tumors. Compared to CISH, this corresponds to a concordance rate of 91.6% and a positive predictive value of 98.5% (Table 2)
- HER2+ tumors had low immunotherapy biomarker profiles (Figure 1)
- There was a low frequency of single cell gene alteration that may predict resistance to HER2 directed therapy (PI3K , KRAS, and PTEN) (Figure 2)

Future Directions:

- Validating these testing platforms by response to HER2 targeted therapies in order to develop USC specific HER2 testing guidelines.

Figure 1. Immunotherapy Biomarkers in HER2+ Uterine Serous Carcinoma



HER2 determined by 2018 Breast Cancer Guidelines (all patients who were CISH+, IHC+ or CNA amplified)

Table 1. Concordance between IHC and CISH by ASCO/CAP Breast Cancer Guidelines.

ASCO/CAP Guidelines (Breast Cancer)	IHC+/CISH+	IHC-/CISH-	IHC+/CISH-	IHC-/CISH+	Concordance (%)	Sensitivity (%)	Specificity (%)	PPV (%)
2007	164	1160	2	8	**99.3**	98.8	99.3	95.3
2018	229	1178	5	11	**98.9**	97.9	99.1	95.4

Figure 2: Biomarker Alterations in HER2+ Uterine Serous Carcinoma via NGS

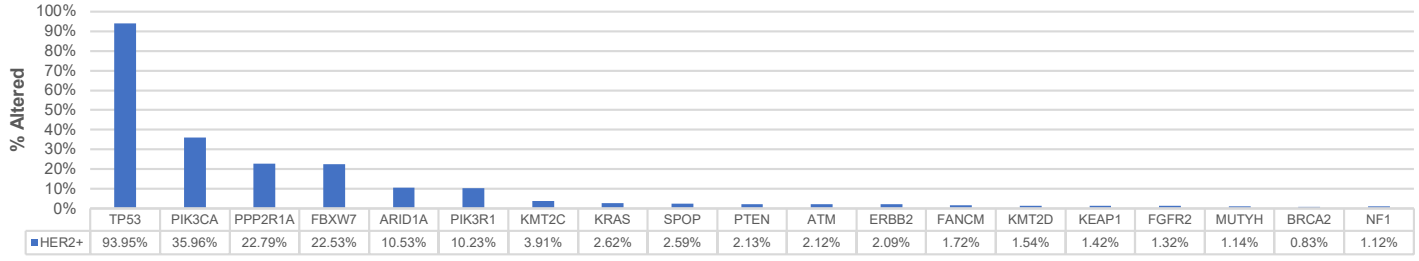


Table 2. Concordance between CISH and ERBB2 Amplification.

ASCO/CAP Guidelines (Breast Cancer)	CISH+/Amplified+	CISH-/Amplified-	CISH-/Amplified+	CISH+/Amplified-	Concordance (%)	Sensitivity (%)	Specificity (%)	PPV (%)
2007	185	1184	4	106	**92.6**	63.6	91.8	97.9
2018	191	1224	3	126	**91.6**	60.3	90.7	98.5