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**EVIDENCE REVIEW**

- 833 Postoperative radiotherapy in resected non-small cell lung cancer: The never-ending story  
*Serrano J, Crespo PC, Taboada B, Gonzalez AA, García RG, Caamaño AG, Reyes JCT, Mielgo-Rubio X, Couñago F*

**REVIEW**

- 845 Relationship between Th17 immune response and cancer  
*Marques HS, de Brito BB, da Silva FAF, Santos MLC, de Souza JCB, Correia TML, Lopes LW, Neres NSM, Dórea RSDM, Dantas ACS, Morbeck LLB, Lima IS, de Almeida AA, Dias MRJ, de Melo FF*

**MINIREVIEWS**

- 868 Human epidermal growth factor receptor 2 targeted therapy in endometrial cancer: Clinical and pathological perspectives  
*Saito A, Yoshida H, Nishikawa T, Yonemori K*
- 882 Role of lenalidomide in the treatment of peripheral T-cell non-Hodgkin lymphomas  
*Cencini E, Fabbri A, Mecacci B, Bocchia M*
- 897 Current update on imaging for pancreatic neuroendocrine neoplasms  
*Segaran N, Devine C, Wang M, Ganeshan D*
- 912 Recent advances and new insights in the management of early-stage epidermal growth factor receptor-mutated non-small-cell lung cancer  
*Sotelo MJ, Luis García J, Torres-Mattos C, Milián H, Carracedo C, González-Ruiz MÁ, Mielgo-Rubio X, Trujillo-Reyes JC, Couñago F*

**ORIGINAL ARTICLE****Retrospective Study**

- 926 A biomarker study in Peruvian males with breast cancer  
*Castaneda CA, Castillo M, Bernabe LA, Sanchez J, Torres E, Suarez N, Tello K, Fuentes H, Dunstan J, De La Cruz M, Cotrina JM, Abugattas J, Guerra H, Gomez HL*

- 935 Jejunostomy in the palliative treatment of gastric cancer: A clinical prognostic score  
*Ramos MFKP, Pereira MA, Dias AR, Sakamoto E, Ribeiro Jr U, Zilberstein B, Nahas SC*

**Observational Study**

- 947 Novel molecular panel for evaluating systemic inflammation and survival in therapy naïve glioma patients  
*Gandhi P, Shrivastava R, Garg N, Sorte SK*

**CASE REPORT**

**960** Gastric myeloid sarcoma: A case report

*Rioja P, Macetas J, Luna-Abanto J, Tirado-Hurtado I, Enriquez DJ*

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## Human epidermal growth factor receptor 2 targeted therapy in endometrial cancer: Clinical and pathological perspectives

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### Abstract

Endometrial cancer is the most common gynecological cancer in developed countries, and its incidence has increased. The majority of patients with endometrial cancer have an early disease and favorable prognosis; however, a significant proportion of endometrial cancer, which mainly comprises high-grade or type II endometrial cancer such as serous, clear cell, and carcinosarcoma, shows advanced/recurrent disease and dismal prognosis. Novel therapeutic development is required for patients with aggressive endometrial cancers. Recent genomic and immunohistochemical analyses revealed human epidermal growth factor receptor 2 (HER2) overexpression/gene amplification in 20%-40% of patients with type II endometrial cancer. Historically, HER2 targeted therapy has been developed for various major cancers, including breast and gastric cancer. Notably, recent advances in HER2 targeted therapy for patients with type II endometrial cancer are also expected to change. Simultaneously, an optimized HER2 test for endometrial cancer as companion diagnostics should be established. In this review, we summarize the recent findings on endometrial cancer, current treatment, optimized HER2 testing, key clinical trials on HER2 targeted therapy, and future directions in aggressive endometrial cancer, including serous carcinoma and carcinosarcoma.

**Key Words:** Endometrial cancer; Serous carcinoma; Carcinosarcoma; Human epidermal growth factor receptor 2; Chemotherapy; Antibody-drug conjugates

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**Core Tip:** Endometrial cancer is the most common gynecological cancer in developed countries, and its incidence has increased. A significant proportion of endometrial cancer, which mainly comprises high-grade or type II endometrial cancer, including serous carcinoma and carcinosarcoma, shows a dismal prognosis. Recent molecular analyses revealed human epidermal growth factor receptor 2 (HER2) overexpression/gene amplification in 20%-40% of patients with type II endometrial cancer. Notably, HER2 targeted therapy for type II endometrial cancer has been dramatically developed. We review the recent findings on endometrial cancer, current treatment, optimized HER2 testing, key clinical trials on HER2 targeted therapy, and future directions in these aggressive endometrial cancers.

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## INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy, with 65000 cases diagnosed and 12000 deaths in the United States in 2020[1]. In Japan, approximately 16000 cases are diagnosed, 2500 deaths occur annually, and the number of patients is increasing[2,3]. The prognosis is relatively good, with a 5-year survival rate of 80%, and many cases are diagnosed at the localized stage[4]. However, a significant proportion of patients with endometrial cancer still have an advanced or recurrent disease and have a dismal prognosis.

Endometrial cancers can be classified into two types. Type I shows endometrioid morphology, which accounts for 80% of endometrial cancers, and type II shows non-endometrioid morphology, such as serous carcinoma, clear cell carcinoma, and carcinosarcoma, which account for the remaining 20%. Each type of carcinoma is known to have a different background and clinical course. Type I is reportedly caused by unopposed estrogen, and obesity is a trigger for carcinogenesis; it is diagnosed at a young age, has low grade and early stage, and is usually curable by surgery. In contrast to type I, type II is more common in elderly patients, occurs on a background atrophic endometrium, is diagnosed at an advanced stage, and is resistant to chemotherapy, resulting in a poor prognosis[5].

An analysis of The Cancer Genome Atlas revealed different molecular genetic pathways that are present in these two types. The results show that endometrial cancers can be divided into four clusters: *POLE* ultramutated (cluster 1), microsatellite instability hypermutated (cluster 2), copy-number low, endometrioid (cluster 3), and copy-number high; serous-like (cluster 4). Uterine serous carcinoma (USC), classified as Type II, accounts for the majority of cluster 4 cases[6]. Differences in common genomic alterations by cluster were characterized by *PTEN*, *PIK3R1*, *FBXW7*, and *KRAS* alterations in cluster 1, *KRAS* alterations in cluster 2, *CTNNB1* alterations in cluster 3, *TP53*, *FBXW7*, *PPP2R1A* alterations, *ERBB2*, and *CCND1* amplification in cluster 4[6].

Surgical treatment is appropriate for early-stage endometrial cancer, and chemotherapy and radiation therapy should be considered according to the risk of recurrence after resection. Women with low-risk endometrial cancer undergoing surgical treatment alone and no adjuvant treatment are indicated. For women with high-risk endometrial cancers undergoing surgery, adjuvant chemotherapy with or without radiation should be offered[7,8]. Although there is no consensus on adjuvant treatment among intermediate-risk cancers, some clinicians may offer adjuvant chemotherapy and/or radiation[5]. For advanced or recurrent uterine cancer, carboplatin, paclitaxel, adriamycin, and cisplatin are often chosen as chemotherapy regimens based on the GOG 122L[9], GOG 209L[10], and JGOG 2043 trials[11]. Furthermore, low-grade endometrial cancer with positive estrogen receptor and progesterone receptor can be expected to benefit from hormone therapy[12].

Molecular targeted agents for patients with endometrial cancer have been developed, similar to other solid tumors. In recent years, the efficacy of pembrolizumab has been demonstrated in solid tumors of microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR)[13,14]. MSI-H/dMMR is found in 20%-30% of endometrial cancers[6,15]. The combination of pembrolizumab and lenvatinib has been shown to be effective in patients with microsatellite stable/mismatch repair proficient, regardless of histologic subtype, with 40% of participants having type II, serous/clear cell carcinoma, and type I[16]. Notably, human epidermal growth factor receptor 2 (HER2) targeted therapy for patients with endometrial cancer has demonstrated practice-changing efficacy in the recent decade. In this review, we aim to overview recent advances in HER2 targeted therapeutics and HER2 testing for endometrial cancer.

## HER2 AMPLIFICATION AND OVEREXPRESSION IN ENDOMETRIAL CANCER

HER2 is a cell surface receptor named after human epidermal growth factor receptor (EGFR)-related 2 in the 1980s. It is encoded by the *ERBB2* gene on chromosome 17. It is known to belong to the EGFR family that includes other receptors: EGFR, HER3, and HER4. When *HER2* is amplified, HER2 is overexpressed and forms active dimers that induce the downstream RAS/RAF/MAPK and PI3K/AKT pathways without ligand stimulation. This, in turn, activates the downstream pathway, contributing to oncogenesis[17,18].

HER2 amplification/overexpression is known to occur in a variety of solid tumors, including about 20% in breast cancer[17], 10%-20% in gastric cancer, 2%-10% in colorectal cancer, 5%-20% in biliary tract cancer, 10% in bladder cancer, and 2%-5% in lung cancer[19,20]. In all endometrial cancers, HER2 overexpression and amplification have been reported 18%-80% and 4%-69%[19]. HER2 positivity differs according to histopathological subtype. Although HER2 overexpression and amplification are rarely seen in low-grade endometrioid adenocarcinoma, USC has the highest prevalence of HER2 positivity. The rates of HER2 overexpression and amplification by histologic subtype are shown in Table 1.

HER2-targeted drugs are being used and developed for various malignancies. Currently, trastuzumab, pertuzumab, lapatinib, neratinib, tucatinib[21], trastuzumab emtansine, and trastuzumab deruxtecan[22] have shown clinical activity in HER2-positive breast cancer[19]. For HER2-positive gastric cancer, trastuzumab[23] and trastuzumab deruxtecan[24] have also shown clinical activity. In other carcinomas, HER2-targeted drug therapies are being developed for tumors with HER2 overexpression, amplification, or mutations[25-28]. In endometrial cancer, treatment options are very limited, especially for type II uterine carcinoma, which is resistant to cytotoxic chemotherapy. Therefore, new therapeutic targets and effective new drugs are required.

HER2 overexpression/amplification is currently assessed using immunostaining and fluorescent *in situ* hybridization (FISH)/dual-color *in situ* hybridization. However, there is variability in positive/negative results depending on the type of cancer. In this article, we summarize the methods used to assess HER2 in type II endometrial cancer and the related development of HER2-targeted drugs.

## HER2 TESTING IN ENDOMETRIAL CANCER; PATHOLOGICAL PERSPECTIVE

A significant proportion of endometrial cancers show HER2 overexpression or gene amplification[19,29-31]. The percentage of HER2 positive cases varies by histological type, with serous carcinomas having the highest prevalence of HER2 positivity[29-31]. Standardization of HER2 testing accompanied with evidence-based treatment has not been performed for all endometrial cancers; thus, HER2 testing methods are currently optimized for each histological type, specifically in serous carcinoma and carcinosarcoma.

HER2 testing as companion diagnostics has been best established for breast and gastric cancers, and ASCO/CAP guidelines have been provided[32,33]. The HER2 assessment algorithm is based on the detection of protein overexpression by immunohistochemistry (IHC) and gene amplification by ISH to determine HER2-positive/-

**Table 1 Human epidermal growth factor receptor 2 overexpression and gene amplification in endometrial cancer**

Histological type	HER2 overexpression	HER2 gene amplification	Ref.
Overall	4%-69%	18%-80%	[19,45,55]
Endometrioid (low grade)	rare	rare	[29,45]
Endometrioid (high grade)	8%-31%	15%-29%	[29,45]
Serous carcinoma	20%-60%	13%-29%	[29,42,43,45]
Clear cell carcinoma	33%-70%	22%-50%	[29,55]
Carcinosarcoma	0-25%	13%-20%	[38,48-51]

negative cases[32,33]. Although HER2 overexpression has been reported in other types of carcinomas, in most cases, these two HER2 testing methods are used[19,34] or modified (*e.g.*, in colorectal cancer[35,36]).

In endometrial cancer, HER2 testing has become more clinically relevant in serous carcinoma[37] and carcinosarcoma[38,39], with the accumulating knowledge of HER2 testing accompanied by ongoing therapeutic developments.

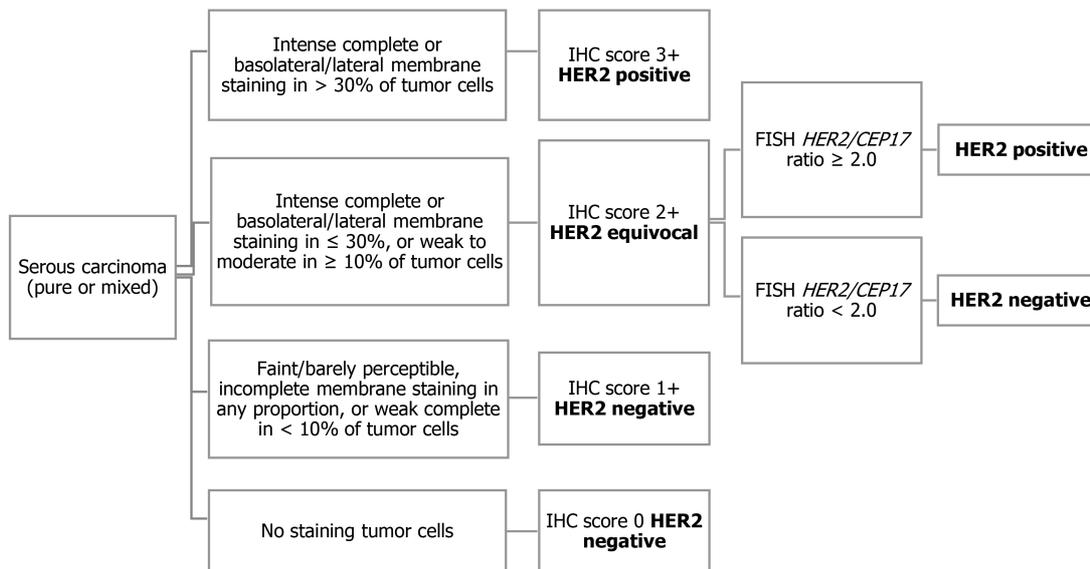
## HER2 TESTING IN SEROUS CARCINOMA

Serous carcinoma accounts for up to 10% of endometrial cancers; however, it is aggressive and responsible for almost 40% of endometrial cancer deaths[40]. Histopathologically, serous carcinoma is usually composed of tumor cells with marked nuclear pleomorphism and presents a complex papillary pattern of typically small, bud-like papillae, irregular slit-like glands, an endometrioid-like glandular pattern, solid nests and sheets, and microcysts[41]. HER2 is overexpressed in 20%-60% of serous carcinomas[29,42-45]; however, less frequent HER2 gene amplification has been reported[43,44]. Notably, the staining pattern of HER2 in serous carcinoma cells has been well studied; approximately 75% of HER2 expressing carcinoma cells reportedly show a basolateral/Lateral membranous staining pattern, similar to that of gastric adenocarcinoma[37]. HER2 assessment of serous carcinoma has been performed using various methods, mainly based on the breast cancer criteria[42-44]. However, an optimal HER2 testing method specific for endometrial serous carcinoma has not been established in the clinical trial setting.

Recently, a randomized phase 2 clinical trial of carboplatin/paclitaxel *vs* carboplatin/ paclitaxel/ trastuzumab in advanced or recurrent HER2 positive serous carcinoma demonstrated the survival benefit of adding trastuzumab[46]. Both prolonged progression-free survival (PFS) and overall survival (OS) were observed in the trastuzumab arm. For patient enrollment in this clinical trial, HER2 status was determined based on the modified 2007 ASCO/CAP breast criteria (Figure 1)[37]. Serous carcinoma showing intense complete or lateral/basolateral membranous HER2 staining in more than 30% of tumor cells were classified as score 3+, and score 2+ was assigned when intense complete or lateral/basolateral membrane staining was seen in  $\leq 30\%$ , or weak to moderate staining in  $\geq 10\%$  of tumor cells. FISH was performed only in tumors with an IHC score of 2+, and a HER2/CEP17 ratio of  $\geq 2.0$  was considered as amplified. Although this HER2 assessment criterion was justified in the context of the treatment effect of trastuzumab-containing regimens, it is still uncertain whether this HER2 testing algorithm should be used in patients receiving HER2 targeted drugs with a different mode of action from that of trastuzumab. For example, HER2-antibody drug conjugate (ADC) has been shown to be clinically effective in patients with low-level HER2 expressing breast cancer who have been assessed as HER2-negative according to the ASCO/CAP breast cancer criteria established for the prediction of response to trastuzumab[47]. The HER2 testing algorithm was optimized to maximize patient benefit and safety for each HER2 targeted therapy.

## HER2 TESTING IN UTERINE CARCINOSARCOMA

Uterine carcinosarcoma (UCS) is a rare and high-grade subtype of endometrial cancer (WHO2020) and is characterized by the presence of both carcinomatous and



**Figure 1** Human epidermal growth factor receptor 2 testing for serous carcinoma used in the Phase 2 clinical trial[37,46]. IHC: Immunohistochemistry; FISH: Fluorescent in situ hybridization.

sarcomatous components that are usually intimately admixed. The carcinomatous component is usually a high-grade endometrioid, serous, clear, or nonspecific carcinoma. HER2 is a promising therapeutic target for UCS. *HER2* gene amplification has been reported in 13%-20% of UCS cases[48,49]. Additionally, HER2 overexpression (IHC score 3+) reportedly ranges from 0 to 25%[38,49-51].

An evidence-based HER2 testing protocol for UCS has not been fully established; thus, several researchers have adopted HER2 testing protocols and assessment methods based on ASCO/CAP recommendations for HER2 testing for breast cancer and gastroesophageal cancer.

Recently, we proposed several requirements for HER2 testing in UCSs[39]. Our evaluation method has been used in the ongoing phase 2 clinical trial of HER2 ADC in patients with recurrent/metastatic UCS (STATICE trial)[52]. In this study, we identified that most UCS showed lateral/basolateral staining patterns (Figure 2), similar to endometrial serous carcinoma and gastric adenocarcinoma[39]. Based on our previous observations, we concluded that a HER2 testing protocol for UCS should contain the following requirements[39]: (1) Established pre-analytical factors of HER2 IHC[32,33] should be carefully controlled; (2) One representative section containing carcinoma components should be submitted from the hysterectomy specimen; (3) HER2 IHC should be performed using an IVD kit or a laboratory-developed test with appropriate quality control[32,33]; (4) Positive lateral/basolateral membranous staining patterns should be considered as positive, according to the 2016 ASCO/CAP gastric cancer criteria[32]; and (5) The proportion of HER2 expressing tumor cells should be determined as an approximate number of HER2-positive tumor cells divided by that of total tumor cells (both carcinoma and sarcomatous elements). Unfortunately, we did not provide supporting data for the best scoring system based on the patient clinical outcomes. However, we would report the correlation between treatment efficacy and HER2 score in patients with UCS in 1-2 years.

## FUTURE DIRECTION OF HER2 TESTING IN ENDOMETRIAL CANCER

Most quality assurance of HER2 testing should be performed in accordance with well-established methods for breast and gastric cancer. In addition, we should consider specific issues for HER2 testing in endometrial cancers, including correlation with specific treatment response, intratumoral heterogeneity of HER2 status, discordant HER2 status between the primary site and metastasis, improvement of interobserver reproducibility of HER2 assessment, and use of liquid biopsy in the future.

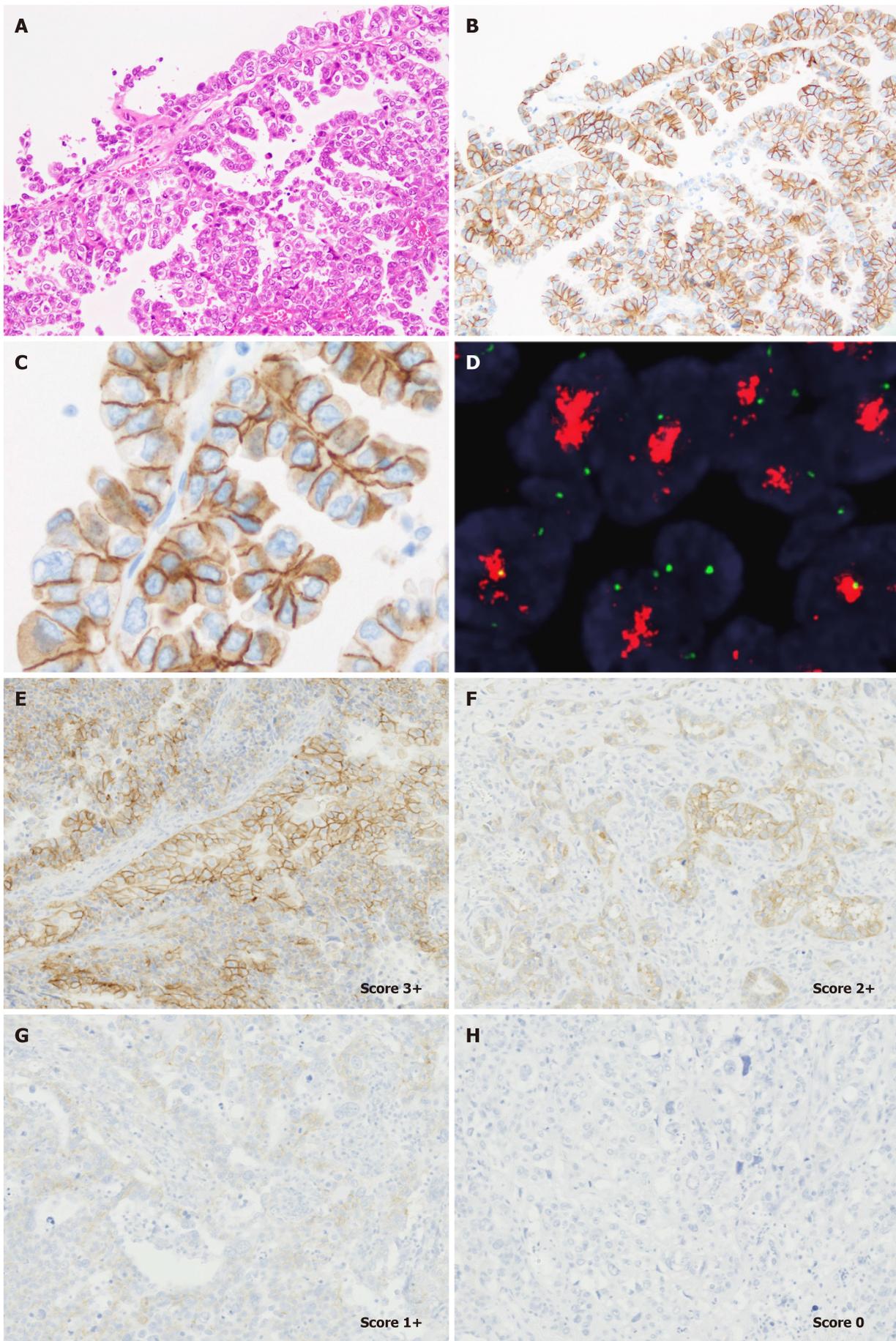


Figure 2 Representative staining patterns of human epidermal growth factor receptor 2 and fluorescent in situ hybridization results in

**uterine carcinosarcoma.** Serous-like carcinoma component (A) shows diffuse strong membranous staining of Human epidermal growth factor receptor 2 (HER2) (B). Most tumor cells show lateral or basolateral membranous staining patterns (C). *HER2* amplification observed in these tumor cells using fluorescent in situ hybridization (D). Representative images of HER2 score according to ASCO/CAP gastric cancer criteria. Score 3+ (E), score 2+ (F), score 1+ (G), and score 0 (H) ( $\times 200$ ). A (H&E,  $\times 100$ ); B, E-G, and H (HER2,  $\times 100$ ); C (HER2,  $\times 400$ ). FISH: Fluorescent in situ hybridization; H&E: Hematoxylin and eosin.

## CURRENT THERAPIES AND FUTURE DIRECTIONS FOR HER2 TARGETED THERAPIES FOR UTERINE SEROUS CARCINOMA AND UTERINE CARCINOSARCOMA

Trastuzumab is the most popular HER2-targeted drug. Several case reports have shown that trastuzumab had clinical activity in patients with endometrial cancer[53, 54]. Fleming *et al*[55] investigated the efficacy of trastuzumab as a single agent in HER2-positive endometrial carcinoma in a GOG study (Table 2). However, the overall response rate was 0%, and no significant clinical activity was observed. A possible issue was that many endometrioid carcinomas with low HER2 positivity were screened, and the study had early termination with poor accrual. Lapatinib is a dual inhibitor of EGFR and HER2 used in HER2-positive breast cancer. The GOG 229D[56] trial examined the efficacy of lapatinib in uterine cancer ( $n = 2$  for HER2-positive) in a phase II trial. The response rate was 3%, the median PFS was 1.82 mo, and clinical activity could not be demonstrated. This lack of clinical activity could be explained by the unselected patient population. Therefore, further studies are warranted to highlight type II endometrial carcinoma patients with high HER2-positivity.

Fader *et al*[46] conducted a randomized phase II trial to evaluate the effect of trastuzumab on carboplatin and paclitaxel, the standard of care for HER2-positive USC. The median PFS [12.6 mo *vs* 8.0 mo; hazard ratio (HR) = 0.44, 90% confidence interval (CI): 0.26-0.76,  $P = 0.005$ ] was significantly different between the two groups. Updated analysis (median PFS 12.9 mo *vs* 8.0 mo; HR = 0.46, 90% CI: 0.28-0.76;  $P = 0.005$ , median OS 29.6 mo *vs* 24.4 mo; HR = 0.58, 90% CI: 0.34-0.99;  $P = 0.46$ ) showed clinically significant benefit[57]. The addition of trastuzumab to carboplatin and paclitaxel chemotherapy represents a new standard treatment for USC. In the NCCN guidelines, carboplatin, paclitaxel, and trastuzumab combination therapy are recommended in Category 2A for advanced or recurrent USC[58].

Several basket trials in HER2-positive solid tumors, including endometrial carcinoma, have been reported. MyPathway is a phase II, multiple basket study with patients with advanced refractory solid tumors harboring molecular alterations such as *HER2*, *BRAF*, *EGFR*, and the Hedgehog pathway[25]. Patients with *HER2* alterations were treated with pertuzumab plus trastuzumab. Eight patients with HER2-positive endometrial carcinoma received trastuzumab plus pertuzumab. No responses were observed. The efficacy of trastuzumab emtansine has also been evaluated in a phase II basket trial, including HER2-positive endometrial carcinoma[59]. This trial demonstrated that 18 patients with uterine cancer (subtype unknown) were included, and two patients had a complete response and two had a partial response (PR), suggesting high efficacy.

Currently, several clinical trials of HER2-targeted drugs are ongoing. The DESTINY-PanTumor02 trial is a basket trial to evaluate the efficacy of trastuzumab deruxtecan in HER2-positive tumors, including endometrial carcinoma (NCT04482309). A phase I trial evaluating combination therapy with trastuzumab deruxtecan and olaparib in HER2-positive USC is also ongoing (NCT04585958). In HER2-positive UCS, the STATICE trial is a phase II trial to evaluate the efficacy of trastuzumab deruxtecan (UMIN00002956, NCCH1615)[52].

Novel therapeutic agents targeting HER2 have emerged. Trastuzumab duocarmazine (known as SYD985) is a novel HER2-targeted ADC that combines trastuzumab with duocarmazine, a DNA alkylating agent, as a payload. Trastuzumab duocarmazine has shown preclinical anti-tumor activity in USC[60]. Banerji *et al*[61] demonstrated phase 1 dose-escalation and dose-expansion study in breast, gastric, urothelial, and endometrial carcinomas that express HER2. Thirteen patients with endometrial cancer were included in the dose-expansion cohort. Five patients (39%) had PR, and the median PFS was 4.3 mo[61]. Treatment-related serious adverse events were reported in 11% of patients, and the frequency of cardiac toxicity did not increase compared with previous anti-HER2 drugs. Most patients had ocular adverse events, such as conjunctivitis, dry eye, and lacrimation. Trastuzumab duocarmazine has a manageable safety toxicity profile[61]. Further investigation of trastuzumab duocarmazine is ongoing in phase III trials for HER2-positive breast cancer (TULIP study,

**Table 2 Human epidermal growth factor receptor 2-targeted therapies for uterine serous carcinoma and carcinosarcoma**

Trial	Phase	Participants	Treatment	Efficacy/identifier
GOG181B[55]	II	HER2-positive EC ( <i>n</i> = 33, endometrioid: 13, serous: 11, clear: 3, others: 6)	Trastuzumab	ORR 0%, mPFS 1.84 mo, mOS 7.8 mo
GOG229D[56]	II	Persistent or recurrent EC ( <i>n</i> = 31, endometrioid: 16, serous: 7, clear: 3, others: 5, HER2-positive: <i>n</i> = 2)	Lapatinib	mPFS 1.82 mo, mOS 7.33 mo
Fader <i>et al</i> [46,57]	II	HER2-positive USC ( <i>n</i> = 61)	carboplatin+paclitaxel+trastuzumab <i>vs</i> carboplatin+paclitaxel	mPFS 12.9 mo <i>vs</i> 8.0 mo, mOS 29.6 <i>vs</i> 24.4 mo
MyPathway[25]	Phase IIa Multiple basket study	Solid tumor(HER2-positive EC, <i>n</i> = 7)	Trastuzumab+pertuzumab	ORR 0%(EC)
Li <i>et al</i> [59]	II	HER2 amplified cancer (endometrial cancer: <i>n</i> = 18)	Trastuzumab emtansine	Endometrial cancers: CR 2, PR 2
DESTINY-PanTumor02[77]	II	HER2 expressing tumor (urothelial, biliary tract, cervical, endometrial, ovarian, pancreatic, rare tumors)	Trastuzumab deruxtecan	NCT04482309
Veneris[78]	I	HER2-positive USC	Trastuzumab deruxtecan+olaparib	NCT04585958
Banerji <i>et al</i> [61]	I	Dose-expansion cohort: HER2-positive breast, gastric, urothelial, endometrial cancer	SYD-985 (Trastuzumab duocarmazine)	Endometrial cancer: ORR 39%, mPFS 4.3 mo
Koper[79]	I	HER2-positive solid tumor	SYD-985 (Trastuzumab duocarmazine)+Niraparib	NCT04235101
Hendriks[80]	II	HER2-positive endometrial cancer	SYD-985 (Trastuzumab duocarmazine)	NCT04205630
STATICE[52]	II	HER2-positive UCS	Trastuzumab deruxtecan	UMIN00002956 (NCCH1615)
Makker[81]	II	HER2-positive endometrial cancer, UCS	ZW25	NCT04513665
Ramos[82]	II	HER2-positive solid tumors	Tucatinib and trastuzumab	NCT04579380

EC: Endometrial cancer; USC: Uterine serous carcinoma; UCS: Uterine carcinosarcoma; CR: Complete response; mOS: Median overall survival; mPFS: Median progression-free survival; ORR: Objective response rate; PR: Partial response.

NCT03262935), phase II trials for HER2-positive endometrial cancer (NCT04205630), and phase I trial for HER2-positive solid tumor combination with niraparib (NCT04235101).

There are important considerations for future studies. Anti-HER2 therapy has been successful in HER2-positive breast cancer, but most of these drugs have not been successful in non-breast HER2-positive solid tumors. One explanation for these differences is the pattern of HER2 expression and heterogeneity within the tumor. Since the HER2 expression pattern of USC and UCS is similar to that of gastric cancer, but not breast cancer, it is possible that the same HER2-targeted therapy may have similar effects.

The first consideration may be to focus on combination therapies and ADC drugs rather than HER2 blockade alone in endometrial cancer. The second consideration is to overcome the resistance to HER2 targeted agents. Mechanisms of resistance to HER2 targeted therapy have been studied and can be classified into four groups: intratumoral heterogeneity, alterations in the binding site, activation of downstream signals, and overexpression of other HER2 family members[62]. The strategy against intratumoral heterogeneity could be a bystander effect of clinical activity against not only targeted cells but also surrounding cells. A novel HER2 ADC drug, trastuzumab deruxtecan, and trastuzumab duocarmazine showed a bystander effect *in vitro* and *in vivo*, and showed anti-tumor activity in clinical trials with low HER2 positivity[47,60, 63-65]. Alteration in the binding site of HER2 and extracellular domain shedding could be overcome using irreversible inhibitors. In preclinical studies, afatinib and neratinib are irreversible pan-HER inhibitors that show anti-tumor activity in USC and gynecologic carcinosarcoma[66-68]. Tucatinib is an HER2 and HER3 kinase inhibitor, combination with trastuzumab are investigated in baskets study of Solid tumor with HER2 alterations, including uterine neoplasms. In downstream pathway alterations, the gain of function in PI3K is well known as resistance to HER2. Combined HER2 and PI3KCA dual inhibition using neratinib and taselisib were effective in cell lines and

xenograft models of USC[69,70]. Of overexpression of other HER2 family members, HER3 overexpression plays an important role. The formation of HER2-HER3 heterodimers is most related to resistance to anti-HER2 therapy. Pertuzumab is an HER2 antibody that binds to a different epitope from that of trastuzumab and inhibits dimerization. In breast cancer, the combination of trastuzumab and pertuzumab improved clinical outcomes[71]. Pertuzumab and trastuzumab showed anti-tumor activity in USC cell lines[72]. Although these drug combinations showed no clinical benefit in the Mypathway trial with HER2 amplification in endometrial cancer[25], further investigation is warranted. Several HER2 bispecific antibodies have been developed that simultaneously bind to two distinct HER2 epitopes, the same domain as trastuzumab and pertuzumab[73]. Researchers demonstrated a phase 1 basket trial to evaluate ZW25, one of HER2 bispecific antibodies, in HER2 positive solid tumors, including endometrial cancer. Of 17 evaluable patients, seven patients (41%) had an objective response, and the median PFS was 6.2 mo[74]. ZW25 is investigated in phase 2 clinical trial of HER2 overexpressed advanced endometrial cancer and carcinosarcomas.

In addition, there is rapidly growing HER2-directed immunotherapy in patients with HER2-positive solid tumors[19,75]. Several drugs with a different target, such as bispecific antibodies, immune-stimulating conjugates, vaccines, and adoptive T-cell therapies, are under investigation[76]. The bispecific HER2/CD3 antibodies BTRC4017A, GBR-1302 and M802 induce cytotoxic effect by interaction with HER2 on tumor cell and CD3 on cytotoxic T cell. NJH395 are immune-stimulating antibody conjugates which HER2 antibody links to payload as toll-like receptor 7 (TLR7) and TLR8. Stimulating TLR activated natural killer cells and antigen-presenting cells and facilitate invasion of CTLs to tumor tissues. PRS-343 increases tumor lymphocyte invasion *via* targeting HER2 and CD137 (4-1BB). CD137 is known as a co-stimulating factor of T cell activation[73]. We expect a further investigation of these drugs in patients with endometrial cancer.

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## CONCLUSION

In this review, we provided an overview of HER2-overexpression/amplification in endometrial cancer, pathological evaluation methods, and the current status of HER2-targeted therapies. With the advent of precision medicine, the development of therapies targeting biomarkers has become increasingly advanced. In the development of anti-HER2 inhibitors and ADC drugs targeting HER2, it may be important to develop not only a single drug but also combination therapies. Since there are limited therapeutic agents for endometrial cancer, especially for type II, the development of HER2-targeted therapy is urgently needed.

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