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Low-level expression of human Epidermal growth Factor Receptor-2 (HER2) in High-Grade Mullerian Tumors: Implications for therapy decision making

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ABSTRACT

Introduction: Reclassification of HER2-negative breast cancers to HER2 low-level expression allowed targeted anti-HER2 therapy in about 60% of patients, improving outcome. The high recurrence rates and often dismal outcomes with current therapies of high-grade Mullerian carcinomas, offers opportunity to explore anti-HER2 therapies in the gynecologic tract carcinomas. We investigated HER2 low expression as currently defined in breast carcinomas.

Methods: We reviewed all high-grade Mullerian cancers between 2016 and 2021, where HER2 by IHC and/or FISH tests were available. Additional clinical information was recorded, and statistical analysis was performed using SPSS (version 27).

Results: Forty (49.4%) tumors were endometrial, 20 (24.7%) ovarian, 16 (19.8%) fallopian tubal, and 5 (6.2%) primarily peritoneal. Overall, 17 (21.0%) were HER2 positive (IHC 3+/IHC 2+/FISH amplified), 31 (38.3%) HER2 low (IHC 1+/2+/FISH non-amplified), and 30 (37.0%) were HER2 negative (IHC = 0). HER2 low expression was noted in 15% ovarian, 25% fallopian tubal, 53% endometrial, and 60% peritoneal tumors; 34% and 21% of serous carcinomas, 63% and 13% of carcinosarcomas, and 67% and 33% of endometrioid carcinomas were HER2 low and HER2 positive respectively. HER2 negative and HER2 low expression had a significant association with primary tumor location ($p = 0.001$); endometrium and peritoneal tumors were more likely to be HER2 low and HER2 negative. During a mean follow-up of 13.2 months (range: 1–34), 5% of the patients were deceased.

Conclusions: Based on the current HER2-low recommendations in the breast, about one-third of patients with high-grade Mullerian carcinomas might qualify for anti-HER2 therapy with a potential for improved progression-free and overall survival.

1. Introduction

The Human Epidermal Growth Factor Receptor 2 (HER2) (also known as ErbB2, c-erbB2, or HER2/neu) is a 185 kDa protein that belongs to the HER family of receptors which includes four structurally related members- HER1 (ErbB1, also known as EGFR), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). (Guzzo et al., 2012) HER2/neu is a type 1 transmembrane glycoprotein composed of three distinct regions: an N-terminal extracellular domain (ECD), a single α-helix transmembrane domain, and an intracellular tyrosine kinase domain (Park et al., 2008; Tai et al., 2010). HER2/neu plays essential roles in cell growth, survival, and differentiation (Park et al., 2008; Tai et al., 2010). The major signaling pathways mediated by HER2/neu involve the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway. As a critical gene for cell survival, HER2/neu gene amplification and protein overexpression lead to malignant transformation (Park et al., 2008; Tai et al., 2010). HER2/neu amplifications have been detected in many human solid tumors, including but not limited to breast, ovarian, endometrial, colon, non-small cell lung cancer, prostate, and cervical cancer (Slichenmyer and Fry, 2001; Schmidt et al., 2005; Ross and Fletcher, 1998; Ladjemi et al., 2010). The HER2/neu protein is over-expressed in uterine

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carcinosarcomas in 17–43% of cases (Livasy et al., 2006), 6.7% of FIGO grade 3 endometrial endometrioid carcinomas (Joehlin-Price et al., 2023; 10.1097/PAS.0000000000002030.), 4.9–52.5% of ovarian serous carcinoma (Lanitis et al., 2012), 21–42% of endometrial serous carcinomas (Santin et al., 2005; Morrison et al., 2006; Grushko TA, Filiaci VL, Mundt AJ, Ridderstrale K, Olopade OI, Fleming GF, Gynecologic Oncology Group, 2008), and 15% of cases with uterine carcinosarcoma with serous morphology (Jenkins et al., 2022).

The investigation of HER2 expression in gynecologic malignancies has produced strong evidence that overexpression is associated with increased tumor aggression (English et al., 2013). Additionally, the HER2 protein is implicated as an important oncogenic driver in high-grade and high-stage endometrial cancers (Morrison et al., 2006). The dismal outcomes associated with high-grade Mullerian carcinomas have made it imperative to explore additional treatment options, particularly in patients who may express some HER2 protein but do not meet current treatment recommendations. The recent re-classification of HER2-negative breast cancers to HER2 low-level expression (defined as immunohistochemistry (IHC) 1 + or 2+/Fluorescent in situ hybridization (FISH) non-amplified) which allowed targeted treatment with trastuzumab- deruxtecan, anti-HER2 therapy (DESTINY-Breast04 Trial) in about 60% of patients thus improving their progression-free and overall survival (Modi et al., 2022), may be explored in the gynecologic tract as a possible adjunctive therapy option for patients with similar levels of expression. With no standardized scoring criteria for HER2 in gynecologic malignancies, the 2023 American Society for Clinical Oncology/College of American Pathology (ASCO/CAP) guidelines for HER2 interpretation in the breast is what is being used routinely in clinical practice (Wolff et al., 2023). According to the guidelines, "complete circumferential intense membrane staining in greater than 10% of the tumor cells constitutes IHC 3 + positive; complete weak to moderate membrane staining in greater than 10% of the tumor cells constitutes IHC 2 + equivocal result; incomplete faint/barely perceptible and in greater than 10% of the tumor cells results in IHC 1 + negative. Finally, no staining or incomplete faint/barely perceptible membrane staining in less than 10% of the tumor cells constitutes IHC 0 Negative. The HER2 status of patients with equivocal IHC scores is further examined with in situ hybridization (ISH). ISH-positive and ISH-negative tumors are then re-classified as HER2-positive and negative respectively (Wolff et al., 2023). Based on this algorithm, only patients with HER2-positive gynecologic tumors have been eligible for anti-HER2 therapy, which has shown significant improvements in survival, when combined with conventional chemotherapy in advanced and recurrent HER2-positive disease (Ferriss et al., 2021; Buza, 2021). We, therefore, aimed to describe the expression of HER2 in high-grade Mullerian carcinomas, with a particular emphasis on HER2 low expression as currently defined in breast carcinomas, as a possible therapeutic consideration in the gynecologic tract.

2. Materials and Methods

This was a retrospective study conducted in the Department of Pathology, Women & Infants Hospital, and The Warren Alpert Medical School of Brown University, Providence, Rhode Island. After obtaining Institutional Review Board (IRB) approval, we searched our institution's database from January 2016 to December 2021 to identify all high-grade gynecologic cancers in which HER2 by IHC and/or FISH tests were previously performed. Search terms used included "serous adenocarcinoma, high-grade endometrioid adenocarcinoma, Mullerian adenocarcinoma, carcinosarcoma, malignant mixed Mullerian tumor, clear cell carcinoma, mucinous adenocarcinoma, peritoneal carcinoma, de-differentiated endometrioid adenocarcinoma, neuroendocrine carcinoma, and sarcomatoid carcinoma." Two gynecologic pathologists (EA and MRQ) reviewed hematoxylin & eosin-stained slides, HER2 IHC/FISH results, and pathology reports to confirm the diagnosis of high-grade gynecologic cancers. Additional clinicopathologic parameters reviewed include demographic information, tumor characteristics (primary tumor location and histologic differentiation), mismatch repair (MMR) status (as appropriate), the surgical procedure performed, the International Federation of Gynecology and Obstetrics (FIGO) stage, follow-up information, and deceased status. Statistical analysis was performed using SPSS (version 27). Descriptive analysis was performed. Associations were investigated using cross-tabulation. Proportions were compared using Chi-Square tests. A P-value of less than 0.05 (2-sided) was considered significant.

3. Results

Following our review, we identified 81 high-grade Mullerian cancers diagnosed with previous HER2 IHC and/or FISH reports during the study time frame. The mean age at diagnosis was 66.4 years (range: 43–85). Most patients were White/Caucasians (63; 77.8%), 7 (8.6%) were Black/African Americans (AA), and 11 (13.6%) belonged to other races. Forty (49.4%) tumors were primarily located in the endometrium, 20 (24.7%) were primarily in the ovary, 16 (19.8%) were primarily in the fallopian tube and 5 (6.2%) primarily occurred in the peritoneum. Seventy-seven (95.1%) were resection cases and 4 (4.9%) were biopsy specimens. Table 1 summarizes the clinicopathologic characteristics of the patient cohort. Most cases were serous carcinomas (70; 86.4%), 8 (9.9%) were carcinosarcomas and 3 (3.7%) were high-grade (FIGO 3) endometrioid carcinomas. Based on the ASCO/CAP 2023 guideline for the IHC interpretation of HER2 status in the breast, 3 (4%) of the Mullerian carcinomas studied in this series, irrespective of the primary

Table 1
Patient Characteristics and Correlation of Clinicopathologic Parameters with HER2 Status.

	All (n = 81)	P value*
Age at diagnosis, mean (range)	66.4 (43,85)	
Follow up, months, mean (range)	13.2 (1–34)	
Race, no. (%)		0.547
White/Caucasians	63 (77.8)	
Black/African American	7 (8.6)	
Others	11 (13.6)	
Primary Tumor Location, no. (%)		***0.001***
Ovary	20 (24.7)	
Fallopian tube	16 (19.8)	
Endometrium	40 (49.4)	
Peritoneum	5 (6.2)	
Procedure, no. (%)		
Biopsy	4 (4.9)	
Resection	77 (95.1)	
Diagnosis, no (%)		0.426
Serous	70 (86.4)	
Carcinosarcoma	8 (9.9)	
Endometrioid FIGO3	3 (3.7)	
HER2 Results, no. (%)		
Negative	30 (37.0)	
HER2 low	31 (38.3)	
HER2 Positive	17 (21.0)	
HER2 2 + on IHC and no FISH	3 (3.7)	
HER2 FISH (n = 20), no. (%)		
Not amplified	13 (16.0)	
Amplified	7 (8.6)	
FIGO Stage (n = 77), no. (%)		0.159
1	30 (39)	
2	8 (10)	
3	30 (39)	
4	9 (12)	
Biopsy	4 (0)	
MMR status (n = 29), no (%)		0.246
Intact	27 (93.1)	
Deficient	2 (6.9)	
Deceased status, no. (%)		0.883
Alive	77 (95.1)	
Dead	4 (4.9)	

* Chi-Square tests as appropriate.

site(s), were IHC 3 + Positive; 20 (24%) were IHC 2 + equivocal; 28 (35%) cases were IHC 1 + negative; and 30 (37%) cases were IHC 0 negative. Combined IHC and FISH, 17 (21.0%) were HER2 positive (IHC 3 + or IHC 2 + and FISH amplified), 31 (38.3%) cases were HER2 low (IHC 1 + or 2+/FISH non-amplified), and 30 (37.0%) were HER2 negative (IHC = 0). In the remaining three (3.7%) cases where HER2 IHC was 2 + but no FISH was performed because of technical issues, either inadequate sample or the test failed. By the current definition used for breast carcinoma, 31 of the 81 (38.3%) Mullerian carcinoma in this series fulfills the criteria for Her2 low (IHC Her2 1 + or 2 + and FISH non-amplified). Fig. 1 (TIF file format) represents routine H&E view of a high-grade serous carcinoma of the endometrium and HER2 score 1+, 2+, and 3 + levels of expressions respectively. The 17 cases with HER2 positive results, occurred in pre-treatment specimens, as HER2 testing prior to therapy is the standard of practice at our institution. Of the 17 patients with positive HER2 status, 9 cases were uterine serous carcinomas, 2 cases were primary ovarian, peritoneal, and fallopian tube serous carcinomas respectively, and 1 case was FIGO3 endometrial endometrioid carcinoma and endometrial carcinosarcoma respectively. Of the 9 cases with uterine serous carcinoma, 3 received anti-HER2 therapy, 5 were treated with other combination chemotherapy/immunotherapy and there was no treatment information for one case. Table 2 summarizes the location, histology, and treatment with anti-HER2 therapy (where applicable) for the HER2 positive tumors in this study. By primary tumor location, HER2 low expression was noted in 15% of ovarian, 25% of fallopian tube, 53% of endometrial and 60% of peritoneal tumors. By histology, 34% and 21% of serous carcinomas were HER2 low and HER2 positive respectively, 63% and 13% of carcinosarcomas were HER2 low and HER2 positive respectively and 67% and 33% of high-grade endometrioid carcinomas were HER2 low and HER2 positive respectively. Table 3 summarizes the relationship of HER2 status with primary tumor site, histology and FIGO stage. FIGO stage was only available in 77 cases and of these, 30 (39%) presented with stage 1 disease, 8 (10%) presented with stage 2 disease, 30 (39%) presented with stage 3 disease, and 9 (12%) presented with stage 4 disease. Four cases were biopsy specimens and had no FIGO stage assigned. MMR was performed in 29 cases and was intact in 27 (93.1%) cases and deficient in 2 (6.9%) cases, with all primarily located in the endometrium. Of the clinicopathologic parameters evaluated, HER2 negative and HER2 low expression levels had a significant association with primary tumor location ($p = 0.001$), meaning that tumors primarily located in the endometrium and peritoneum were more likely to be HER2 low and HER2 negative. HER2 expression, however, had no significant association with the histologic type of cancer, race, MMR expression, FIGO stage, or deceased status. Additionally, there was no significant difference in HER2 expression between serous, endometrioid and carcinosarcoma ($p = 0.582$). During a mean follow-up of 13.2 months (range: 1–34), 5% of the patients were deceased.

Table 2
Use of Anti-HER2 Therapy in HER2 Positive (IHC 3 + or IHC 2 + and FISH amplified) Tumors by Primary Location and Tumor Histology (N = 17).

Case Number	Primary Tumor Location	Tumor Histology	Anti-HER2 used? Yes/No
1	Endometrium	Serous	No
2	Endometrium	Serous	Yes
3	Endometrium	Serous	No
4	Endometrium	Serous	No
5	Endometrium	Serous	Yes
6	Fallopian tube	Serous	No
7	Ovary	Serous	No
8	Endometrium	Serous	Yes
9	Ovary	Serous	No
10	Endometrium	Serous	Unknown
11	Peritoneum	Serous	No
12	Endometrium	Serous	No
13	Endometrium	Serous	No
14	Endometrium	High-grade endometrioid	No
15	Fallopian tube	Serous	No
16	Peritoneum	Serous	No
17	Endometrium	Carcinosarcoma	No

4. Discussion

To the best of our knowledge, this study is the first to characterize HER2 low status in high-grade Mullerian tumors, including tumors of the endometrium, ovary, fallopian tube, and peritoneum. At our institution, prior to therapy, HER2 testing is routinely performed for all high-grade serous carcinomas, carcinosarcomas and unequivocal high-grade FIGO3 endometrioid/serous carcinomas. This testing is also performed in primary ovarian, peritoneal, and fallopian tube cancers with serous histology. The results of HER2 testing provide prognostic relevance as positive cases are considered to behave more aggressively. HER2 protein overexpression has been described in gynecologic carcinosarcomas (1), grade 3 endometrial endometrioid carcinomas (Rice et al., 2006), and ovarian and endometrial serous carcinomas (English et al., 2013). However, low-level expression of HER2 in these tumors with the

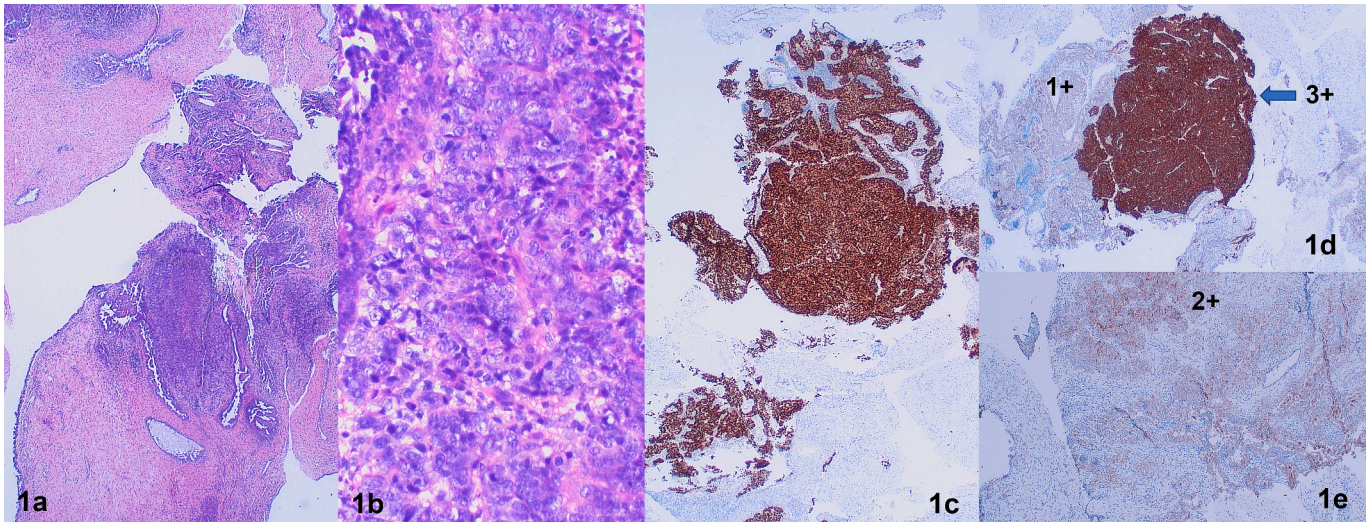

Fig. 1. 1a. High grade serous carcinoma of fallopian tube (H&E 1x); 1b. High grade serous carcinoma (H&E, 20x); 1c. p53 mutated pattern (IHC 2x); 1d. Her2/neu overexpression (3 +) on right and low-level expression (1 +) on left in the same tumor (IHC 2x); 1e. Her2/neu equivocal expression (2 +) (IHC 4x).

Table 3
Relationship of HER2 Status with primary tumor site, histology and FIGO Stage.

	HER2 neg	HER2 low	HER2 pos	HER2 2+, no FISH	P value
Primary site (N = 81)					**0.001**
Ovary (20)	13 (65%)	3 (15%)	2 (10%)	2 (10%)	
Fallopian tube (16)	10 (63%)	4 (25%)	2 (12%)	0	
Endometrium (40)	7 (18%)	21 (53%)	11 (28%)	1 (3%)	
Peritoneum (5)	0	3 (60%)	2 (40%)	0	
Histology (N = 81)					0.582
Serous (70)	28 (40%)	24 (34%)	15 (21%)	3 (4%)	
Carcinosarcoma (8)	2 (25%)	5 (63%)	1 (13%)	0	
Endometrioid (3)	0	2(67%)	1 (33%)		
FIGO Stage (N = 77)					0.159
1 (30)	5 (17%)	15 (50%)	9 (30%)	1 (3%)	
2 (8)	6 (75%)	1 (13%)	1 (13%)	0	
3 (30)	14 (47%)	10 (33%)	5 (17%)	1 (3%)	
4 (9)	3 (33%)	14 (44%)	2 (22%)	0	

Neg = negative (Immunohistochemistry (IHC) = 0); low = IHC 1+/2 + and fluorescence in situ hybridization (FISH) not amplified); pos = positive (IHC 2 + and FISH amplified/IHC 3 +).

potential for anti-HER2-dependent therapy for these patients is largely unknown. Given the high recurrence rates and dismal outcomes of high-grade Mullerian tumors, it has become increasingly necessary to explore the potential benefit of anti-HER2 adjunctive therapies in patients with sub-optimal expression of the HER2 protein. Multiple trials exploring combination adjuvant chemotherapy, radiotherapy or chemo-radiotherapy in high-risk endometrial cancers have produced variable and frequently suboptimal responses to treatment in terms of overall survival (OS) and progression free survival (PFS) (de Boer et al., 2018; van den Heerik et al., 2021), thus emphasizing the need to explore additional treatment options in these patients. The combination of chemotherapy and anti-HER2 therapies for patients has shown significant improvements in survival in advanced and recurrent HER2-positive gynecologic disease (Ferriss et al., 2021). Fader and colleagues in a randomized phase II clinical trial described an improvement in PFS and OS in patients with advanced/recurrent HER2 positive uterine serous carcinoma, with the greatest benefit seen for treatment of stage III to IV disease (Fader et al., 2020). HER2 gene amplification has been shown to have significant prognostic and predictive effects in endometrial serous carcinoma (Bozkurt et al., 2023). While these studies have focused on tumors with HER2 gene amplification or over-expressing the HER2 protein, the over-arching question is whether patients with low HER2 expression could also see potential survival benefits with anti-HER2 therapies. To answer this question, an initial step would be to investigate the degree of low expression of the HER2 protein in these tumors, which is a gap our study attempts to close. Based on our findings, a third of patients with high-grade Mullerian tumors express the HER2 protein in low levels and therefore these patients will be eligible for novel anti-HER2 targeted therapies, as seen in breast cancers. This low level of expression of the HER2 protein is seen in all primary tumor sites, including the ovary, fallopian tube, endometrium, or peritoneum. Additionally, low-level expression of the HER2 protein is not precluded by the tumor's histology (serous, carcinosarcomas or high-grade endometrioid) or FIGO stage status, this potentially opening a therapeutic door of opportunity for tumors from these other anatomic sites. Currently, in the gynecologic tract, anti-HER2 therapy is only administered in advanced/recurrent HER2 positive uterine serous carcinoma (Fader et al., 2020).

Prior to the breakthrough study in the breast (Modi et al., 2022), the addition of anti-HER2 therapy to chemotherapy in the neoadjuvant setting resulted in increased rates of pathologic complete response (PCR), (Wolff et al., 2023), in HER2 positive tumors. Similarly, in the metastatic setting, the addition of anti-HER2 therapy to advanced-stage breast cancer resulted in significant improvements in OS for these patients (Mendes et al., 2015). Furthermore, in the gastrointestinal tract, the addition of anti-HER2 therapy to standard chemotherapeutic agents has shown significant improvements in OS and PFS in advanced gastric and gastroesophageal cancers (Ha et al., 2020; Bang et al., 2010). While the benefit of anti-HER2 therapy in HER2 low breast cancers has been elucidated (Lanitis et al., 2012), the potential therapeutic value of anti-HER2 therapy in HER2 low tumors of the gynecologic and gastrointestinal tract is largely unknown, thus leaving room for future research studies.

Given the current HER2 treatment guidelines in the gynecologic tract, only 21% of patients in this study with HER2 positive interpretation (IHC 2 + and FISH amplified/IHC 3 +) would qualify for anti-HER2 therapy. However, if the HER2 low interpretation status currently introduced in breast cancers is also applied to gynecologic cancers, the percentage of patients who would qualify for anti-HER2 therapy with potential treatment benefits would significantly increase to 63% [HER2 low (31, 38.3%) + HER2 + on IHC, no FISH (3, 3.7%) + HER2 positive (17, 21%)], which represents about two-thirds of this patient population. In this study, of the 17 patients with positive HER2 status, 9 cases were uterine serous carcinomas and were eligible for anti-HER2 therapy. Of these, 3 received anti-HER2 therapy, 5 were treated with other combination chemotherapy/immunotherapy and treatment information was not available in one case. Investigating the utility of HER2 low status in gynecologic cancers, including tumors primarily located outside the uterine cavity, might herald a therapeutic landscape not hitherto explored. A recent study by Joehlin-Price and colleagues revealed that a subset of high-grade endometrial endometrioid carcinomas express the HER2 in sub-amplified statuses (HER2 low and HER2 very low) and may benefit from additional targeted anti-HER2 therapy (Joehlin-Price et al., 2023; 10.1097/PAS.0000000000002030.). Additional studies, including large-scale prospective trials, are needed to validate these findings.

In summary, based on our findings, about a third of patients with high-grade Mullerian cancers might qualify for anti-HER2 therapy with a potential for improved progression-free and overall survival.

Our study is not devoid of limitations. Indeed, its retrospective nature introduces its own inherent bias which may limit the interpretation of our findings. This is however not unexpected as high-grade gynecologic cancers are an aggressive class of disease and exploring the expression of oncogenic proteins, as well as the utility of targeted therapies in these patients, is an ongoing clinical, research, and development process. Nonetheless, despite this limitation, we have been able to show with our study that a significant number of high-grade gynecologic cancers show low-level expression of the HER2 protein.

CRediT authorship contribution statement

Evi Abada: . **Kamaljeet Singh:** Formal analysis, Methodology, Writing – review & editing. **Katrine Hansen:** . **M. Ruhul Quddus:** Conceptualization, Investigation, Methodology, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Bang, Y.J., van Cutsem, E., Feyereislova, A., et al., 2010. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive

advanced gastric or gastro-oesophageal junction cancer (ToGA): A Phase 3, open-label, randomised controlled trial. Lancet 376 (9742), 687–697.
Bozkurt, K.K., Ciris, I.M., Baspinar, S., Cetin, B., Erdemoglu, E., Bircan, S., Ertunc, O., 2023. The prognostic effect of HER2 gene amplification in high-grade endometrial carcinomas and its correlation with protein overexpression. International Journal of Surgical Pathology 31 (4), 365–374. https://doi.org/10.1177/10668969221102529.
Buza, N. (2021). HER2 Testing and Reporting in Endometrial Serous Carcinoma: Practical Recommendations for HER2 Immunohistochemistry and Fluorescent In Situ Hybridization: Proceedings of the ISGyP Companion Society Session at the 2020 USCAP Annual Meeting. Int J Gynecol Pathol, 40(1), 17-23. https://doi.org/10.1097/PGP.0000000000000711.
de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial [published correction appears in Lancet Oncol. 2018 Apr;19(4):e184]. *Lancet Oncol.* 2018;19(3):295-309. doi:10.1016/S1470-2045(18)30079-2.
English, D.P., Roque, D.M., Santin, A.D., 2013. HER2 expression beyond breast cancer: Therapeutic implications for gynecologic malignancies. Molecular Diagnosis & Therapy 17 (2), 85–99. https://doi.org/10.1007/s40291-013-0024-9.
Fader, A.N., Roque, D.M., Siegel, E., et al., 2020. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (Stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): Updated overall survival analysis. Clinical Cancer Research 26 (15), 3928–3935. https://doi.org/10.1158/1078-0432.
Ferriss, J.S., Erickson, B.K., Shih, I.M., Fader, A.N., 2021. Uterine serous carcinoma: Key advances and novel treatment approaches. International Journal of Gynecological Cancer 31 (8), 1165–1174. https://doi.org/10.1136/ijgc-2021-002753.
Grushko, TA., Filiaci, VL., Mundt, AJ., Ridderstrale, K., Olopade, OI., Fleming, GF., 2008. Gynecologic oncology group an exploratory analysis of HER-2 amplification and overexpression in advanced endometrial carcinoma: A gynecologic oncology group study. Gynecologic Oncology 108 (1), 3–9.
Guzzo, F., Bellone, S., Buza, N., et al., 2012. HER2/neu as a potential target for immunotherapy in gynecologic carcinosarcomas. International Journal of Gynecological Pathology 31 (3), 211–221. https://doi.org/10.1097/PGP.0b013e31823bb24d.
Ha, G.Y., Yang, S.H., Kang, H.J., et al., 2020. Comparison of survival outcomes according of patients with metastatic gastric cancer receiving trastuzumab with systemic chemotherapy. Korean J Clin Oncol. 16 (2), 63–70. https://doi.org/10.14216/kjco.20011.
Jenkins, T.M., Cantrell, L.A., Stoler, M.H., Mills, A.M., 2022. HER2 overexpression and amplification in uterine carcinosarcomas with serous morphology. The American Journal of Surgical Pathology 46 (4), 435–442. https://doi.org/10.1097/PAS.0000000000001870.
A.S. Joehlin-Price M.K. Komforti N.R. Ladwig et al. HER2 IHC Expression and Gene Amplification in p53-aberrant High-grade Endometrial Endometrioid Carcinoma Suggests That This Population May Benefit From HER2 Testing and Targeted Therapy [published online ahead of print, 2023 Mar 20] Am J Surg Pathol. 2023; 10.1097/PAS.0000000000002030. 10.1097/PAS.0000000000002030.
Ladjemi, M.Z., Jacot, W., Chardès, T., Pèlegrin, A., Navarro-Teulon, I., 2010. Anti-HER2 vaccines: New prospects for breast cancer therapy. Cancer Immunology, Immunotherapy 59 (9), 1295–1312. https://doi.org/10.1007/s00262-010-0869-2.
Lanitis, E., Dangaj, D., Hagemann, I.S., et al., 2012. Primary human ovarian epithelial cancer cells broadly express HER2 at immunologically-detectable levels. PLoS One1 7 (11), e49829.
Livasy, C.A., Reading, F.C., Moore, D.T., et al., 2006. EGFR expression and HER2/neu overexpression/amplification in endometrial carcinosarcoma. Gynecologic Oncology 100 (1), 101–106.
Mendes, D., Alves, C., Afonso, N., et al., 2015. The benefit of HER2-targeted therapies on overall survival of patients with metastatic HER2-positive breast cancer–a systematic review. Breast Cancer Research 17, 140. https://doi.org/10.1186/s13058-015-0648-2.
Modi, S., Jacot, W., Yamashita, T., et al., 2022. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. The New England Journal of Medicine 387 (1), 9–20. https://doi.org/10.1056/NEJMoa2203690.
Morrison, C., Zanagnolo, V., Ramirez, N., Cohn, D.E., Kelbick, N., Copeland, L., Maxwell, G.L., Fowler, J.M., 2006. HER-2 is an independent prognostic factor in endometrial cancer: Association with outcome in a large cohort of surgically staged patients. Journal of Clinical Oncology 24 (15), 2376–2385.
Park, J.W., Neve, R.M., Szollosi, J., Benz, C.C., 2008. Unraveling the biologic and clinical complexities of HER2. Clinical Breast Cancer 8 (5), 392–401. https://doi.org/10.3816/CBC.2008.n.047.
Rice, L.W., Stone, R.L., Xu, M., et al., 2006. Biologic targets for therapeutic intervention in endometrioid endometrial adenocarcinoma and malignant mixed müllerian tumors. American Journal of Obstetrics and Gynecology 194 (4), 1119–1128. https://doi.org/10.1016/j.ajog.2005.12.020.
Ross, J.S., Fletcher, J.A., 1998. The HER-2/neu oncogene in breast cancer: Prognostic factor, predictive factor, and target for therapy. The Oncologist 3 (4), 237–252.
Santin, A.D., Bellone, S., Van Stedum, S., Bushen, W., Palmieri, M., Siegel, E.R., De Las Casas, L.E., Roman, J.J., Burnett, A., Pecorelli, S., 2005. Amplification of c-erbB2 oncogene: A major prognostic indicator in uterine serous papillary carcinoma. Cancer 104 (7), 1391–1397.
Schmidt, M., Lewark, B., Kohlschmidt, N., et al., 2005. Long-term prognostic significance of HER-2/neu in untreated node-negative breast cancer depends on the method of testing. Breast Cancer Research 7 (2), R256–R266. https://doi.org/10.1186/bcr991.
Slichenmyer, W.J., Fry, D.W., 2001. Anticancer therapy targeting the erbB family of receptor tyrosine kinases. Seminars in Oncology 28 (5 Suppl 16), 67–79. https://doi.org/10.1016/s0093-7754(01)90284-2.
Tai, W., Mahato, R., Cheng, K., 2010. The role of HER2 in cancer therapy and targeted drug delivery. Journal of Controlled Release 146 (3), 264–275. https://doi.org/10.1016/j.jconrel.2010.04.009.
van den Heerik, A.S.V.M., Horeweg, N., de Boer, S.M., Bosse, T., Creutzberg, C.L., 2021. Adjuvant therapy for endometrial cancer in the era of molecular classification: radiotherapy, chemoradiation and novel targets for therapy. International Journal of Gynecological Cancer 31 (4), 594–604. https://doi.org/10.1136/ijgc-2020-001822.
Wolff, A.C., Hammond, M.E.H., Allison, K.H., et al., 2023. Human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of american pathologists clinical practice guideline focused update [published online june 7, 2023]. Arch Pathol and Lab Med 36 (20), 2105–2122. https://doi.org/10.5858/arpa.2023-0950-SA.