Review Article | Data-Driven Clinical Practice and Policy Making

Narrative review on the evolving role of HER2/neu targeting in uterine serous cancers

Aarthi S. Jayraj[1]^, Salamatu Abdul-Aziz[1], Anisa Mburu[2]^, Avinash Upadhyay[3]^, Nilanchali Singh[4]^, Prafull Ghatage[5]^

[1]Department of Gynaecologic Oncology, James Cook University Hospital, South Tees NHS Foundation Trust, Middlesbrough, UK; [2]Department of Gynaecologic Oncology, Aga Khan Hospital, Mombasa, Kenya; [3]Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India; [4]Department of Gynaecologic Oncology, All India Institute of Medical Sciences, New Delhi, India; [5]Department of Gynecological Oncology, Tom Baker Cancer Centre, Calgary, Alberta, Canada

Contributions: (I) Conception and design: AS Jayraj, P Ghatage; (II) Administrative support: AS Jayraj, S Abdul-Aziz, P Ghatage; (III) Provision of study materials or patients: AS Jayraj, S Abdul-Aziz; (IV) Collection and assembly of data: AS Jayraj, S Abdul-Aziz, A Mburu; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prafull Ghatage, FRCSC. Department of Gynecological Oncology, Tom Baker Cancer Centre, 1331-29th Street NW, Calgary, Alberta T2N 4N2, Canada. Email: Prafull.Ghatage@albertahealthservices.ca.

Background and Objective: Serous endometrial cancers (ECs) are an aggressive histotype of ECs which are disproportionately responsible for 40% of cancer-specific mortality rates despite constituting only 5–10% of all uterine cancers in incidence. In recent times, it has become increasingly evident that about 20–40% of uterine serous cancers (USCs) have molecular alterations in *ERBB2* pathway with human epidermal growth factor receptor 2 (HER2/neu) amplification or overexpression. We summarise the evidence on genetic and molecular alterations in HER2/neu pathway in USC with a focus on testing criteria, targeting agents and resistance mechanisms.

Methods: We conducted a database search of PubMed/Medline up to 28th February 2023 for articles published in the English language using pre-defined search terms. One hundred and seventy-one relevant articles were subsequently reviewed for eligibility and inclusion in the review.

Key Content and Findings: The Cancer Genome Atlas (TCGA) classification is a significant development in the molecular profiling of ECs with a positive impact on the treatment of these tumors including USCs. Testing criteria for HER2/neu in USC with immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) has evolved in more than a decade with progress made towards EC specific testing guidelines. The findings of a recent phase III study have led to the development of practice changing guidelines towards improving patient outcomes.

Conclusions: Molecular aberration in the HER2/neu pathway contributes to the aggressive behaviour of USC. Considering the clinical benefit conferred by HER2/neu targeted therapy, HER2/neu testing is recommended for all cases of serous EC in advanced and recurrent settings. Trastuzumab in combination with platinum and taxanes based chemotherapy is the recommended treatment option for patients with advanced or recurrent serous cancers who test positive to HER2/neu. Clinical trials on targeted therapy are ongoing and future research should focus on selection of patients who will derive the most benefit from such therapy.

Keywords: Human epidermal growth factor receptor 2 (HER2/neu); targeted therapy; uterine serous cancer (USC); trastuzumab

^ ORCID: Aarthi S. Jayraj, 0000-0002-6913-6876; Anisa Mburu, 0000-0002-6481-3110; Avinash Upadhyay, 0000-0002-7306-0499; Nilanchali Singh, 0000-0002-4141-8441; Prafull Ghatage, 0000-0002-2371-0844.

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Introduction

Background

Endometrial cancer (EC) is one of the most common cancers affecting women worldwide. In the year 2020, there were over 417,000 new cases of EC and 97,000 deaths globally (1). Uterine serous cancer (USC) is an aggressive histological subtype of EC which accounts for 39% of all deaths due to EC despite constituting only 10% of all ECs in incidence (2). Historically, EC was categorised in to two groups: type I which are predominantly low-grade endometroid tumors and type II consisting of USC, clear cell carcinoma, carcinosarcoma and grade 3 endometroid tumors (3). Similar to endometroid EC, USC usually presents with postmenopausal bleeding but often arises from an endometrial polyp on a background of atrophic endometrium (4). In apparently early-stage disease, there is a tendency for lympho-vascular space invasion (LVSI), lymph node involvement and intra-peritoneal spread despite minimal or no myometrial invasion. All stage 5-year overall survival (OS) of USC is much lower than endometroid EC at 52% *vs.* 83% respectively (5). Therefore, in contrast to endometroid EC which has an excellent prognosis at early stages of the disease, USC is a high-grade tumor with high recurrence rates and poorer prognosis (6,7).

USC has been associated with increasing age, women of black ethnicity, history of breast cancer and tamoxifen use (8). Contrary to previous data, obesity is reported to be a risk factor for USC although it appears to be hormone independent (8,9). Population studies on EC have demonstrated racial disparities in the incidence, management and outcomes of women affected by the disease. Data suggest that black women are at increased risk of non-endometroid tumors including USC, present at advanced stages and have lower OS rates in comparison with white women (10,11).

Objective

In the recent years, the HER2/neu pathway has emerged as a commonly affected molecular aberration in USCs that contributes to their aggressive nature. Biomarker testing guidelines have not yet been defined for such tumors and the efficacy of HER2/neu targeting agents have been uncertain. The main objective of this article is to review the evidence regarding testing and reporting of HER2/neu amplification/overexpression in USCs and define the role of HER2/neu targeting agents in these cases. We focus on the methods of testing and interpreting HER2/neu overexpression/amplification in USCs. A summary of various preclinical and clinical trials available for HER2/neu targeting agents in USCs, the efficacy of such therapeutic targeting, emerging therapies and future directions have been outlined. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1465/rc).

Methods

PubMed/Medline database was searched for articles on HER2/neu testing and targeting in USCs from inception to 28th February 2023. The search terms used were "HER2", "HER2/neu", "Her2neu", "uterine serous cancer", "uterine papillary serous cancer", "serous endometrial cancer", "trastuzumab", "pertuzumab", "T-DM1" and "trastuzumab emtansine" (*Table 1*). Backward and forward reference searching was done on retrieved articles to include any articles which answer the study objectives. Results and references of interim study reports were updated after the date of the initial search when full results were published. The retrieved articles were analysed and summarized in the review (*Figure 1*).

Discussion

Molecular profile and classification

USCs demonstrate the typical histological features of serous differentiation, papillary architecture, nuclear atypia and pleomorphism, slit-like spaces, scanty cytoplasm and psammoma bodies in one-third of cases (12,13). Historically, the Bokhman's binary system was used to classify ECs into type I and type II tumors with distinct clinical, pathological and prognostic indicators. The Cancer Genome Atlas (TCGA) classification system categorises EC into four

Table 1 Summary of search strategy

Items	Specification
Date of search	28th February 2023
Databases and other sources searched	PubMed/Medline
Key search terms used	"HER2", "HER2/neu", "Her2neu", "uterine serous cancer", "uterine papillary serous cancer", "serous endometrial cancer", "trastuzumab", "pertuzumab", "T-DM1" and "trastuzumab emtansine"
Timeframe	Inception to February 2023
Inclusion and exclusion criteria	Inclusion: original and review articles in English language with a focus on HER2/neu testing and HER2/neu targeted therapy in USC
	Exclusion: studies where main topic is not focussed on USC
Selection process	Retrieved articles were reviewed independently for eligibility for inclusion by two reviewers (A.S.J. and S.A.A.). Differences in opinion were resolved by third author (P.G.)

HER2/neu, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; USC, uterine serous cancer.

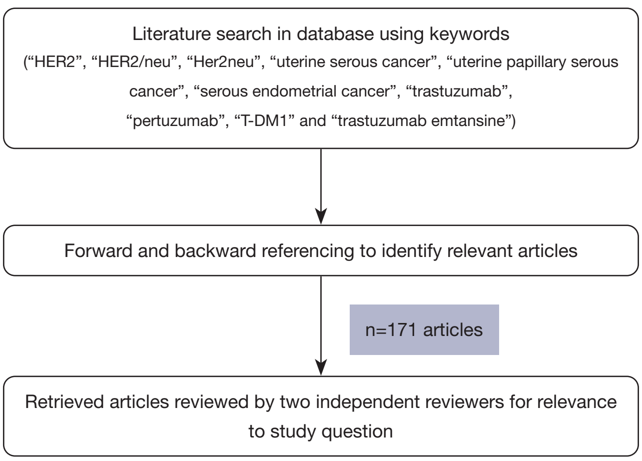

Figure 1 Literature search strategy. HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

groups: (I) POLE ultra-mutated EC; (II) microsatellite instability hypermutated EC due to dysfunctional DNA mismatch repair proteins; (III) copy number low/microsatellite stable EC which are mostly endometroid (49%); (IV) copy number high with *TP53* mutations in >90% and include USC (14). In the study by the TCGA Network, 50 of the 53 (94%) serous tumors analysed were classified under the cluster 4 (copy number high) group and had significantly recurring amplifications of *HER2/neu* oncogene. This group was also associated with significantly worse progression-free survival (PFS) compared to the endometrioid clusters and was suggested as a potential therapeutic target (15). Several other studies have shown a strong correlation between *TP53* mutation and HER2/neu expression and/or amplification in ECs (16,17). Other gene mutations identified in USC include *PIK3CA*, *PPP2R1A*, *ERBB2* (also known as *HER2* and *HER2/neu*) and *CHD4* (12,15,18).

HER2/neu receptor in USC

HER2/neu receptor is a 185-kDa, 1,225-aminoacid transmembrane glycoprotein tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family encoded on the *ErbB-2* gene found on the long arm of chromosome 17 and is also known as *Erb-b2*, *ERBB2*, *c-erbB-2* or $p185^{HER2}$. It consists of an extracellular domain which binds with other members of the EGFR family, a membrane spanning hydrophobic transmembrane domain and an intracellular domain responsible for the kinase action (19). HER2/neu receptor is an orphan receptor as it does not have a direct ligand. Instead, it binds with the extracellular domain to other EGFR family ligands activated by EGF ligand interaction. Such homo- or hetero-dimerization leads to activation of the intracellular tyrosine kinase function by autophosphorylation which in turn leads to activation of downstream signaling molecules and results in growth and proliferation. The various downstream pathways that are activated by HER2/neu receptor activation includes Ras/Raf/mitogen-activated protein (MAP) kinase, the PI3K/Akt, and the phospholipase Cγ (PLCγ)/protein kinase C (PKC) pathways. In malignant cells, activation of these mitogenic cell signaling pathways leads to proliferation, invasion, angiogenesis, migration and cell survival (20). HER2/neu mediated tumorigenesis can occur due to overexpression of the proto-oncogene coding for HER2/neu receptor or by overactivation of the receptor, though the former appears to be the most common case in clinical studies (19).

Non oncogenic activity of the HER2/neu receptors is important for the development of organs such as skin, breast, gastrointestinal, reproductive and urinary tracts (21). HER2/neu receptor overexpression has been described in tumorigenesis of a number of cancers including breast, gastric, ovary and uterine serous carcinoma (22,23). In USC, overexpression and/or amplification of HER2/neu by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) respectively ranges from 16–48% (24-28). HER2/neu positive tumors were associated with advanced disease, myometrial invasion (24,25), lymphovascular space invasion (LVSI) (25,26), higher recurrence rates (24,26), as well as poorer overall and disease-free survival (24-28). In essence, the presence of the HER2/neu oncogene confers a more biologically aggressive disease with poorer prognosis.

There also appears to be a trend towards higher expression and amplification of HER2/neu in black women. Retrospective single centre studies by Santin *et al.* and Morrison *et al.* reported HER2/neu amplification in black women in the range of 18–67% (27,29). Similarly, overexpression of HER2/neu in black women ranges from 33–90% in comparison to 13–48% in white women (29,30). These findings have also been correlated with poorer survival in both studies. Further analysis of intensity of IHC staining revealed that heavy (3+) IHC staining in keeping with HER2/neu overexpression was increased in black women and appears to be the strongest prognostic factor for shorter survival (30).

HER2/neu testing and reporting in USC

HER2/neu testing in patients with USC is of paramount importance, as therapeutic decisions and prognostication depends on the accuracy of testing. The criteria for testing in USC were derived from pre-existing standardised protocols for testing in breast and gastric cancers (31-33). HER2/neu protein overexpression on IHC and amplification by FISH or chromogenic in situ hybridization (CISH) have been described in the literature to define HER2/neu positivity in tumor (34-36) (*Table 2*).

HER2/neu overexpression

Correlation between HER2/neu overexpression, IHC scoring systems and clinical performance have not been satisfactorily elucidated in women with serous ECs. Data on HER2/neu expression from breast cancer cells cannot be extrapolated for USC as it has been widely recognised now that the staining pattern and expression are different for different organs (46). The expression and amplification of HER2/neu differs between tumors of different organs so does the pattern of staining observed in breast, gastric and USC (33). HER2/neu positive breast tumors usually demonstrate a relatively uniform and circumferential staining on IHC while lateral or basolateral, i.e., 'U-shaped' staining is seen more frequently in gastric and USC (31). In addition, tumors with basolateral/lateral membranous staining as seen in gastric and serous ECs demonstrated a glandular or pseudo-glandular pattern. Recognition of these differences is important when applying existing guidelines for breast and gastric cancer to HER2/neu testing in USC and highlights the need for testing guidelines specific to EC. Previous studies evaluating HER2/neu expression in endometrial tumors have used the IHC scoring definition of 3+ if >10% cells in the tumor have shown strong complete membrane staining to define HER2/neu positive cells (24,30,38,40,47). Recent studies have found that using a scoring criterion of >30% cells showing strong complete membrane staining to define HER2/neu positive tumors to be more concordant with clinical behaviour (43). Another issue to consider is whether to consider 2+ IHC scoring tumors as HER2/neu positive or equivocal. Though the initial GOG trials have considered such tumors to be HER2/neu positive (38,40), the eligibility as HER2/neu positive tumor in the recent trial by Fader *et al.* necessitates all 2+ IHC scoring tumors to be confirmed with FISH for gene amplification. The criteria employed defined a specific group with HER2/neu positive tumors who derived significant clinical benefit from targeted therapy as demonstrated even in the subsequent OS results (43,48).

HER2/neu amplification

Amplification by FISH is expressed as the ratio of HER2/neu to chromosome enumeration probe 17 (HER2/neu:CEP17) and HER2/neu copy number signal per cell (49). The International Society of Gynecological Pathologists (ISGyP) published practical recommendations

Table 2 HER2/neu amplification and overexpression in uterine papillary serous carcinoma

Study	Sample size	HER2/neu overexpression by IHC				HER2/neu amplification by FISH			Concordance between IHC and FISH
		Test kit	Scoring criteria	2+	3+	Probe	Criteria	Incidence	
Villella *et al.*, 2006 (37)	17 USC	DAKO Herceptest (positive if >5% crisp membranous staining of tumor cells)	Negative: 0; focally positive: 1+; strongly positive: 3+	Not described	29.4% (5/17)	PathVysion HER2 probe	HER2/neu:CEP17 >2.5	36.4% (4/11)	27.3% (3/11)
Morrison *et al.*, 2006 (29)	58 USC, 425 non-serous	Ventana Pathway HER2	Negative: 0/1+; positive: 2+/3+	43.1% (25/58)		PathVysion HER2 DNA probe	HER2/neu:CEP17 ≥2.2	29.3% (17/58)	Not reported
Grushko *et al.*, 2008 (GOG 177) (38)	38 USC and 196 non-serous EC	DAKO Herceptest	Negative: 0/1+; positive: 2+/3+	34.2% (13/38)	26.3% (10/38)	Path Vision DNA probe	Modified ASCO/CAP breast [2007]	21.4% (6/28)	Overall: 60%
Xu *et al.*, 2010 (39)	75 pure serous carcinomas + additional 13 pure serous analysed	HercepTest	Scoring criteria not described	2.7% (2/75), 30.8% (4/13)	9.3% (7/75), 23.1% (3/13)	PathVysion DNA probe	Modified ASCO/CAP breast [2007]	9/75, 4/13	–
Fleming *et al.*, 2010 (40)	286 advanced or recurrent EC (only FISH positive tumors included), 11 USC, 22 non-serous	DAKO Herceptest	Negative: 0/1+; positive: 2+/3+	61.1% (22/36)	38.9% (14/36)	PathVysion HER2 DNA Probe Kit	Modified ASCO/CAP breast [2007]	11.5% (33/286)	Positive correlation; Spearman's correlation coefficient =0.354 (95% CI: 0.17–0.51)
Todeschini *et al.*, 2011 (41)	10 USC	DAKO Herceptest kit	Positive: 3+	10.0% (1/10)	50.0% (5/10)	PathVysion HER2 DNA Probe Kit	Modified ASCO/CAP breast [2007]	50%	Not reported
Buza *et al.*, 2013 (31)	85 USC & 23 mixed EC with a serous component	DAKO Hercept testing	Manufacturer *vs.* modified 2007 ASCO/CAP; positive: 3+; equivocal: 2+; negative: 0/1	FDA scoring criteria: 14.8%; ASCO/CAP scoring criteria: 21.3%	FDA scoring criteria: 27.8%; ASCO/CAP scoring criteria: 23.2%	PathVysion HER2 DNA Probe Kit	Modified ASCO/CAP breast [2007]	16.7% (18/108)	75% when using the FDA criteria and 81% when using the 2007 ASCO/CAP criteria; after excluding 2+ IHC: 78% using the FDA criteria and 86% using the 2007 ASCO/CAP criteria
Buza & Hui, 2013 (42)	17 USC with heterogenous HER2 expression	DAKO Herceptest	Modified 2007 ASCO/CAP; positive: 3+/2+; negative: 0/1+	8/17	9/17	PathVysion HER2 DNA Probe Kit	Modified ASCO/CAP breast [2007]	47.1% (8/17) including 2+ initial reflex FISH testing; 82% on repeat testing showing diffuse and cluster amplification	Not reported
Fader *et al.*, 2018 (43)	58 advanced or recurrent USC	–	Modified 2007 ASCO/CAP; positive: 3+/2+ (confirmed with FISH)	Not reported	Not reported	–	Modified ASCO/CAP breast [2007]	Not reported	Not reported
Erickson *et al.*, 2020 (26)	169 stage 1 USC	DAKO HercepTest or Ventana PATHWAY anti-HER2 (4B5)	Modified 2007 ASCO/CAP; negative: 0/1+; equivocal: 2+ (confirmed with FISH); positive: 3+	24.9% (42/169)	16.6% (28/169)	PathVysion HER2 DNA Probe Kit and Dako IQFISH kit	ASCO/CAP breast [2013]	38.1% (16/42)	Not reported
Tymon-Rosario *et al.*, 2021 (44)	12 USC cell lines	Thermo Fisher Scientific c-erbB-2 antibody	Modified 2007 ASCO/CAP; positive: 3+; equivocal 2+; negative: 0/1+	16.7% (2/12)	25.0% (3/12)	PathVysion HER2 DNA Probe Kit	Modified ASCO/CAP breast [2007] (39)	25.0% (3/12)	Not reported
Buza & Hui, 2022 (33)	66 USC, 13 mixed endometrial (94 tumor specimens)	Abcam EP3 Clone	Modified 2007 ASCO/CAP; positive: 3+; equivocal 2+ reflex HER2 FISH; negative: 0/1+	90.4% (85/94)	3.2% (3/94)	PathVysion HER2 DNA Probe Kit	Four criteria used: (I) modified ASCO/CAP breast [2007]; (II) ASCO/CAP breast [2013]; (III) ASCO/CAP gastric [2016]; (IV) ASCO/CAP breast [2018]	38.3% (36/94) based in modified ASCO/CAP [2007]; 39.4% (37/94) based on the other 3 guidelines	Not reported

Scoring criteria for overexpression on IHC: manufacturer's scoring criteria (FDA approved): (I) Vertana pathway: 0, no staining or staining without membranous pattern; 1+, incomplete membranous staining or complete membranous staining in <10% of tumor cells; 2+, complete moderate intensity membranous staining in >10% of tumor cells; 3+, complete strong intensity membranous staining in >10% of tumor cells; (II) Dako Hercept: 0, undetectable staining or membrane staining in <10% of the tumor cells; 1+, faint and incomplete membrane staining in >10% of the tumor cells; 2+, weak to moderate complete membrane staining in >10% of the tumor cells; 3+, strong complete membrane staining observed in >10% of the tumor cells; ASCO/CAP [2007] scoring (45): 0, no staining is observed in invasive tumor cells; 1+, weak, incomplete membrane staining in any proportion of invasive tumor cells or weak, complete membrane staining in o10% of cells; 2+, complete membrane staining that is non-uniform or weak but with obvious circumferential distribution in at least 10% of cells or intense complete membrane staining in ≤30% of tumor cells; 3+, uniform intense membrane staining in >30% of invasive tumor cells. Scoring criteria for amplification with FISH (33): (I) modified ASCO/CAP breast [2007]: HER2/neu:CEP17 ≥2.2 OR HER2/neu copy number >6.0/nucleus; (II) ASCO/CAP breast [2013]: HER2/neu:CEP17 ≥2.0 OR HER2/neu:CEP17 <2.0 AND HER2/neu copy number ≥6.0/nucleus; (III) ASCO/CAP gastric [2016]: HER2/neu:CEP17 ≥2.0 OR HER2/neu:CEP17 <2.0 AND HER2/neu IHC is 2+ AND CEP17 ≥3.0/nucleus AND HER2/neu copy number >6.0/nucleus; (IV) ASCO/CAP breast [2018]: HER2/neu:CEP17 ratio ≥2.0 AND average HER2/neu copy number ≥4.0/ nucleus (Gr 1); OR Gr 2 with IHC 3+, Gr 3 with IHC 2+ OR 3+, Gr 4 with IHC 3+. HER2/neu, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; USC, uterine serous cancer; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; EC, endometrial cancer; CI, confidence interval; FDA, Food and Drug Administration.

allowing tumors with an IHC score of 2+ with FISH HER2/neu:CEP17 ratio ≥2.0 or <2.0 with average HER2/neu copy number ≥6/nucleus to be designated as HER2/neu positive tumors, in addition to those scoring 3+ on IHC. While definite testing guidelines are yet to be established, these criteria could form the basis for future guideline development for EC (46).

Challenges in HER2/neu testing for USC

Concordance between the two testing modalities has also been an important subject area of previous studies. Reported concordance rates between IHC and FISH/CISH in USC differ significantly with estimated rates between 32% and 100% (35,36). The highest concordance was observed in tissues staining 3+ on IHC (35). It is important to note however that testing methods and scoring criteria do vary between studies and could have contributed to the differences reported. Buza *et al.* showed that the concordance between HER2/neu overexpression and amplification was 75% when Food and Drug Administration (FDA) criteria for breast cancer was used for IHC scoring while the concordance increased to 81% when American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) scoring system for breast cancer was used (31). Another challenge encountered with HER2/neu testing in USC is intra-tumoral heterogeneity which is described as the presence of at least 2 degrees of difference in staining in at least 5% of tumor cells or amplification of HER2/neu within the same tissue sample (50). Intra-tumoral heterogeneity ranging from 31–97% in HER2/neu expression has been reported with IHC (31,32,36). In small samples, this could be misleading as results may not be entirely representative of the whole tumor and potentially risks excluding some patients from targeted therapy. Therefore, testing multiple sections or larger area of tissue is recommended to reduce the occurrence of false results (31,32,42).

Novel methods of testing HER2/neu

Next-generation sequencing (NGS) is a novel technology used in the identification of gene mutations in cancers and provides a molecular basis for targeted therapy. NGS isolates nucleic acid (DNA or RNA) from the tumor sample, generates sequencing libraries prior to amplification of DNA and subsequently analyses the data (51). A comparative study of targeted NGS with IHC and FISH for the *ErbB2* gene in USC showed that NGS was comparable to IHC and FISH in detecting *ErbB2* gene amplification with 100% concordance (52). Although the results of this study were positive, it had a small sample size and did not demonstrate the superiority of NGS over current testing modalities.

In breast cancer, alternative HER2/neu testing techniques like immunodetection using Phosphor Integrate Dot fluorescent nanoparticles (53), novel gene protein (54) and the HER2DX clinical response prediction assays (55) have been reported. Hou *et al.* used the novel gene protein assay on double equivocal cases (IHC and FISH) to determine both gene copy number and protein expression simultaneously and also identified HER2/neu heterogeneity in breast cancer cells (54). This is a promising finding but requires further clinical testing in other tumors including EC. Larger studies are required to confirm the results and cost effectiveness of adopting alternative testing techniques including targeted NGS in clinical practice in comparison with IHC and FISH.

Targeting HER2/neu in uterine serous papillary cancers

Various pharmacologic agents have been developed to inhibit the activity of HER2/neu receptor in breast cancer cell lines with improvement in survival outcomes. Given the molecular similarities of USC with breast cancer, these agents are being actively investigated in EC in preclinical and clinical settings with considerable success.

They can be grouped as follows:

Agents with demonstrable activity in clinical studies:

- ❖ Trastuzumab.

Agents with demonstrable activity in preclinical studies:

- ❖ Targeting extracellular domain of HER2/neu receptors: pertuzumab;
- ❖ Antibody drug conjugates (ADCs): trastuzumab emtansine (T-DM1), DHES0815A, SYD985 (Byondis B.V., Nijmegen, the Netherlands);
- ❖ Targeting intracellular domain of HER2/neu receptors: afatinib, neratinib, dacomitinib, lapatinib;
- ❖ Targeting the downstream pathway of HER2/neu receptor activation such as PIK3CA/Akt/mTOR signaling pathways: GDC-0980 (Genentech Inc., South San Francisco, CA, USA), taselisib.

The only drug tested and used in current clinical practice is trastuzumab, while the other HER2/neu targeting agents were tested in preclinical trials on cell lines. Though promising, the clinical efficacy of these drugs is yet to be established in real world settings.

Trastuzumab

The most important and well-studied of these drugs is trastuzumab (Herceptin, Genentech, San Francisco, CA, USA/Hoffman-Roche, Switzerland). Trastuzumab is a humanized murine IgG1 immunoglobulin that targets the extracellular domain IV of HER2/neu and interferes with dimerization leading to suppression of downstream signaling pathways (56). It also acts by reducing HER2/neu activity by inducing receptor degradation through the ubiquitin proteosome pathway (57). Binding of trastuzumab to HER2/neu receptor also activates immune recognition of tumor cells via antibody dependent cellular cytotoxicity (ADCC) (56). As early as 2002, Santin *et al.* proposed that trastuzumab can be a potential therapeutic option targeting HER2/neu overexpressing USC. They made this proposition on the basis of their finding that cell lines from patients with chemotherapy and radiotherapy resistant USC were highly sensitive to trastuzumab mediated ADCC (58). In 2006, Jewell *et al.* reported the successful use of trastuzumab in achieving a partial response on two subsequent recurrences in a patient with HER2/neu overexpressing stage IIIA endometrioid EC (59). Villella *et al.* reported two patients with HER2/neu positive advanced USC (stage IIIC & IVB) who achieved stable disease and complete response with trastuzumab, respectively (37).

The GOG 181B trial was a phase II trial conducted to evaluate the efficacy of single agent trastuzumab in HER2/neu positive advanced/recurrent endometrial carcinoma. The trial initially recruited patients who were considered HER2/neu positive based on IHC results alone (2+/3+ overexpressing tumors) from 2000 to November 2002. But when 23 patients (Sample A) included during this time (Period A) showed no response, the trial was modified to include patients who were FISH positive for HER2/neu amplification between 2004 and 2007 (Period B). Sample B included patients who showed HER2/neu amplification in Period B plus patients who were FISH positive amongst Sample A. Despite these amendments, the study did not show major objective tumor responses amongst its participants. Tumor response and survival was not associated with HER2/neu amplification or overexpression. The authors concluded that trastuzumab has no activity in HER2/neu positive EC, though the study closed before completion due to poor accrual (40).

A phase II randomized controlled trial by Fader *et al.* evaluated the addition of trastuzumab to conventional chemotherapy in 58 evaluable patients with advanced and recurrent USC. The experimental arm received paclitaxel and carboplatin for 6 cycles with trastuzumab followed by trastuzumab maintenance till disease progression or toxicity. The trastuzumab arm experienced significant increase in median PFS [12.9 *vs.* 8.0 months, hazard ratio (HR) =0.46, P=0.005] and OS (29.6 *vs.* 24.4 months, HR =0.58, P=0.046) compared to the control arm. The greatest benefit was observed in the subset of women who received trastuzumab as primary treatment (OS: not reached *vs.* 24.4 months, HR =0.49, P=0.041; PFS: 17.7 *vs.* 9.3 months, HR =0.44, P=0.015) (43,48). As a result of these encouraging results, National Comprehensive Cancer Network (NCCN) guidelines have incorporated trastuzumab to conventional chemotherapy as primary treatment for advanced stage USC and as a first-line option for recurrent USC (60). A modelling study based on a theoretical cohort of 4,000 women also showed that addition of trastuzumab to conventional chemotherapy is cost-effective in advanced and recurrent USC until the cost of treatment for 6 months crosses $38,505 (61). Trastuzumab has good tolerability and an acceptable toxicity profile when given in patients with USC. The most common side effects are gastrointestinal of which almost 95% are low grade. No significant toxicity was observed between experimental arm including trastuzumab and control arms, even in cardiac toxicity (62). *Table 3* shows summary of clinical trials evaluating USC treated with the HER2/neu targeting agent trastuzumab.

In stage I serous ECs, conventional staging surgery and chemotherapy seems inadequate as the observed recurrence rate is 25.4% despite 71% of patients receiving some form of chemoradiation. Almost 26% of this cohort show HER2/neu positivity and are associated with poorer overall [adjusted R (aHR) =2.00, 95% confidence interval (CI): 1.04–3.88, P=0.039] and PFS (aHR =3.50, 95% CI: 1.84–6.67, P<0.001) compared to HER2/neu negative tumors (26). Clinical trials targeting HER2/neu in this early-stage USCs of patients are lacking (66).

Pertuzumab

Pertuzumab is another humanized monoclonal antibody that targets extracellular domain IV of HER2/neu receptor, which is a different epitope than that targeted by trastuzumab. This binding of pertuzumab to HER2/neu

Table 3 Summary of clinical trials evaluating USC treated with HER2/neu targeting agents in literature

Author, year	Sample size	Age (years)	Stage	Disease site	HER2/neu testing	HER2/neu testing on primary tumor/ recurrence	HER2/neu targeting at diagnosis/recurrence	Drug used	Dose	Cycles/months of HER2/neu targeted therapy	Response	PFS (months)	OS (months)	Comments
Villella *et al*., 2006 (37)	2	–	IIIC	–	3+ overexpression & amplification >10 copies	Primary tumor	–	Trastuzumab alone	–	3 months	SD → PD	3	–	–
		–	IVA	–	3+ overexpression & amplification >10 copies	Primary tumor	–	Trastuzumab alone	–	6 months	CR → PD	6	–	–
Santin *et al*., 2008 (63)	1	63	IIIC	RPLN, vaginal cuff	2+ overexpression & amplification (c-erbB2 gene: reference gene, 3.10)	Primary tumor	Recurrence	Trastuzumab alone	LD: 4 mg/kg, MD: 4 mg/kg every 2 weeks	7 months	PR	7	–	CA-125 levels dropped from 144 at start of therapy to 41 U/mL and nodal disease disappeared
Vandenput *et al*., 2009 (64)	1	71	IVB	Vagina, lungs	3+ overexpression & amplification	Primary and recurrent tumor	Recurrence	Trastuzumab alone ×4 cycles trastuzumab + paclitaxel ×11 cycles	LD: 8 mg/kg, MD: 6 mg/kg 3 weekly; combined with weekly paclitaxel: LD 4 mg/kg, MD 3 mg/kg weekly	Alone: 4 cycles; with paclitaxel: 11 cycles	PD	–	–	–
Fleming *et al*., 2010 (40)	33 HER2/neu-positive tumors out of which 11 were USC	–	Advanced: 7, recurrent: 26	–	Sample A: 2+/3+ IHC overexpression (n=23)	Primary and recurrent tumor	Diagnosis for advanced tumors/ recurrence for recurrent tumors	Trastuzumab alone	4 mg/kg in week 1, then 2 mg/kg weekly until disease progression	Mean: 2 cycles	SD: 12; PD: 18; indeterminate: 3	1.84	7.85	Testing strategy changed to mandate FISH testing in later part of trial and hence analyses as sample A and sample B; trial closed early due to poor accrual; trastuzumab showed no discernible activity in HER2/ne-positive endometrial cancers; serous and clear cell tumors more likely to show HER2/neu amplification
					Sample B: amplification (HER2/neu:CEP17 ratio >2.0) +/– 2+/3+ IHC overexpression (n=18 including 8 patients from sample A)	Primary and recurrent tumor						1.81	6.80	
Fader *et al*., 2018, 2020 (43,48)	Control arm: 28; experimental arm: 30	Median: 69; control arm: 67; experimental arm: 73	Advanced: stage III, 23; stage IV, 18; recurrent, 17	–	3+ IHC overexpression & 2+ IHC overexpression confirmed by FISH amplification	Primary and recurrent tumor	Diagnosis for advanced tumors/ recurrence for recurrent tumors	Control arm: TP ×6 cycles; experimental arm: TP ×6 cycles + trastuzumab till toxicity or progression	T: 175 mg/m^2; P: AUC, 5; trastuzumab: 1st cycle, 8 mg/kg; subsequent cycles, 6 mg/kg	Median: 15 (range, 5–53)	–	Control arm: 8.0; experimental arm: 12.9 (P=0.005; HR =0.46)	Control arm: 24.4; experimental arm: 29.6 (P=0.046; HR =0.58)	Greatest benefit of trastuzumab seen in stage III/IV disease (OS: 24.4 *vs.* NR, P=0.041, HR =0.49)
Pelligra *et al*., 2020 (65)	2	69	IVB	Omentum	3+ IHC overexpression & amplified	Primary	Diagnosis	Trastuzumab	–	TP + trastuzumab: 6 cycles; trastuzumab alone: 11 cycles	PD	–	–	HER2/neu status on biopsy at progression was 1+; received 9 cycles of TP, ixabepilone + bevacizumab, abraxane + bevacizumab + oral cyclophosphamide, doxorubicin and bevacizumab, BSC
		76	IVB	Omentum	2+ IHC score with HER2/neu:CEP17 ratio of 3.69 to 1.8	Primary	Recurrence	Trastuzumab	–	Trastuzumab: 31 cycles	PD	–	–	HER2/neu status on biopsy at progression was 0 and FISH was negative

USC, uterine serous cancer; HER2/neu, human epidermal growth factor receptor 2; PFS, progression-free survival; OS, overall survival; SD, stable disease; PD, progressive disease; CR, complete response; RPLN, retroperitoneal lymph node; LD, loading dose; MD, maintenance dose; PR, partial response; CA-125, cancer antigen 125; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; T, paclitaxel; P, carboplatin; AUC, area under curve; HR, hazard ratio; NR, not reported; BSC, best supportive care.

receptor inhibits heterodimerization of HER2 and HER3 which is considered the most potent cellular signaling heterodimer of the EGFR family (67). Pertuzumab works predominantly by stimulating immune activation by ADCC. Pertuzumab has been shown to have efficacy similar to trastuzumab in HER2/neu overexpressing USC cells *in vitro*. Interestingly, it has also been shown that addition of pertuzumab to trastuzumab significantly increased the ADCC dependent cell killing *in vitro* in USC cells with low or no expression of HER2/neu receptors compared to either drug alone (68).

T-DM1

T-DM1 is an antibody-drug conjugate of trastuzumab linked to the anti-microtubule cytotoxic agent DM1 through a nonreducible thioether linkage. Each molecule of trastuzumab carries 3.5 molecules of DM1. When trastuzumab binds to HER2/neu receptors, the T-DM1 antibody-drug complex enters the cell via a receptor-mediated endocytosis. Upon proteolytic degradation, the DM1 molecules are released intracellularly and exert their antimicrotubular activities. English *et al.* showed that T-DM1 was more effective *in vitro* by inhibition of cell proliferation and induction of apoptosis in HER2/neu positive USC cell lines and *in vivo* by decreasing tumor formation and prolonging survival of severe combined immunodeficient (SCID) mice harbouring USC xenografts (69).

DHES0815A

DHES0815A is also an ADC in which the antibody against HER2/neu receptor named MHES0488A is bound to pyrrolo[2,1-c][1,4] benzodiazepine monoamide (PBD-MA) which is an alkylating agent at a drug antibody ratio (DAR) of 2. DHES0815A significantly decreases growth of HER2/neu overexpressing USC cell lines in an *in vitro* study (44).

SYD985

SYD985 is a new antibody-drug conjugate in which trastuzumab is linked to duocarmycin, a DNA alkylating agent having an average DAR of 2.8. In USC cell lines, SYD985 was shown to be 10 to 70 times more potent than T-DM1 and was also effective in USC cells with low to moderate HER2/neu expression, unlike T-DM1 which was only effective against USC with strong HER2/neu expression (70).

Afatinib

Afatinib (BIBW-2992) is an oral HER2/neu inhibiting antibody that works by targeting the intracellular tyrosine kinase domains of ErbB1, ErbB2 and ErbB4 and inhibits transphosphorylation of ErbB3. Afatinib was shown to be active *in vitro* and *in vivo* in chemotherapy resistant USC harbouring HER2/neu gene amplification (71).

Neratinib

Neratinib (HKI 272) is another tyrosine kinase inhibitor that binds to the adenosine triphosphate (ATP) pocket of ErbB1 and HER2/neu, thereby inhibiting the downstream signaling pathway. Schwab *et al.* showed that USC lines with HER2/neu amplification were more sensitive to growth inhibition by neratinib compared to non-amplified cell lines. Neratinib also showed *in vitro* activity by increasing OS and decreasing tumor growth (72). Olaparib and neratinib showed synergistic activity in USC with high HER2/neu expression. Olaparib treatment increased HER2/neu expression in USC cell lines while treatment with neratinib increased poly(ADP-ribose) polymerases (PARP) activity (73).

Dacomitinib

Dacomitinib is an oral small molecule inhibitor that acts by inhibiting the tyrosine kinase activity of HER1, HER2 and HER4. Dacomitinib has shown to significantly inhibit growth of USC lines harbouring HER2/neu amplification in a dose dependent manner (74).

Lapatinib

Lapatinib is a dual ErbB1/HER2/neu tyrosine inhibitor molecule which has shown antitumor activity in combination with trastuzumab in HER2/neu amplified USC which were impervious to trastuzumab alone *in vitro* and *in vivo* (75).

GDC-0980

GDC-0980 is a small molecule inhibitor which selectively inhibits class 1 PIK3 and mTORC1/mTORC2 kinase. PIK3/Akt/mTOR pathway is a signaling cascade that is located downstream to HER2/neu receptor activation. GDC-0980 was found to inhibit growth in USC harbouring

HER2/neu amplifications. Among HER2/neu amplified USC lines, those lines that also harboured *PIK3CA* mutations were more sensitive to inhibition by GDC-0980 compared to *PIK3CA* wild type USC cell lines (76).

Taselisib

Taselisib, otherwise known as GDC-0032, is an oral small molecule inhibitor of PIK3CA. A strong differential growth inhibition was seen with taselisib in HER2/neu FISH positive tumors with *PIK3CA* mutation compared to those without HER2/neu amplification or *PIK3CA* mutation. *In vivo* survival benefits were observed in HER2/neu FISH positive/PIK3CA-mutated xenografts treated with taselisib compared to controls (77).

The pre-clinical evidence for HER2/neu targeting agents in USC cell lines is summarized in *Table 4*.

Mechanisms of resistance to HER2/neu targeted therapy in USC and ways to overcome it

Solid tumors that express HER2/neu may not respond to HER2/neu targeting therapy either from the initiation of therapy (primary resistance) or after some time of response (secondary resistance). Several factors have been proposed to account for such resistance.

Presence of p95HER2 variant

P95HER2 is a variant of HER2/neu receptor which loses the extracellular binding site for trastuzumab while retaining the intracellular domain responsible for activation of downstream signaling pathway. As a result, these HER2/neu overexpressing tumors are resistant to the effects of trastuzumab. Growdon *et al.* showed that almost 53% of high-grade ECs (predominantly consisting of USC) showed p95HER2 expression. This was considerably higher than p95HER2 expression in a matched breast cancer cohort (78).

Upregulation of downstream pathways

Tumors that show increased activity/signaling of HER2/neu downstream pathways such as PIK3CA and mTOR pathways are resistant to HER2/neu targeting agents. Black *et al.* showed that HER2/neu amplified/PIK3CA-mutated tumors were more resistant to trastuzumab compared to HER2/neu amplified/PIK3CA wild type cell lines. Resistance of tumors to trastuzumab that were transfected with oncogenic *PIK3CA* mutations increased compared to baseline (79).

Signaling from other HER receptors

Tumors may escape HER2/neu receptor targeting by increasing activation of other HER receptors like HER3. HER2-HER3 receptor signaling is considered the most potent signal among signaling by EGFR family of receptors. HER3 overexpression may lead to heterodimerization with HER2/neu receptors which may in turn lead to activation of downstream signaling pathways leading to tumor proliferation and growth.

Tumor selection of resistant clones

Treatment of HER2/neu positive serous endometrial tumors may induce the proliferation of HER2/neu negative clones within the tumor as a way of resistance. In a case report on two patients with initial tumor cells shown to be overexpressing HER2/neu by IHC and *ErbB2* amplification by FISH, biopsy at the time of disease progression on trastuzumab therapy demonstrated loss of HER2/neu overexpression in the resistant tumors (65).

Overcoming resistance in HER2/neu targeted therapy

Resistance to HER2/neu targeted therapy can be mitigated in various ways. Combination of HER2/neu targeted therapy to a drug that acts on the downstream pathways is the most common strategy employed in such cases. Lopez *et al.* showed that combination therapy with neratinib and taselisib is found to produce stronger and long-lasting growth inhibition of tumor cell lines compared to either treatment alone. They also showed that combination therapy is effective even when initiated after tumor progression compared to single targeted therapy with either agent alone in mice xenografts that are HER2/neu and PIK3CA overexpressed/amplified (80). Combination of a intracellular HER2/neu targeting agent with a drug that targets extracellular domain is also a way of overcoming resistance (75).

Table 4 Summary of pre-clinical trials evaluating USC treated with HER2/neu targeting agents in literature

Author, year	Sample	*In vitro/in vivo*	Drug	*In vitro* comparison	Tumor growth inhibition (μM), IC50 ± SEM	*In vivo* comparison	P value		Comments
							OS	Tumor growth inhibition	
El-Sahwi *et al*., 2010 (68)	6 USC cell lines	*In vitro*	Pertuzumab and/or trastuzumab	3 USC cells with HER2/neu amplification and overexpression *vs.* 3 HER2/neu-negative USC cells	–	–	–	–	Combination of pertuzumab and trastuzumab was more cytostatic than trastuzumab alone in all cell lines (P<0.005); combination of pertuzumab and trastuzumab was significantly more cytostatic against the high HER2/neu expressor cell lines when compared with pertuzumab used alone (P<0.01)
English *et al*., 2013 (76)	22 USC cell lines	*In vitro*	GDC-0980	9 USC cell lines with HER2/neu amplification *vs.* 13 cell lines without HER2/neu amplification	0.29±0.05 *vs.* 1.09±0.20 (P=0.02)	–	–	–	FISH USC harboring PIK3CA mutations were significantly more sensitive to GDC-0980 exposure when compared with USC cell lines harboring wild-type PIK3CA (P=0.03)
Lopez *et al*., 2014 (77)	9 USC cell lines	Both	Taselisib	4 lines with HER2/neu amplification (FISH) (2 with PIK3CA mutations) *vs.* 5 lines without HER2/neu amplification	0.042±0.006 *vs.* 0.38±0.06 (P<0.0001)	10 mice with PIK3CA-mutated/ HER2/neu-amplified tumor xenograft (taselisib *vs.* placebo)	<0.0001	0.007	–
Schwab *et al*., 2014 (72)	24 USC cell lines (8 were HER2/neu-amplified)	Both	Neratinib	4 lines with HER2/neu amplification *vs.* 4 lines without HER2/neu amplification	0.011±0.0008 *vs.* 0.312±0.0456 (P<0.0001)	10 mice with HER2/neu-amplified tumor xenograft (neratinib *vs.* placebo)	0.0019	0.0027	–
Schwab *et al*., 2014 (71)	15 USC cell lines (5 were HER2/neu-amplified)	Both	Afatinib	4 lines with HER2/neu amplification *vs.* 4 lines without HER2/neu amplification	0.0056±0.0006 *vs.* 0.563±0.092 (P<0.0001)	10 mice with HER2/neu-amplified tumor xenograft (afatinib *vs.* placebo)	0.0017	–	–
Zhu *et al*., 2015 (74)	8 USC cell lines	*In vitro*	Dacomitinib (PF-00299804)	4 lines with HER2/neu amplification *vs.* 4 lines without HER2/neu amplification	0.02803±0.003355 *vs.* 1.498±0.2209 (P<0.0001)	–	–	–	–
English *et al*., 2014 (69)	15 USC cell lines	Both	T-DM1 *vs.* trastuzumab	5 lines with HER2/neu amplification or overexpression *vs.* 10 HER2/neu-negative cell lines	–	15 mice with HER2/neu-amplified tumor xenograft not harbouring a PIK3CA mutation (rituximab *vs.* trastuzumab *vs.* T-DM1)	≤0.0001	0.04	T-DM1 was considerably more effective than Trastuzumab in inhibiting cell proliferation and in causing apoptosis (P=0.004) of USC showing HER2/neu overexpression
Groeneweg *et al*., 2014 (75)	42 USC cell lines (10 were HER2/neu-amplified)	Both	Lapatinib + trastuzumab *vs.* trastuzumab alone	3 cell lines treated with trastuzumab alone or combination of trastuzumab and lapatinib	–	Mice bearing xenograft randomized into groups of 5 or 6 (lapatinib *vs.* vehicle)	–	0.02	Dual anti-HER2/neu therapy with lapatinib led to improved inhibition of tumor growth in HER2/neu-amplified USC
Tymon-Rosario *et al*., 2021 (44)	12 USC cell lines	Both	DHES0815A *vs.* MHES0488A (unconjugated antibody)	3 lines with HER2/neu amplification *vs.* 1 line without HER2/neu amplification	P<0.05	12 mice with xenograft model with 3+ HER2/neu expression (DHES0815A *vs.* MHES0488A)	<0.01	<0.01	–
Yadav *et al*., 2022 (73)	6 USC cell lines	Both	Neratinib *vs.* olaparib *vs.* both	2 lines with HER2/neu amplification *vs.* 1 line without HER2/neu amplification	–	5–6 mice with xenograft model with 3+ HER2/neu expression per group (vehicle, olaparib, neratinib, combination)	–	<0.05 (combination of the two inhibitors caused a stronger and durable growth inhibition in both USC xenografts)	Neratinib was more potent than olaparib in suppression of *in-vitro* growth of HER2/neu 3+ cell lines while no difference was noted against HER2/neu 1+ tumors. combination of olaparib with neratinib synergistically improved tumor suppression compared to either single-agent *in vitro*

USC, uterine serous cancer; HER2/neu, human epidermal growth factor receptor 2; IC50, half maximal inhibitory concentration; SEM, standard error of the mean; OS, overall survival; FISH, fluorescence in situ hybridization.

Ongoing trials

Several ongoing trials are evaluating the efficacy of HER2/neu targeting agents in serous ECs. Most are basket trials which require tumors of different organs to harbour HER2/neu overexpression and/or amplification to be included in the trial.

DESTINY-Breast01 was a two-part open labelled phase 2 trial to evaluate the efficacy of trastuzumab deruxtecan on metastatic breast cancer patients who were previously treated with T-DM1. Trastuzumab deruxtecan showed a overall response rate (ORR) of 60.9% and a median PFS of 16.4 months (81). DESTINY-PanTumor02 trial is an open label phase II multicentre basket trial that evaluated the efficacy of trastuzumab deruxtecan in 40 patients with advanced or metastatic EC in addition to other tumors including biliary tract, bladder, cervical, ovarian, pancreatic, or other tumors (excluding breast, gastric, colorectal, and non-small cell lung cancer). Only patients with tumors expressing 2+/3+ were included in the study. The highest ORR among all tumor groups was observed in ECs at 57.5%. In uterine tumors that showed strong positivity (3+) for HER2/neu expression, the ORR was 84.6% (82,83).

MyPathway is a non-randomised phase 2a basket trial evaluating targeted therapy in solid tumors with specific molecular alterations which are not currently approved in clinical practice. The combination of pertuzumab and trastuzumab was used in HER2/neu overexpressing or amplified tumors including EC. Early reports published show no objective response in seven cases of HER2/neu positive EC recruited but conclusive results are still awaited (84). NCT04585958 is a phase II trial looking at the maximum tolerated dose of trastuzumab deruxtecan when combined with olaparib in HER2/neu expressing tumors including ECs (85). A multicentre phase II/III trial involving 172 centers in the USA is currently evaluating the effect of adding Trastuzumab or a combination of trastuzumab and pertuzumab in uterine carcinosarcomas and serous carcinomas (86).

Future directions

HER2/neu testing and interpretation varies between studies as demonstrated in this review and was mostly extrapolated from the ASCO/CAP guidelines for HER2/neu testing in breast cancer. Despite these extrapolated recommendations, testing criteria/guidelines specific to EC should be established as was done for breast (ASCO/CAP), gastric (ASCO/CAP) and most recently colorectal cancer (HERACLES trial) (50). The criteria employed by Fader *et al.* provides a basis upon which further trials can be designed towards standardising testing practices and interpretation (43).

It is observed that in addition to USC, other non-serous endometrial tumors also demonstrate HER2/neu overexpression and amplification. Whether these histological subtypes might derive benefit from HER2/neu targeted therapy is a question that needs to be answered. In this respect, molecular analysis of patients enrolled in PORTEC-3 trial showed that there was a stronger correlation between HER2/neu amplification and *TP53* mutation than there is with serous cancer (16). The STATICE trial which evaluated the effect of trastuzumab on carcinosarcoma recently concluded that targeted therapy with trastuzumab deruxtecan, an ADC in which trastuzumab is linked to a topoisomerase I inhibitor, confers some benefit even in non-serous tumors (87). NCCN guidelines recommend HER2/neu IHC testing in patients with carcinosarcomas and *TP53* mutations, in addition to advanced and recurrent serous ECs (60).

HER2/neu targeting agents appear to be clinically more meaningful in the primary treatment of advanced serous uterine cancers compared to recurrent settings. Novel antibody-drug conjugates and suitable combinations with immune check-point inhibitors and PI3K/Akt/mTOR inhibitors should be evaluated to improve outcomes in advanced and recurrent cancer. Another avenue that warrants investigation is the use of these agents in neoadjuvant setting for cases that are unsuitable for surgical cytoreduction. Early-stage serous ECs overexpress HER2/neu in approximately one quarter of the cases and HER2/neu positive serous cancers are associated with a significant increase in recurrence and death compared to HER2/neu negative serous tumors. Beyond prognostication, the role of HER2/neu as an actionable target in these tumor remains to be elucidated in early-stage serous ECs.

Conclusions

USC is a biologically aggressive disease associated with a poor prognosis. Alteration of HER2/neu pathway is a commonly found molecular aberration that contributes to aggressive behaviour of these tumors. Considering its negative prognostic implications and clinical benefit conferred by HER2/neu targeted therapy, HER2/neu testing is recommended for all cases of serous EC in advanced and recurrent settings. Trastuzumab in combination with platinum and taxanes based chemotherapy is the recommended treatment option for patients with advanced or recurrent serous cancers who test positive to HER2/neu. Role of HER2/neu as a therapeutic target in early-stage serous cancers remains to be seen but appears promising given that greatest benefits have been in patients treated with HER2/neu targeting agents in the first-line therapy. Focus of future research should be directed towards refining biomarker testing and selection of patients who will derive the most benefit from such therapy.

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Footnote

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