In: Endometrial Cancer
Editor: Samir A. Farghaly
ISBN: 978-1-63463-163-1

Chapter 18

ErbB Targeted Therapy in Endometrial Cancer

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Abstract

The Epidermal Growth Factor system is present in human organs and play important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development. It has four receptors (EGFR, ErbB-2, ErbB-3 and ErbB-4) and numerous ligands.

ErbB receptors are trans-membrane glycoproteins. Their dimerization leads to intracellular kinase activation. As a result, a number of tyrosine residues in the COOH-terminal portion of ErbB receptors become phosphorylated. Those phosphorylated tyrosine residues function as docking sites for cytoplasmic proteins. Recruitment of proteins initiates intracellular signalling via several pathways: 1) Ras/Raf/mitogen-activated protein kinase (MAPK) pathway (regulates cell proliferation and survival), 2) Phosphatidylinositol 3-kinase (PI3K)/Akt pathway (regulates cell growth, apoptosis, tumour invasion, migration and resistance to chemotherapy), 3) Signal transducers and activators of transcription (STAT) pathway (regulates oncogenesis and tumour progression), 4) Src Kinase pathway (regulates cell proliferation, migration, adhesion, angiogenesis and immune function), 5) Phospholipase Cγ/protein kinase C pathway.

Dysregulation of the Epidermal Growth Factor system signalling network is implicated in the pathogenesis of various disorders. Especially in cancer, it becomes hyperactivated with various mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation). It is also contributes in proliferation, transformation, angiogenesis, migration and invasion.

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During menstrual cycle, ErbB receptors have different levels in normal endometrium. Moreover due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the 4 ErbB receptors in endometrial cancer tissue.

Especially in patients with type II endometrial cancer (papillary serous or clear cell), there are high expression levels of ErbB receptors. Among them, many patients with dismal outcome are positive for all ErbB receptors. EGFR overexpression in type I endometrial cancer, did not affect disease progression. However EGFR overexpression in type II endometrial cancer, associated with high grade and adverse clinical outcome. Moreover ErbB-2 overexpression, especially in type II endometrial cancer, is an indicator of a highly aggressive disease with poor overall survival.

The potential role of ErbB receptors (especially EGFR and ErbB-2) as targets for cancer therapy has been investigated for over 20 years. There are 2 major classes of ErbB targeted therapies: 1) anti-ErbB monoclonal antibodies (MoAbs): Anti-EGFR MoAbs bind to the extracellular domain of EGFR and prevent ligand binding and ligand dependent receptor activation. Anti-ErbB-2 MoAb binds to the extracellular domain of ErbB-2 and interferes with ligand independent receptor activation, 2) ErbB-specific tyrosine kinase inhibitors (TKIs): TKIs block the binding of ATP to the intracellular domain of EGFR and/or ErbB-2 and blocks ErbB activity and subsequent intracellular signalling. The overall response rate to ErbB targeted therapies is modest, unless they are associated with chemotherapy or radiotherapy. Moreover molecular targeted therapies have still shown modest effect, in unselected endometrial cancer patients. However, preclinical data suggest that ErbB targeted therapies may be clinically active as adjuvant therapy, in well-defined subgroups of type II endometrial cancer patients with EGFR and ErbB-2 overexpression.

1. Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract. [1] It occurs primarily in postmenopausal women. [1, 2] Overall, about 2.64% of women develop EC during their lifetime. [1] In those patients, the most common presenting symptom is abnormal uterine bleeding. [2]

Based on clinical and pathological features, sporadic EC is classified into 2 types. [3,4] Type I EC, represents the majority of sporadic EC cases (70-80%). [3,4] It is usually well differentiated and endometrioid in histology. [3,5] Type II EC, represents the minority of sporadic EC cases (10-20%). [3,4] It is poorly differentiated and usually papillary serous or clear cell in histology. [3,5]

The epidermal growth factor system (EGF system) is present in human organs and play important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development. [6,7]

Dysregulation of the EGF signaling network is implicated in cancer, diabetes, autoimmune, inflammatory, cardiovascular and nervous system disorders. [6,8] In cancer, the EGF system contributes in proliferation, transformation, angiogenesis, migration and invasion. [9]

2. Epidermal Growth Factor System

2.1. Receptors and Ligands

The EGF system is present in human organs and play important role during embryogenesis and postnatal development. [6,7]

The EGF system has 4 receptors: epidermal growth factor receptor (EGFR) (also known as ErbB-1, HER1), ErbB-2 (also known as HER2, Neu), ErbB-3 (also known as HER3) and ErbB-4 (also known as HER4)]. [6,9,10]

ErbB receptors belong to subclass I of the superfamily of Receptor Tyrosine Kinases (RTKs). [6,9] They are trans-membrane glycoproteins with an extracellular region containing two ligand-binding domains, an extracellular juxtamembrane region, a hydrophobic transmembrane domain and an intracellular domain with tyrosine kinase activity. [10,11] They catalyse the transfer of the γ phosphate of ATP to hydroxyl groups of tyrosines in target proteins. [12] However, ErbB-3 lacks intrinsic tyrosine kinase activity. [13]

The extracellular region of ErbB receptors has 4 subdomains (I-IV). Subdomains I and III (also called L1 and L2) are important for ligand binding. Subdomain II (also called S1) is important for dimerization between two receptors. [14]

Moreover, EGF system has numerous ligands. According to their affinity for one or more ErbB receptors, they divided into three groups:

1. The first group includes ligands with binding specificity for EGFR: EGF, transforming growth factor-a (TGF-a) and amphiregulin (AR). [9,10,15]
2. The second group includes ligands with dual binding specificity for EGFR and ErbB4: betacellulin (BTC), heparin-binding growth factor (HB-EGF) and epiregulin (EPR). [9,10,15]
3. The third group includes ligands with binding specificity for ErbB-3 and ErbB-4: neuregulins (NRGs) or heregulins (HRGs). They divided in two subgroups based on their ability to bind ErbB-3 and ErbB-4 (NRG-1 and NRG-2) or only ErbB-4 (NRG-3 and NRG-4). [9,10,15-17]

The ligands for ErbB receptors bind to the extracellular domain, resulting in receptor activation by homodimer and/or heterodimer formation and the subsequent transphosphorylation of tyrosine residues in the cytoplasmic region. [9,10,18] However, no direct ligand for ErbB-2 has been described. [9]

2.2. Receptor Homodimerization and Heterodimerization

The extracellular region of EGFR, ErbB-3 and ErbB-4 has two distinct conformations:

1. The closed conformation (inactive) has intramolecular interactions between subdomains II and IV. [11,19,20]

2. The open conformation (active), where subdomains I and III form a ligand-binding pocket that permits interactions between a single ligand and subdomains I and III. [11,19,20]

In the absence of ligand binding, the extracellular region of EGFR, ErbB-3 and ErbB-4 has equilibrium between closed and open conformation. [11,19-21] This equilibrium favours the closed conformation. [11,21]

Ligand binding stabilizes extracellular region in the open conformation and leads to the formation of both homodimeric and heterodimeric ErbB receptor complexes. [11,20-22] The dimeric formation triggers receptor activation by an allosteric mechanism. [23] That leads to intracellular kinase activation and initiation of downstream signalling pathways. [10,22,24]

The extracellular region of ErbB-2 has a conformation not suitable for ligand binding. [25] However, this conformation allows extension of the receptor dimerization arm in subdomain II. [11,25] This suggests that ErbB-2 is capable for ligand independent dimerization and signalling. [11] ErbB-2 heterodimerizes with other ErbB receptors and it is their preferred heterodimerization partner. [10,22,25-27] At elevated expression levels ErbB-2 homodimerizes. [25]

ErbB-3 lacks intrinsic tyrosine kinase activity and therefore can initiate signalling only in association with another ErbB receptor, usually ErbB-2. [13]

Although both homodimerization and heterodimerization result in activation of the EGF system network, heterodimers are more potent and mitogenic. [8] ErbB-2 and ErbB-3 heterodimer is the most transforming and mitogenic receptor complex and increases cell motility on stimulation with a ligand. [10,28,29]

The dimerization of ErbB receptors represents the fundamental mechanism that drives transformation [Figure 1]. [30]

2.3. Signaling Pathways

Dimerization of ErbB receptors leads to intracellular kinase activation. [10,22,24] As a result, a number of tyrosine residues in the COOH-terminal portion of ErbB receptors become phosphorylated. [9,25,30] These phosphorylated tyrosine residues function as docking sites for cytoplasmic proteins containing Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains. [8,10,30,31] Recruitment of proteins initiates intracellular signalling via several pathways [Figure 1]:

2.3.1. Ras / Raf / Mitogen-Activated Protein Kinase (MAPK) Pathway

The Ras / Raf / mitogen-activated protein kinase (MAPK) pathway regulates cell proliferation and survival. [32] Following ErbB phosphorylation, the complex of Grb2 and Sos adaptor proteins binds directly or indirectly (through Shc adaptor protein) to specific intracellular ErbB docking sites. [33,34]

This interaction results in conformational modification of Sos, leading to recruitment of Ras-GDP and subsequent Ras activation (Ras-GTP). [35] Ras-GTP activates Raf-1 and, through intermediate steps, phosphorylates MAPK-1 and MAPK-2. [35,36] Activated MAPKs phosphorylate and regulate specific intranuclear transcription factors involved in cell migration and proliferation. [32,37,38]

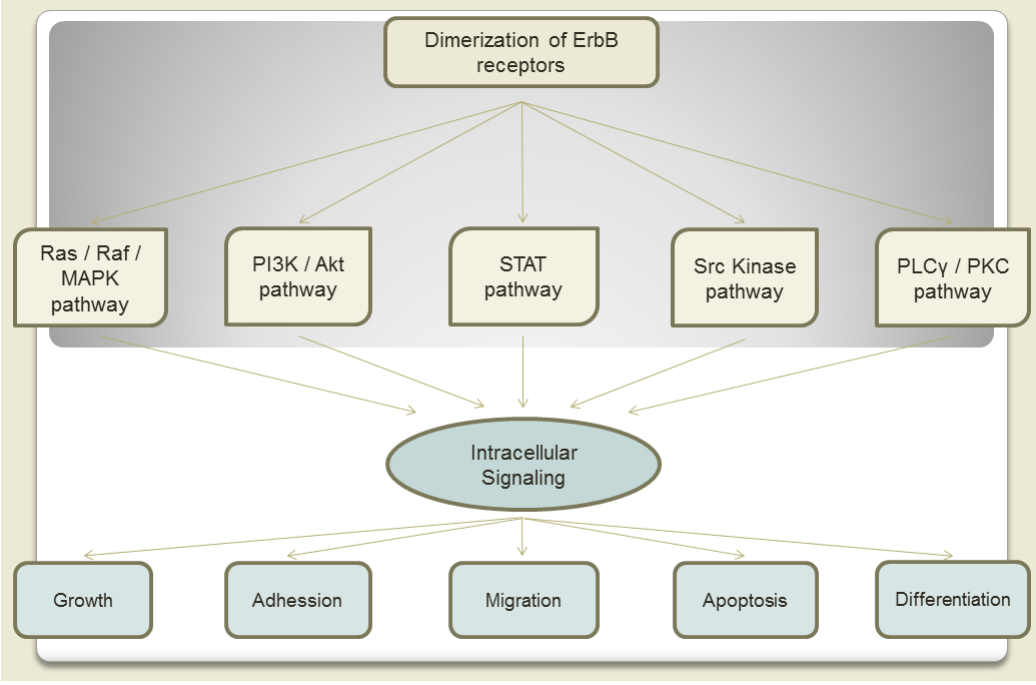

Figure 1. ErbB receptors signalling.

2.3.2. Phosphatidylinositol 3-Kinase (PI3K) / Akt Pathway

The Phosphatidylinositol 3-kinase (PI3K) / Akt pathway regulates cell growth, apoptosis, tumour invasion, migration and resistance to chemotherapy. [39,40]

PI3K is a dimeric enzyme that composed of a regulatory p85 subunit and a catalytic p110 subunit. [39] The regulatory p85 subunit, is responsible of the anchorage to ErbB receptor specific docking sites, through interaction of its Src homology domain 2 (SH2) with phosphotyrosine residues. [41] The catalytic p110 subunit, catalyse the phosphorylation of phosphatidylinositol 4, 5 diphosphate at the 3' position. [39] Phosphatidylinositol 3, 4, 5 triphosphate, phosphorylates and activates the protein serine/threonine kinase Akt. [39,42]

ErbB receptor specific docking sites for p85 subunit are present on ErbB-3 and absent on EGFR. [10,43] EGFR dependent PI3K activation occurs through dimerization of EGFR with ErbB-3 or through the docking protein Gab-1. [32,44]

2.3.3. Signal Transducers and Activators of Transcription (STAT) Pathway

Signal transducers and activators of transcription (STAT) pathway regulates oncogenesis and tumour progression. [45]

STAT proteins interact with phosphotyrosine residues via their Src homology domain 2 (SH2) and, on dimerization, translocate to the nucleus and induce the expression of specific target genes. [46-48] Constitutive activation of STAT proteins (especially STAT-3 and STAT-5) is present in various primary cancers. [45,46]

EGFR regulate STAT pathway through a Janus kinase (JAK) or a JAK independent mechanism. [49,50] Augmented activity of EGFR and ErbB-2, promote persistent STAT-3 activation and subsequently induce oncogenesis and tumour progression. [45]

2.3.4. Src Kinase Pathway

The Src kinase pathway regulates cell proliferation, migration, adhesion, angiogenesis, and immune function.

Src is a member of a 10 gene family (FYN, YES, BLK, FRK, FGR, HCK, LCK, LYN, SRMS) of non-RTKs. It is located in the cytoplasm and cross-connected with other signalling pathways, such as PI3K and STAT pathway. [51,52]

Although Src functions independently, it may interact with RTKs such as EGFR. The interaction between Src and EGFR may enhance ErbB signalling and may be involved in resistance to EGFR targeted therapy. [53,54]

2.3.5. Phospholipase Cγ / Protein Kinase C Pathway

Phospholipase Cγ (PLCγ) interacts directly with activated EGFR and ErbB-2 and hydrolyses phosphatidylinositol 4, 5 diphosphate to inositol 1, 3, 5 triphosphate (IP3) and 1, 2 diacylglycerol (DAG). [55,56]

IP3 is important for intracellular calcium release. DAG is cofactor in protein kinase C (PKC) activation. Activated PKC activates MAPK and c-Jun NH2-terminal kinase. [57,58]

2.4. Dysregulation and Carcinogenesis

Dysregulation of the EGF system signalling network is implicated in cancer, diabetes, autoimmune, inflammatory, cardiovascular, and nervous system disorders. [6,8]

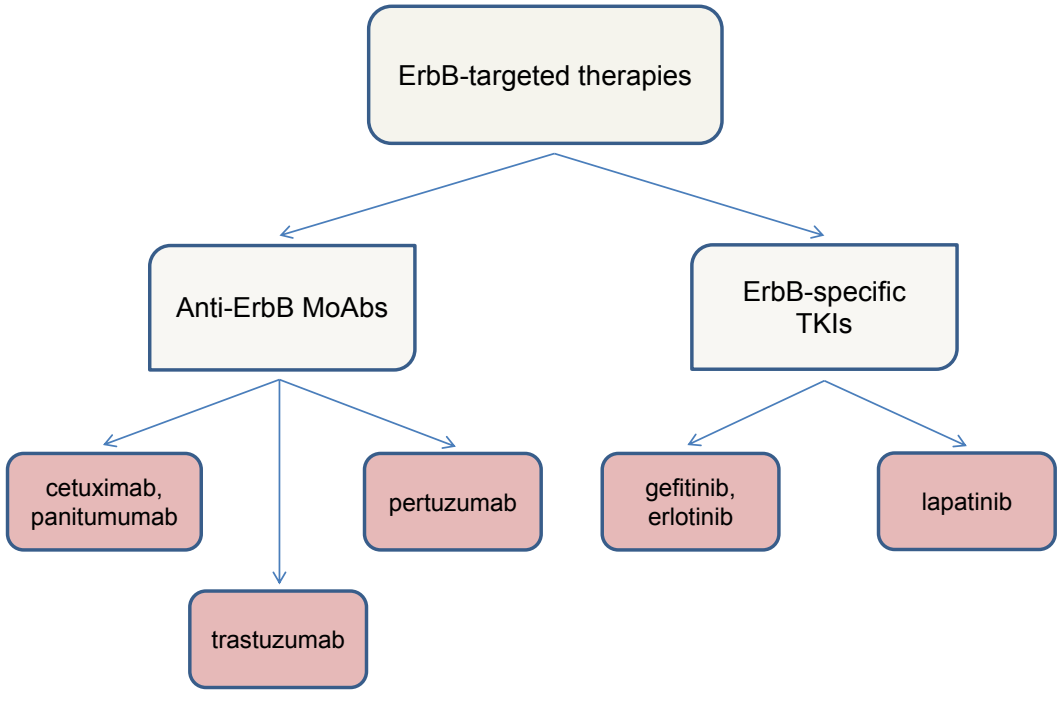

Figure 2. ErbB-targeted therapies.

Loss of control of the cell functions mediated by the EGF system signalling network is a hallmark of oncogenesis, in which the balance between cell proliferation and differentiation is disturbed. Several types of human cancers associated with dysregulation of the EGF system signalling network. [6]

The EGF system signalling network in cancer becomes hyperactivated with a range of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation). [8,10,59] It is also contributes in proliferation, transformation, angiogenesis, migration and invasion. [9]

2.5. Expression and Clinical Significance in Various Cancers

Overexpression and structural alterations of EGFR are frequent in head, neck, oesophageal, breast, lung, gastric, liver, kidney, colorectal, prostate, bladder and ovarian cancer.[6,10,60] They associated with higher grade, disease progression, poor survival and resistance to radiotherapy and chemotherapy. [10,61]

Overexpression of ErbB-2 is frequent in head, neck, breast, lung, pancreatic, oesophageal, liver, colorectal, prostate, bladder, ovarian, endometrial and cervical cancer. [6,10 62,63] It is an indicator of a more aggressive clinical behaviour. [10 62 63]

Overexpression of ErbB-3 is frequent in head, neck, breast, gastric, liver, colorectal, prostate and ovarian cancer.[6,10] Although ErbB-3 overexpression related with ErbB-2 positivity and lymph node involvement, a definitive relationship with survival has not been established. [64-66]

Overexpression of ErbB-4 is frequent in head, neck, lung and liver cancer. [6,10] It is related with favourable prognosis in breast and bladder cancer. [67-69]

3. Endometrial Cancer

3.1. Classification and Molecular Biology

EC is the most common malignancy of the female genital tract. [1] Based on clinical and pathological features, sporadic EC is classified into 2 types. [3,4]

1. Type I EC, represents the majority of sporadic EC cases (70-80%). [3,4] It is usually well differentiated and endometrioid in histology. [3-5] It is estrogen-related, usually arises from endometrial hyperplasia, has less aggressive clinical course, and favourable prognosis. [3,4,70]
   Type I EC overexpress genes hormonally regulated during the menstrual cycle and involved in endometrial homeostasis (MGB2, LTF, END1, MMP11). [71,72] It is also associated with defects in DNA mismatch repair, microsatelite instability MLH1/MSH6 and specific mutations in PTEN, K-ras and β-catenin genes. [5,73-76]
2. Type II EC, represents the minority of sporadic EC cases (10-20%). [3,4] It is poorly differentiated and usually papillary serous or clear cell in histology. [3-5] It is not

estrogen-related, arises from atrophic endometrium, has aggressive clinical course, and propensity for early spread and poor prognosis. [3,77,78]

Type II EC overexpress genes involved in the regulation of the mitotic spindle checkpoint and associated with aneuploidy and aggressive clinical behaviour (STK15, BUB1, CCNB2). [71,72,75] It is also associated with mutations in p53 gene, inactivation of p16, ErbB-2 amplification/overexpression and decreased expression of E-cadherin. [5,74-76,79-83]

3.2. Expression and Clinical Significance of ErbB Receptors

Due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the 4 ErbB receptors in EC tissue. [84]

EGFR, in endometrium, is localized to the basal part of surface epithelial cells, only in stromal cells, or both to epithelial and stromal cells. [85-93] It is primarily located to the cell membrane but also located to the cytoplasm. [84,90-97]

In unselected patients with EC, it has been reported EGFR expression in 43-67% of cases. [90-92,95-100] In patients with type I EC, it has been reported EGFR expression in 46% of cases. [92] In patients with type II EC, it has been reported EGFR expression in 34-50% of cases. [92,93,99]

Although the clinical significance of EGFR has not been studied well in EC, it may have a dual role. [99] EGFR overexpression did not affect disease progression in type I EC, although affects disease progression in type II EC. [99] EGFR overexpression in type II EC associated with high grade disease and adverse clinical outcome. [92,93,99]

ErbB-2, in endometrium, is localized baso-laterally in the glands and surface epithelial cells. [85,86,89-93,101] It is located to the cell membrane. [62,84,90-93,95,96]

In unselected patients with EC, ErbB-2 amplification/overexpression represents a rare event. [100] In patients with type I EC, it has been reported ErbB-2 receptor overexpression in 8% of cases and ErbB-2 gene amplification in 1.4-3% of cases. [99,102] Although ErbB-2 amplification/overexpression is more common in patients with type II EC, the exact frequency remains controversial. [92,93,99] Moreover, there are racial differences regarding ErbB-2 overexpression in patients with type II EC. [103] ErbB-2 overexpression is more common in Black race patients with type II EC. [103]

In patients with papillary serous EC, it has been reported ErbB-2 receptor overexpression in 18%-80% of cases and ErbB-2 gene amplification in 17-47% of cases. [82,83,92,93,99,102,104] In patients with clear cell EC, it has been reported ErbB-2 receptor overexpression in 33% of cases and ErbB-2 gene amplification in 16-50% of cases. [83,92,93,99,102] ErbB-2 overexpression especially in type II EC, is an indicator of a highly aggressive disease with poor overall survival. [62,82,92,93,102,105,106]

ErbB-3, in endometrium, is localized to surface epithelial cells. [89-93,107,108] It is located to the cytoplasm, with membrane staining in a minority of samples. [84,90-93,108]

The clinical significance of ErbB-3 has not been studied well in EC. [84,90-93,108]

ErbB-4, in endometrium, is localized to epithelial and stromal cells. [89-93,108,109] It is located to the cytoplasm, with membrane staining in a minority of samples. [84,90-93,108]

The clinical significance of ErbB-4 has not been studied well in EC. [84,90-93,108]

4. ErbB-Targeted Therapies

4.1. Classification

EGFR and ErbB-2 as targets for cancer therapy have been investigated for over 30 years. [110] Two major classes of ErbB-targeted therapies have been developed [Figure 2]: [61,110]

4.1.1. Anti-ErbB Monoclonal Antibodies (MoAbs)

1. Anti-EGFR MoAbs (cetuximab, panitumumab) bind to the extracellular domain of EGFR and prevent ligand binding and ligand dependent receptor activation. [61,110]
2. Anti-ErbB-2 MoAb (trastuzumab) binds to the extracellular domain of ErbB-2 and interferes with ligand independent receptor activation, but the exact mechanism of action is still subject of on-going debate. [61,110]
3. Anti-ErbB MoAb (pertuzumab) prevents receptor heterodimerization. [61,110]

4.1.2. ErbB-specific Tyrosine Kinase Inhibitors (TKIs)

1. EGFR TKIs (gefitinib, erlotinib) block the binding of ATP to the intracellular domain of EGFR and prevent tyrosine kinase activity and subsequent intracellular signalling. [61,110]
2. EGFR and ErbB-2 TKI (lapatinib) block the binding of ATP to the intracellular domain of EGFR and ErbB-2 and prevents tyrosine kinase activity and subsequent intracellular signalling. [61,110]

4.2. Effectiveness in Endometrial Cancer

4.2.1. Anti-ErbB Monoclonal Antibodies (MoAbs) in Endometrial Cancer

Anti-ErbB-2 MoAb (trastuzumab) may be an attractive and viable therapeutic option in patients with advanced, recurrent and/or metastatic EC overexpressing ErbB-2. [111]

Clinical responses to trastuzumab as single agent or in combination with chemotherapy have been reported in several case reports. [111-114]

However a phase II study of trastuzumab as single agent in unselected patients with advanced or recurrent EC overexpressing ErbB-2, failed to demonstrate significant activity. [115]

Moreover a phase II study of carboplatin/paclitaxel with or without trastuzumab in patients with advanced or recurrent type II EC (papillary serous) overexpressing ErbB-2, is currently underway (NCT01367002). [116]

4.2.2. ErbB-Specific Tyrosine Kinase Inhibitors (TKIs) in Endometrial Cancer

ErbB-specific TKIs (gefitinib, erlotinib, lapatinib) may be another viable therapeutic option in patients with advanced, recurrent and/or metastatic EC overexpressing EGFR and ErbB-2. [117-119]

However a phase II study of gefitinib as single agent in unselected patients with persistent or recurrent EC overexpressing EGFR, demonstrate 4.1% complete response rate and 16.6% progression free survival ≥6 months. [117]

Also a phase II study of erlotinib as single agent in unselected patients with metastatic or recurrent EC, demonstrate 12.5% partial response rate. [118]

Moreover a phase II study of lapatinib as single agent in unselected patients with persistent or recurrent EC; demonstrate 3.3% partial response rate and 10% progression free survival ≥6 months. [119]

4.3. Effectiveness in Well-Defined Subgroups of Endometrial Cancer

Recent years, molecular targeted therapies have still shown modest effect in unselected EC patients.[120] Overall response rate to these drugs is modest, unless they are associated with chemotherapy or radiotherapy. [110]

ErbB-targeted therapies have not clinically tested in type II EC.[99] Perhaps they may be clinically active as adjuvant therapy in well-defined subgroups of type II EC patients with EGFR and ErbB-2 overexpression. [93,99,111,113,121-128]

The role of ErbB-targeted therapies in EC should be further investigated in clinical trials to evaluate their therapeutic efficacy. [62,92,99,111,114-116,118] Moreover additional studies into the molecular pathways of EC development and progression, will increase our knowledge and lead to the discovery of new generation molecules with higher therapeutic efficacy. [92]

References

[1] Siegel, R; Naishadham, D; Jemal, A. Cancer statistics, 2013. *CA Cancer J Clin*, 2013, 63(1), 11-30.

[2] Sorosky, J. Endometrial cancer. *Obstet Gynecol*, 2012, 120(2 Pt 1), 383-97.

[3] Bokhman, J. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol*, 1983, 15(1), 10-7.

[4] Doll, A; Abal, M; Rigau, M; Monge, M; Gonzalez, M; Demajo, S; et al. Novel molecular profiles of endometrial cancer-new light through old windows. *J Steroid Biochem Mol Biol*, 2008, 108(3-5), 221-29.

[5] Lax, S. Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. *Virchows Arch*, 2004, 444(3), 213-23.

[6] Uberall, I; Kolar, Z; Trojanec, R; Berkovcova, J; Hajduch, M. The status and role of ErbB receptors in human cancer. *Exp Mol Pathol*, 2008, 84(2), 79-89.

[7] Casalini, P; Iorio, M; Galmozzi, E; Menard, S. Role of HER receptors family in development and differentiation. *J Cell Physiol*, 2004, 200(3), 343-50.

[8] Marmor, M; Skaria, K; Yarden, Y. Signal transduction and oncogenesis by ErbB/HER receptors. *Int J Radiat Oncol Biol Phys*, 2004, 58(3), 903-13.

[9] Holbro, T; Civenni, G; Hynes, N. The ErbB receptors and their role in cancer progression. *Exp Cell Res*, 2003, 284(1), 99-110.

[10] Yarden, Y. The EGFR family and its ligands in human cancer. signalling mechanisms and therapeutic opportunities. *Eur J Cancer*, 2001, 37 Suppl 4:S3-8.

[11] Riese, D; Gallo, R; Settleman, J. Mutational activation of ErbB family receptor tyrosine kinases: insights into mechanisms of signal transduction and tumorigenesis. *Bioessays*, 2007, 29(6), 558-65.

[12] Hunter, T. The Croonian Lecture 1997. The phosphorylation of proteins on tyrosine: its role in cell growth and disease. Philos *Trans R Soc Lond B Biol Sci*, 1998, 353(1368), 583-605.

[13] Mass, R. The HER receptor family: a rich target for therapeutic development. *Int J Radiat Oncol Biol Phys*, 2004, 58(3), 932-40.

[14] Ogiso, H; Ishitani, R; Nureki, O; Fukai, S; Yamanaka, M; Kim, JH; et al. Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. *Cell*, 2002, 110(6), 775-87.

[15] Normanno, N; Bianco, C; De Luca, A; Maiello, M; Salomon, D. Target-based agents against ErbB receptors and their ligands: a novel approach to cancer treatment. *Endocr Relat Cancer*, 2003, 10(1), 1-21.

[16] Zhang, D; Sliwkowski, M; Mark, M; Frantz, G; Akita, R; Sun, Y; et al. Neuregulin-3 (NRG3): a novel neural tissue-enriched protein that binds and activates ErbB4. *Proc Natl Acad Sci* U S A, 1997, 94(18), 9562-7.

[17] Harari, D; Tzahar, E; Romano, J; Shelly, M; Pierce, J; Andrews, G; et al. Neuregulin-4: a novel growth factor that acts through the ErbB-4 receptor tyrosine kinase. *Oncogene*, 1999, 18(17), 2681-9.

[18] Alroy, I; Yarden, Y. The ErbB signaling network in embryogenesis and oncogenesis: signal diversification through combinatorial ligand-receptor interactions. *FEBS Lett*, 1997, 410(1), 83-6.

[19] Ferguson, K; Berger, M; Mendrola, J; Cho, H; Leahy, D; Lemmon, M. EGF activates its receptor by removing interactions that autoinhibit ectodomain dimerization. *Mol Cell*, 2003, 11(2), 507-17.

[20] Dawson, J; Berger, M; Lin, C; Schlessinger, J; Lemmon, M; Ferguson, K. Epidermal growth factor receptor dimerization and activation require ligand-induced conformational changes in the dimer interface. *Mol Cell Biol*, 2005, 25(17), 7734-42.

[21] Ozcan, F; Klein, P; Lemmon, M; Lax, I; Schlessinger, J. On the nature of low- and high-affinity EGF receptors on living cells. *Proc Natl Acad Sci U S A*, 2006, 103(15), 5735-40.

[22] Olayioye, M; Neve, R; Lane, H; Hynes, N. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J*, 2000, 19(13), 3159-67.

[23] Zhang, X; Gureasko, J; Shen, K; Cole, PA; Kuriyan, J. An allosteric mechanism for activation of the kinase domain of epidermal growth factor receptor. *Cell*, 2006, 125(6), 1137-49.

[24] Qian, X; LeVea, C; Freeman, J; Dougall, W; Greene, M. Heterodimerization of epidermal growth factor receptor and wild-type or kinase-deficient Neu: a mechanism of interreceptor kinase activation and transphosphorylation. *Proc Natl Acad Sci U S A*, 1994, 91(4), 1500-4.

[25] Garrett, T; McKern, N; Lou, M; Elleman, T; Adams, T; Lovrecz, G; et al. The crystal structure of a truncated ErbB2 ectodomain reveals an active conformation, poised to interact with other ErbB receptors. *Mol Cell*, 2003, 11(2), 495-505.

[26] Hynes, N; Stern, D. The biology of erbB-2/neu/HER-2 and its role in cancer. *Biochim Biophys Acta*, 1994, 1198(2-3), 165-84.

[27] Graus-Porta, D; Beerli, R; Daly, J; Hynes, N. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. *EMBO J*, 1997, 16(7), 1647-55.

[28] Alimandi, M; Romano, A; Curia, M; Muraro, R; Fedi, P; Aaronson, S; et al. Cooperative signaling of ErbB3 and ErbB2 in neoplastic transformation and human mammary carcinomas. *Oncogene*, 1995, 10(9), 1813-21.

[29] Wallasch, C; Weiss, F; Niederfellner, G; Jallal, B; Issing, W; Ullrich, A. Heregulin-dependent regulation of HER2/neu oncogenic signaling by heterodimerization with HER3. *EMBO J*, 1995, 14(17), 4267-75.

[30] Zhang, H; Berezov, A; Wang, Q; Zhang, G; Drebin, J; Murali, R; et al. ErbB receptors: from oncogenes to targeted cancer therapies. *J Clin Invest*, 2007, 117(8), 2051-8.

[31] Songyang, Z; Shoelson, S; Chaudhuri, M; Gish, G; Pawson, T; Haser, W; et al. SH2 domains recognize specific phosphopeptide sequences. *Cell*, 1993, 72(5), 767-78.

[32] Scaltriti, M; Baselga, J. The epidermal growth factor receptor pathway: a model for targeted therapy. *Clin Cancer Res*, 2006, 12(18), 5268-72.

[33] Lowenstein, E; Daly, R; Batzer, A; Li, W; Margolis, B; Lammers, R; et al. The SH2 and SH3 domain-containing protein GRB2 links receptor tyrosine kinases to ras signaling. *Cell*, 1992, 70(3), 431-42.

[34] Batzer, A; Rotin, D; Urena, J; Skolnik, E; Schlessinger, J. Hierarchy of binding sites for Grb2 and Shc on the epidermal growth factor receptor. *Mol Cell Biol*, 1994, 14(8), 5192-201.

[35] Hallberg, B; Rayter, S; Downward, J. Interaction of Ras and Raf in intact mammalian cells upon extracellular stimulation. *J Biol Chem*, 1994, 269(6), 3913-6.

[36] Liebmann, C. Regulation of MAP kinase activity by peptide receptor signalling pathway: paradigms of multiplicity. *Cell Signal*, 2001, 13(11), 777-85.

[37] Hill, C; Treisman, R. Transcriptional regulation by extracellular signals: mechanisms and specificity. *Cell*, 1995, 80(2), 199-211.

[38] Gaestel, M. MAPKAP kinases - MKs - two's company, three's a crowd. *Nat Rev Mol Cell Biol*, 2006, 7(2), 120-30.

[39] Vivanco, I; Sawyers, C. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nat Rev Cancer*, 2002, 2(7), 489-501.

[40] Shaw, R; Cantley, L. Ras, PI(3) K and mTOR signalling controls tumour cell growth. *Nature*, 2006, 441(7092), 424-30.

[41] Yu, J; Wjasow, C; Backer, J. Regulation of the p85/p110alpha phosphatidylinositol 3'-kinase. Distinct roles for the n-terminal and c-terminal SH2 domains. *J Biol Chem*, 1998, 273(46), 30199-203.

[42] Stokoe, D; Stephens, L; Copeland, T; Gaffney, P; Reese, C; Painter, G; et al. Dual role of phosphatidylinositol-3,4,5-trisphosphate in the activation of protein kinase B. *Science*, 1997, 277(5325), 567-70.

[43] Carpenter, C; Auger, K; Chanudhuri, M; Yoakim, M; Schaffhausen, B; Shoelson, S; et al. Phosphoinositide 3-kinase is activated by phosphopeptides that bind to the SH2 domains of the 85-kDa subunit. *J Biol Chem*, 1993, 268(13), 9478-83.

[44] Mattoon, D; Lamothe, B; Lax, I; Schlessinger, J. The docking protein Gab1 is the primary mediator of EGF-stimulated activation of the PI-3K/Akt cell survival pathway. *BMC Biol*, 2004, 2:24.

[45] Bromberg, J. Stat proteins and oncogenesis. *J Clin Invest*, 2002, 109(9), 1139-42.

[46] Haura, E; Turkson, J; Jove, R. Mechanisms of disease: Insights into the emerging role of signal transducers and activators of transcription in cancer. *Nat Clin Pract Oncol*, 2005, 2(6), 315-24.

[47] Yu, H; Jove, R. The STATs of cancer--new molecular targets come of age. *Nat Rev Cancer*, 2004, 4(2), 97-105.

[48] Zhong, Z; Wen, Z; Darnell, J; Jr. Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. *Science*, 1994, 264(5155), 95-8.

[49] Kloth, M; Laughlin, K; Biscardi, J; Boerner, J; Parsons, S; Silva, C. STAT5b, a Mediator of Synergism between c-Src and the Epidermal Growth Factor Receptor. *J Biol Chem*, 2003, 278(3), 1671-9.

[50] Andl, C; Mizushima, T; Oyama, K; Bowser, M; Nakagawa, H; Rustgi, A. EGFR-induced cell migration is mediated predominantly by the JAK-STAT pathway in primary esophageal keratinocytes. *Am J Physiol Gastrointest Liver Physiol*, 2004, 287(6), G1227-37.

[51] Yeatman, T. A renaissance for SRC. *Nat Rev Cancer*, 2004, 4(6), 470-80.

[52] Summy, J; Gallick, G. Treatment for advanced tumors: SRC reclaims center stage. *Clin Cancer Res*, 2006, 12(5), 1398-401.

[53] Jorissen, R; Walker, F; Pouliot, N; Garrett, T; Ward, C; Burgess, A. Epidermal growth factor receptor: mechanisms of activation and signalling. *Exp Cell Res*, 2003, 284(1), 31-53.

[54] Leu, T; Maa, M. Functional implication of the interaction between EGF receptor and c-Src. *Front Biosci*, 2003, 8, s28-38.

[55] Chattopadhyay, A; Vecchi, M; Ji, Q; Mernaugh, R; Carpenter, G. The role of individual SH2 domains in mediating association of phospholipase C-gamma1 with the activated EGF receptor. *J Biol Chem*, 1999, 274(37), 26091-7.

[56] Patterson, R; van Rossum, D; Nikolaidis, N; Gill, D; Snyder, S. Phospholipase, C-gamma: diverse roles in receptor-mediated calcium signaling. *Trends Biochem Sci*, 2005, 30(12), 688-97.

[57] Schonwasser, D; Marais, R; Marshall, C; Parker, P. Activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway by conventional, novel, and atypical protein kinase C isotypes. *Mol Cell Biol*, 1998, 18(2), 790-8.

[58] McClellan, M; Kievit, P; Auersperg, N; Rodland, K. Regulation of proliferation and apoptosis by epidermal growth factor and protein kinase C in human ovarian surface epithelial cells. *Exp Cell Res*, 1999, 246(2), 471-9.

[59] Salomon, D; Brandt, R; Ciardiello, F; Normanno, N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*, 1995, 19(3), 183-232.

[60] Moscatello, D; Holgado-Madruga, M; Godwin, A; Ramirez, G; Gunn, G; Zoltick, P; et al. Frequent expression of a mutant epidermal growth factor receptor in multiple human tumors. *Cancer Res*, 1995, 55(23), 5536-9.

[61] Lurje, G; Lenz, HJ. EGFR signaling and drug discovery. *Oncology*, 2009, 77(6), 400-10.

[62] Odicino, F; Bignotti, E; Rossi, E; Pasinetti, B; Tassi, R; Donzelli, C; et al. HER-2/neu overexpression and amplification in uterine serous papillary carcinoma: comparative analysis of immunohistochemistry, real-time reverse transcription-polymerase chain reaction, and fluorescence in situ hybridization. *Int J Gynecol Cancer*, 2008, 18(1), 14-21.

[63] Ross, J; Fletcher, J. The HER-2/neu Oncogene in Breast Cancer: Prognostic Factor, Predictive Factor, and Target for Therapy. *Oncologist*, 1998, 3(4), 237-52.

[64] Lemoine, N; Barnes, D; Hollywood, D; Hughes, C; Smith, P; Dublin, E; et al. Expression of the ERBB3 gene product in breast cancer. *Br J Cancer*, 1992, 66(6), 1116-21.

[65] Gasparini, G; Gullick, W; Maluta, S; Dalla Palma, P; Caffo, O; Leonardi, E; et al. c-erbB-3 and c-erbB-2 protein expression in node-negative breast carcinoma--an immunocytochemical study. *Eur J Cancer*, 1994, 30A(1), 16-22.

[66] Bieche, I; Onody, P; Tozlu, S; Driouch, K; Vidaud, M; Lidereau, R. Prognostic value of ERBB family mRNA expression in breast carcinomas. *Int J Cancer*, 2003, 106(5), 758-65.

[67] Suo, Z; Risberg, B; Kalsson, M; Willman, K; Tierens, A; Skovlund, E; et al. EGFR family expression in breast carcinomas. c-erbB-2 and c-erbB-4 receptors have different effects on survival. *J Pathol*, 2002, 196(1), 17-25.

[68] Memon, A; Sorensen, B; Melgard, P; Fokdal, L; Thykjaer, T; Nexo, E. Expression of HER3, HER4 and their ligand heregulin-4 is associated with better survival in bladder cancer patients. *Br J Cancer*, 2004, 91(12), 2034-41.

[69] Barnes, N; Khavari, S; Boland, G; Cramer, A; Knox, W; Bundred, N. Absence of HER4 expression predicts recurrence of ductal carcinoma in situ of the breast. *Clin Cancer Res*, 2005, 11(6), 2163-8.

[70] Sherman, M; Sturgeon, S; Brinton, L; Potischman, N; Kurman, R; Berman, M; et al. Risk factors and hormone levels in patients with serous and endometrioid uterine carcinomas. *Mod Pathol*, 1997, 10(10), 963-8.

[71] Moreno-Bueno, G; Sanchez-Estevez, C; Cassia, R; Rodriguez-Perales, S; Diaz-Uriarte, R; Dominguez, O; et al. Differential gene expression profile in endometrioid and nonendometrioid endometrial carcinoma: STK15 is frequently overexpressed and amplified in nonendometrioid carcinomas. *Cancer Res*, 2003, 63(18), 5697-702.

[72] Risinger, J; Maxwell, G; Chandramouli, G; Jazaeri, A; Aprelikova, O; Patterson, T; et al. Microarray analysis reveals distinct gene expression profiles among different histologic types of endometrial cancer. *Cancer Res*, 2003, 63(1), 6-11.

[73] Basil, J; Goodfellow, P; Rader, J; Mutch, D; Herzog, T. Clinical significance of microsatellite instability in endometrial carcinoma. *Cancer*, 2000, 89(8), 1758-64.

[74] Lax, S; Kendall, B; Tashiro, H; Slebos, R; Hedrick, L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. *Cancer*, 2000, 88(4), 814-24.

[75] Hecht, J; Mutter, G. Molecular and pathologic aspects of endometrial carcinogenesis. *J Clin Oncol*, 2006, 24(29), 4783-91.

[76] Bansal, N; Yendluri, V; Wenham, R. The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. *Cancer Control*, 2009, 16(1), 8-13.

[77] Abeler, V; Kjorstad, K. Clear cell carcinoma of the endometrium: a histopathological and clinical study of 97 cases. *Gynecol Oncol*, 1991, 40(3), 207-17.

[78] Goff, B; Kato, D; Schmidt, R; Ek, M; Ferry, J; Muntz, H; et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol*, 1994, 54(3), 264-8.

[79] Hetzel, D; Wilson, T; Keeney, G; Roche, P; Cha, S; Podratz, K. HER-2/neu expression: a major prognostic factor in endometrial cancer. *Gynecol Oncol*, 1992, 47(2), 179-85.

[80] Tashiro, H; Isacson, C; Levine, R; Kurman, R; Cho, K; Hedrick, L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. *Am J Pathol*, 1997, 150(1), 177-85.

[81] Holcomb, K; Delatorre, R; Pedemonte, B; McLeod, C; Anderson, L; Chambers, J. E-cadherin expression in endometrioid, papillary serous, and clear cell carcinoma of the endometrium. *Obstet Gynecol*, 2002, 100(6), 1290-5.

[82] Santin, A; Bellone, S; Van Stedum, S; Bushen, W; Palmieri, M; Siegel, E; et al. Amplification of c-erbB2 oncogene: a major prognostic indicator in uterine serous papillary carcinoma. *Cancer*, 2005, 104(7), 1391-7.

[83] Grushko, T; Filiaci, V; Mundt, A; Ridderstrale, K; Olopade, O; Fleming, G. An exploratory analysis of HER-2 amplification and overexpression in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*, 2008, 108(1), 3-9.

[84] Ejskjaer, K; Sorensen, BS; Poulsen, SS; Forman, A; Nexo, E; Mogensen, O. Expression of the epidermal growth factor system in endometrioid endometrial cancer. *Gynecol Oncol*, 2007, 104(1), 158-67.

[85] Bigsby, R; Li A; Bomalaski, J; Stehman, F; Look, K; Sutton, G. Immunohistochemical study of HER-2/neu, epidermal growth factor receptor, and steroid receptor expression in normal and malignant endometrium. *Obstet Gynecol*, 1992, 79(1), 95-100.

[86] Wang, X; Das, S; Damm, D; Klagsbrun, M; Abraham, J; Dey, S. Differential regulation of heparin-binding epidermal growth factor-like growth factor in the adult ovariectomized mouse uterus by progesterone and estrogen. *Endocrinology*, 1994, 135(3), 1264-71.

[87] Imai, T; Kurachi, H; Adachi, K; Adachi, H; Yoshimoto, Y; Homma, H; et al. Changes in epidermal growth factor receptor and the levels of its ligands during menstrual cycle in human endometrium. *Biol Reprod*, 1995, 52(4), 928-38.

[88] Moller, B; Rasmussen, C; Lindblom, B; Olovsson, M. Expression of the angiogenic growth factors VEGF, FGF-2, EGF and their receptors in normal human endometrium during the menstrual cycle. *Mol Hum Reprod*, 2001, 7(1), 65-72.

[89] Ejskjaer, K; Sorensen, BS; Poulsen, SS; Mogensen, O; Forman, A; Nexo, E. Expression of the epidermal growth factor system in human endometrium during the menstrual cycle. *Mol Hum Reprod*, 2005, 11(8), 543-51.

[90] Androutsopoulos, G; Adonakis, G; Gkermpesi, M; Gkogkos, P; Ravazoula, P; Kourounis, G. Expression of the epidermal growth factor system in endometrial cancer after adjuvant tamoxifen treatment for breast cancer. *Eur J Gynaecol Oncol*, 2006, 27(5), 490-4.

[91] Adonakis, G; Androutsopoulos, G; Koumoundourou, D; Liava, A; Ravazoula, P; Kourounis, G. Expression of the epidermal growth factor system in endometrial cancer. *Eur J Gynaecol Oncol*, 2008, 29(5), 450-4.

[92] Adonakis, G; Androutsopoulos, G. The role of ErbB receptors in endometrial cancer. In: Saldivar JS; editor. Cancer of the uterine endometrium - advances and controversies: *InTech*, 2012:23-38.

[93] Androutsopoulos, G; Adonakis, G; Liava, A; Ravazoula, P; Decavalas, G. Expression and potential role of ErbB receptors in type II endometrial cancer. *Eur J Obstet Gynecol Reprod Biol*, 2013, 168(2), 204-08.

[94] Nyholm, H; Nielsen, A; Ottesen, B. Expression of epidermal growth factor receptors in human endometrial carcinoma. *Int J Gynecol Pathol*, 1993, 12(3), 241-5.

[95] Reinartz, J; George, E; Lindgren, B; Niehans, G. Expression of p53, transforming growth factor alpha, epidermal growth factor receptor, and c-erbB-2 in endometrial carcinoma and correlation with survival and known predictors of survival. *Hum Pathol*, 1994, 25(10), 1075-83.

[96] Khalifa, MA; Mannel, RS; Haraway, SD; Walker, J; Min, KW. Expression of EGFR, HER-2/neu, P53, and PCNA in endometrioid, serous papillary, and clear cell endometrial adenocarcinomas. *Gynecol Oncol*, 1994, 53(1), 84-92.

[97] Niikura, H; Sasano, H; Kaga, K; Sato, S; Yajima, A. Expression of epidermal growth factor family proteins and epidermal growth factor receptor in human endometrium. *Hum Pathol*, 1996, 27(3), 282-9.

[98] Scambia, G; Benedetti Panici, P; Ferrandina, G; Battaglia, F; Distefano, M; D'Andrea, G; et al. Significance of epidermal growth factor receptor expression in primary human endometrial cancer. *Int J Cancer*, 1994, 56(1), 26-30.

[99] Konecny, G; Santos, L; Winterhoff, B; Hatmal, M; Keeney, GL; Mariani, A; et al. HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer. *Br J Cancer*, 2009, 100(1), 89-95.

[100] Brys, M; Semczuk, A; Rechberger, T; Krajewska, W. Expression of erbB-1 and erbB-2 genes in normal and pathological human endometrium. *Oncol Rep*, 2007, 18(1), 261-5.

[101] Miturski, R; Semczuk, A; Jakowicki, J. C-erbB-2 expression in human proliferative and hyperplastic endometrium. *Int J Gynaecol Obstet*, 1998, 61(1), 73-4.

[102] Morrison, C; Zanagnolo, V; Ramirez, N; Cohn, D; Kelbick, N; Copeland, L; et al. HER-2 is an independent prognostic factor in endometrial cancer: association with outcome in a large cohort of surgically staged patients. *J Clin Oncol*, 2006, 24(15), 2376-85.

[103] Santin, A; Bellone, S; Siegel, E; Palmieri, M; Thomas, M; Cannon, M; et al. Racial differences in the overexpression of epidermal growth factor type II receptor (HER2/neu): a major prognostic indicator in uterine serous papillary cancer. *Am J Obstet Gynecol*, 2005, 192(3), 813-8.

[104] Slomovitz, B; Broaddus, R; Burke, T; Sneige, N; Soliman, P; Wu, W; et al. Her-2/neu overexpression and amplification in uterine papillary serous carcinoma. *J Clin Oncol*, 2004, 22(15), 3126-32.

[105] Lukes, A; Kohler, M; Pieper, C; Kerns, B; Bentley, R; Rodriguez, G; et al. Multivariable analysis of DNA ploidy, p53, and HER-2/neu as prognostic factors in endometrial cancer. *Cancer*, 1994, 73(9), 2380-5.

[106] Togami, S; Sasajima, Y; Oi, T; Ishikawa, M; Onda, T; Ikeda, S; et al. Clinicopathological and prognostic impact of human epidermal growth factor receptor type 2 (HER2) and hormone receptor expression in uterine papillary serous carcinoma. *Cancer Sci*, 2012, 103(5), 926-32.

[107] Prigent, S; Lemoine, N; Hughes, C; Plowman, G; Selden, C; Gullick, W. Expression of the c-erbB-3 protein in normal human adult and fetal tissues. *Oncogene*, 1992, 7(7), 1273-8.

[108] Srinivasan, R; Benton, E; McCormick, F; Thomas, H; Gullick, W. Expression of the c-erbB-3/HER-3 and c-erbB-4/HER-4 growth factor receptors and their ligands, neuregulin-1 alpha, neuregulin-1 beta, and betacellulin, in normal endometrium and endometrial cancer. *Clin Cancer Res*, 1999, 5(10), 2877-83.

[109] Chobotova, K; Karpovich, N; Carver, J; Manek, S; Gullick, W; Barlow, D; et al. Heparin-binding epidermal growth factor and its receptors mediate decidualization and potentiate survival of human endometrial stromal cells. *J Clin Endocrinol Metab*, 2005, 90(2), 913-9.

[110] Baselga, J; Arteaga, CL. Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. *J Clin Oncol*, 2005, 23(11), 2445-59.

[111] Santin, A; Bellone, S; Roman, J; McKenney, J; Pecorelli, S. Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. *Int J Gynaecol Obstet*, 2008, 102(2), 128-31.

[112] Jewell, E; Secord, A; Brotherton, T; Berchuck, A. Use of trastuzumab in the treatment of metastatic endometrial cancer. *Int J Gynecol Cancer*, 2006, 16(3), 1370-3.

[113] Villella, J; Cohen, S; Smith, D; Hibshoosh, H; Hershman, D. HER-2/neu overexpression in uterine papillary serous cancers and its possible therapeutic implications. *Int J Gynecol Cancer*, 2006, 16(5), 1897-902.

[114] Santin, A. Letter to the Editor referring to the manuscript entitled: "Phase II trial of trastuzumab in women with advanced or recurrent HER-positive endometrial carcinoma: a Gynecologic Oncology Group study" recently reported by Fleming et al., (Gynecol Oncol., 116, 15-20, 2010). *Gynecol Oncol*, 2010, 118(1), 95-6, author reply 96-7.

[115] Fleming, G; Sill, M; Darcy, K; McMeekin, D; Thigpen, J; Adler, L; et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*, 2010, 116(1), 15-20.

[116] Roque, D; Santin, A. Updates in therapy for uterine serous carcinoma. *Curr Opin Obstet Gynecol*, 2013, 25(1), 29-37.

[117] Leslie, K; Sill, M; Fischer, E; Darcy, K; Mannel, R; Tewari, K; et al. A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*, 2013, 129(3), 486-94.

[118] Oza, A; Eisenhauer, E; Elit, L; Cutz, J; Sakurada, A; Tsao, M; et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol*, 2008, 26(26), 4319-25.

[119] Leslie, K; Sill, M; Lankes, H; Fischer, E; Godwin, A; Gray, H; et al. Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. *Gynecol Oncol*, 2012, 127(2), 345-50.

[120] Hogberg, T. What is the role of chemotherapy in endometrial cancer? *Curr Oncol Rep*, 2011, 13(6), 433-41.

[121] Konecny, G; Venkatesan, N; Yang, G; Dering, J; Ginther, C; Finn, R; et al. Activity of lapatinib a novel HER2 and EGFR dual kinase inhibitor in human endometrial cancer cells. *Br J Cancer*, 2008, 98(6), 1076-84.

[122] Vandenput, I; Vanden Bempt, I; Leunen, K; Neven, P; Berteloot, P; Moerman, P; et al. Limited clinical benefit from trastuzumab in recurrent endometrial cancer: two case reports. *Gynecol Obstet Invest*, 2009, 67(1), 46-8.

[123] El-Sahwi, K; Bellone, S; Cocco, E; Cargnelutti, M; Casagrande, F; Bellone, M; et al. In vitro activity of pertuzumab in combination with trastuzumab in uterine serous papillary adenocarcinoma. *Br J Cancer*, 2010, 102(1), 134-43.

[124] Androutsopoulos, G. Current treatment options in patients with endometrial cancer. *J Community Med Health Educ*, 2012, 2(12), e113.

[125] Androutsopoulos, G; Decavalas, G. Management of endometrial cancer. International *Journal of Translation & Community Medicine*, 2013, 1(1), 101.

[126] Elsahwi, K; Santin, A. ErbB2 overexpression in uterine serous cancer: a molecular target for trastuzumab therapy. *Obstet Gynecol Int*, 2011, 2011:128295.

[127] Fader A; Santin A; Gehrig P. Early stage uterine serous carcinoma: management updates and genomic advances. Gynecol Oncol 2013, 129(1), 244-50.

[128] Gadducci, A; Tana, R; Cosio, S; Fanucchi, A; Genazzani, A. Molecular target therapies in endometrial cancer: from the basic research to the clinic. *Gynecol Endocrinol*, 2008, 24(5), 239-49.