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HER2 as a Therapeutic Target in Ovarian Cancer

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1. Introduction

Members of the human epidermal growth factor receptor (HER) family—epidermal growth factor receptor (EGFR, HER1), HER2, HER3, and HER4—are transmembrane tyrosine kinase receptors that are important mediators of cell growth, development, and survival. Activation of the HER tyrosine kinases triggers intracellular signaling pathways, including the MAPK and PI3K-Akt pathways (Olayioye et al., 2000) (Figure 1).

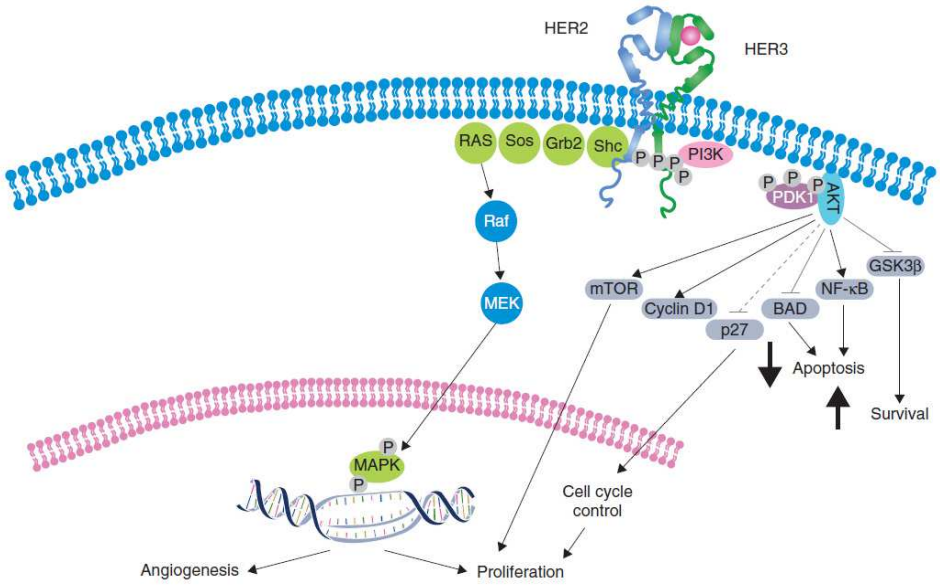

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Fig. 1. Dimerization of HER2–HER3 initiates the PI3K and MAPK signaling pathways.

Ligand binding to HER1, 3, and 4 results in a conformational change in the extracellular domain of each protein that opens a dimerization domain and allows the receptor to form

either a homo- or heterodimer with another member of the HER family (Cho & Leahy, 2002; Zhang et al., 2006). No ligand has been identified for HER2, and it exists in a conformation that is constitutively available for dimerization (Garrett et al., 2003). HER2 is therefore the preferred dimer partner of other HER family members (Graus-Porta et al., 1997). While HER2 has no known ligand, HER3 lacks intracellular tyrosine kinase activity, rendering HER2–HER3 signaling dependent on heterodimerization (Yarden & Sliwkowski, 2001). HER2–HER3 dimerization results in phosphorylation of the tyrosine kinase domain, which in turn activates intracellular signaling pathways (Zhang et al., 2006). The effect of these signaling pathways on gene transcription determines how the cell responds to the ligand activation.

HER family members can also be activated by ligand-independent mechanisms, including activation by other tyrosine kinase receptors, G-protein coupled receptors, and adhesion proteins (Siwak et al., 2010).

1.1 Role of HER2 in oncology

Members of the HER family were first associated with oncogenesis after the discovery that the sequence of the EGFR receptor was found to be very similar to that of v-*ErbB*, a transforming retroviral oncogene carried by the avian erythroblastosis virus (Downward et al., 1984). The v-*ErbB* oncogene encodes a truncated form of EGFR that can form ligand-independent dimers, thereby initiating cell signaling pathways and inducing cellular proliferation in the absence of ligand stimulation (Adelsman et al., 1996). Examination of a series of rat neuro/gliobalstomas revealed a commonly transforming gene, neu, encoding a protein serologically related to ErbB (EGFR), subsequently shown to be the HER2 oncoprotein (Coussens et al., 1985; Schechter et al., 1984).

HER2 expression is frequently dysregulated in several types of human tumors including those of the breast, head and neck, prostate, and ovary (Hynes, 1993). Of particular significance was the discovery that the HER2 protein was overexpressed, commonly by gene amplification, in about 30% of breast cancers. These studies also showed that overexpression of HER2 indicated an aggressive subtype of breast cancers with a particularly poor prognosis for the patient (Slamon et al., 1987, 1989). Overexpression of HER2 facilitates the formation of HER2 heterodimers, which trigger HER2 signaling pathways (Yarden and Sliwkowski, 2001), with excess HER2 signaling resulting in signaling cascades that promote oncogenic cell survival and proliferation (Olayioye et al., 2000; Rowinsky, 2004).

HER2 amplification /overexpression has also been reported in patients with gastric tumors where it is again linked to a poor prognosis (Jaehne et al., 1992). In addition, increased HER2 levels have been reported in some patients with salivary gland tumors (Cornolti et al., 2007) and non-small cell lung cancer (NSCLC) (Cappuzzo et al., 2006). Mutations in tumor suppressor genes may be partly responsible for the aberrant expression of HER2 in these tumors. Foe example, one tumor suppressor, *FOXP3*, normally maintains low levels of HER2 in normal cells; however, in breast cancer models the absence of *FOXP3* results in high expression of HER2 (Zuo et al., 2007).

Overexpression of HER2 is only one of several mechanisms, albeit the most frequent, by which HER2 signaling can be activated in oncogenesis. Mutations in the kinase domain of HER2 can potentially trigger signaling that is independent of ligand binding or dimerization (Anglesio et al., 2008). Ligand-dependent activation of HER2 via dimerization with other

HER family members may also play a role in HER2 oncogenesis. Of all of the different HER family dimers, the HER2–HER3 heterodimer appears to have the most potent signaling effects in cancer cells (Tzahar et al., 1996).. It appears that HER3 is crucial for mediating the dysregulated signaling in tumors overexpressing HER2 (Lee-Hoeflich et al., 2008). Cancers with HER2 amplification are frequently observed to have increased Akt activity even though HER2 cannot directly activate the PI3K–Akt pathway (Hsieh & Moasser, 2007). However, the intracellular domain of HER3 contains several binding sites for PI3K, enabling direct activation of the PI3K–Akt pathway (Figure 1), which may explain the mitogenic activity of HER2–HER3 dimers (Hsieh & Moasser, 2007). HER2 can also form a dimer with EGFR, which initiates intracellular signaling via the MAPK pathway (Campiglio et al., 1999). In summary, while HER2 amplification leading to overexpression is clearly linked to activation of HER2 in some tumor cells, activating mutations in HER2, as well as ligand-dependent activation of HER2 signaling, are also likely important mechanisms leading to HER2 oncogenesis.

2. HER2 in ovarian cancer

The HER family are important mediators of normal ovarian follicle development, and regulate the growth of ovarian epithelial cells (Conti et al., 2006). Dysregulation of HER signaling in the ovary due to overexpression of, or mutations in HER family members have been linked to the growth and proliferation of ovarian tumors.

2.1 HER2 overexpression in ovarian cancer

The proportion of ovarian cancers overexpressing HER2 is a matter of debate (Sheng & Liu, 2011). Various studies have reported that between 5% and 35% of ovarian tumors overexpress HER2 (Table 1). Some of these differences are likely to be attributable to the diagnostic technique used to measure HER2 expression. HER2 protein expression is commonly measured using immunohistochemistry (IHC), whereas *HER2* gene amplification is typically measured using hybridization techniques, such as fluorescence in situ hybridization (FISH) (Wolff et al., 2007). Recent technical improvements also enable measurement of HER2 mRNA expression levels using the quantitative real time-polymerase chain reaction (qRT-PCR) in archival samples (Muller et al., 2011).

However, the reported levels of HER2 overexpression and/or amplification may be affected by other factors including variable definitions of overexpression, small sample sizes, and variable testing conditions or assay performance (Wolff et al., 2007). It should also be noted that studies investigating only *HER2* gene amplification are likely to account for only a proportion of cancers that overexpress of the protein without amplification of the gene (Mano et al., 2004).

In a recent study of somatic copy number alterations in 489 ovarian cancer samples using multiple microarray-based platforms, 63 regions of recurrent focal amplification were identified, of which 26 regions encoded eight or fewer genes. The most common focal amplifications encoded *CCNE1*, *MYC*, and *MECOM*, each of which was highly amplified in more than 20% of tumors. By contrast, *HER2* was highly amplified in 3.1% of tumors, and a further 7% of tumors had a more moderate level of *HER2* amplification. The correlation between *HER2* copy number and mRNA expression was 0.59 (Cancer Genome Atlas Research Network, 2011).

Study	Method of assay	Pts with HER2-positive tumors, n/N (%)	Definition of 'HER2-positive'	Correlation between expression and survival[1]?	
				Yes/No	p-value
Rubin et al., 1993	IHC	36/105 (34) 12/105 (11)	2+ or 3+ membrane staining 1+ membrane staining	No†‡	NA
Meden et al., 1994	IHC	51/275 (19)	NS	Yes	p=0.001† p=0.006‡
Meden et al., 1995	IHC	48/266 (18)	NS	Yes	p=0.002† p=0.012‡
Meden et al., 1998	IHC	46/208 (22)	>5% cells had membrane staining at 100× magnification	Yes	p=0.0003†
Bookman et al., 2003	IHC	95/837 (11)	2+ or 3+ membrane staining	NA	NA
Hogdall et al., 2003	IHC	24/181 (13) 71/181 (39)	2+ or 3+ membrane staining 1+ membrane staining	Yes	p=0.003‡
Cloven et al., 2004	IHC	227/1420 (16)	≥1+ staining	NA	NA
Lassus et al., 2004[2]	IHC	66/390 (17)	2+ or 3+ membrane staining	Yes	p<0.0001†
	CISH	26/381 (7) 55/381 (14)	>5 copies of HER2 per nucleus 3–5 copies of HER2 per nucleus	Yes	p<0.0001† p<0.006‡
Kupryjanczyk et al., 2004	IHC	63/233 (27) 35/233 (15)	2+ or 3+ membrane staining 1+ membrane staining	No	NA
Nielsen et al., 2004	IHC	272/783 (35)	2+ or 3+ staining of cytoplasm or membrane	Yes/No	p=0.021†[3] p=0.76‡
Lee et al., 2005	IHC	5/102 (5)	≥1+ staining	NA	NA
Verri et al., 2005	IHC	27/194 (14) 26/194 (13)	2+ or 3+ membrane staining 1+ membrane staining	Yes/No	p=0.04† p<0.30‡
Steffensen et al., 2007[2]	IHC	18/160 (11) 39/160 (24)	2+ or 3+ membrane staining 1+ membrane staining	Yes	p=0.03†
	FISH	10/145 (7)	HER2:CEP17 ratio >2	No	p=0.39†
Tuefferd et al., 2007	IHC	41/320 (13)	2+ or 3+ membrane staining	No	p=0.6† p=0.152‡
Farley et al., 2009	FISH	9/133 (7)	HER2:CEP17 ratio >2	No	p=0.12† p=0.152‡
		12/133 (9)	HER2:nuclei ratio >4	No	p=0.42† p=0.980‡

CEP17, chromosome enumeration probe 17; CISH, chromogenic in situ hybridization; FISH; fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not applicable; NS, not specified; Pts, patients.
1 Overall survival of patients with HER2 positive tumors versus those with HER2 negative tumors. † Univariate analysis; ‡ Multivariate analysis.
2 Not all IHC samples were analyzable by CISH/FISH due to DNA degradation.
3 Patients with HER2 positive tumors had increased survival versus those with HER2 negative tumors.

Table 1. Expression level of HER2 in ovarian tumors in studies with >100 patients.

The HER2 mRNA level in samples taken from ovarian tumors of patients who were enrolled in a clinical trial studying platinum-sensitive disease (Kaye et al., 2008) showed a dichotomous distribution of HER2 mRNA expression (Figure 2A) similar to that observed in tumor samples from a study of patients with breast cancer (Figure 2B) (Burris et al., 2011). The prevalence of mRNA overexpression in the ovarian cancer samples was approximately 5% (Yulei Wang & Lukas Amler, unpublished data).

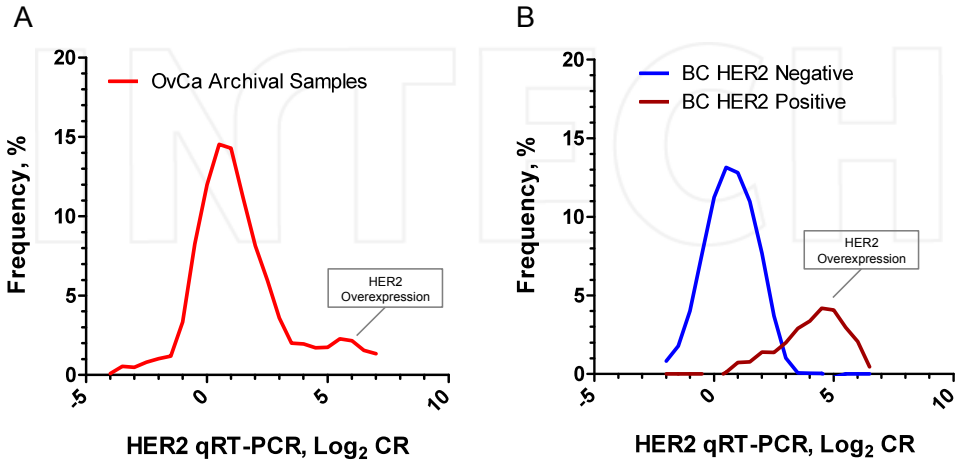

Fig. 2. Distribution of HER2 mRNA expression levels in (A) ovarian cancer and (B) breast cancer (Yulei Wang & Lukas Amler, unpublished data).

Samples from ovarian tumors were randomly chosen from archived samples collected during a clinical trial (Kaye et al., 2008). Samples from breast tumors were also collected during a clinical trial (Burris et al., 2011) but had known HER2 status (75% were HER2 negative, 25% were HER2 positive by IHC). HER2 mRNA levels in both data sets were determined by qRT-PCR (method as published in Makhija et al., 2010).

The CR of HER2:G6PDH expression was plotted as a histogram, and a smooth curve was fitted over the histogram. The ovarian cancer samples show a bimodal distribution of HER2 expression, with a small peak indicating the population of tumors that overexpress HER2 mRNA.

(BC, breast cancer; CR, concentration ratio; HER2, human epidermal growth factor receptor 2; G6PDH, glucose-6-phosphate dehydrogenase; IHC, immunohistochemistry; qRT-PCR, quantitative real time-polymerase chain reaction).

Steffenson et al. also used qRT-PCR to measure HER2 mRNA expression in 99 ovarian tumors and found that the tumor tissue had an average 5.7-fold higher level of HER2 mRNA compared with normal ovarian tissue. IHC showed HER2 overexpression (2+/3+ staining) in 11% (11/99) of tumors with a further 33% (33/99) of tumors showing 1+ staining. In contrast, all samples from normal ovarian tissue (n=23) were shown to be negative for HER2 staining (Steffensen et al., 2008).

Several studies have shown that overexpression of HER2 in ovarian tumors is an independent predictor of shorter progression-free survival and/or overall survival after

multivariate analysis. However, this has not been supported by other studies (Table 1) (Serrano-Olvera et al., 2006). This discrepancy may indicate that while HER2 overexpression is of prognostic value in some groups of patients, this is not true for all patients in whom other biomarkers may be more significant. Assay quality, execution, and interpretation of data, as discussed above, may also explain differences in the observed levels of HER2 expression and its prognostic value.

2.2 Activation of HER2 in ovarian cancer

HER2 amplification and/or overexpression occurs in relatively few patients with ovarian cancer, although "normal" expression of HER2 measured by IHC 1+ staining is relatively common (Table 1). Other mechanisms, such as mutations in *HER2* or ligand-dependent activation of HER2, may play a role in HER2 oncogenesis.

Mutations in the *HER2* kinase domain are indeed found in ovarian tumors (Table 2), and the pattern of these in-frame insertions and missense mutations is similar to activating mutations found in other kinases, strongly suggesting that these mutations activate the HER2 kinase. For example, mutations in *HER2* are adjacent to or overlap with the analogous structural region of EGFR in-frame deletions that are associated with some lung tumors (Stephens et al., 2004). One study found that 6% of serous borderline ovarian tumors of low malignant potential (LMP) expressed a mutated version of HER2. LMP ovarian tumors also have a high rate of *KRAS* (18%) and *BRAF* (48%) mutations indicating that constitutive activation of the RAS–MAPK pathway may be one of the key mechanisms in the development of this type of ovarian tumor (Anglesio et al., 2008).

Nucleotide change	Amino acid change	Frequency n/N (%)	Tumor subtype	Reference
c.2325_2326 12 bp insertion	p.A775_G776 insert YVMA	1/84 (1)	Serous borderline tumors	Anglesio et al., 2008
c.2322_2323 12 bp insertion	p.M774_A775 insert AYVM	2/84 (2)	Serous borderline tumors	
c.2324_2325 12 bp insertion	p.A775_G776 insert YVMA	2/84 (2)	Serous borderline tumors	
12 bp insertion between c.2313 and c.2324	NK	2/21 (10)	Serous borderline tumors	Nakayama et al., 2006
c.2315_2316 12 bp insertion	p.A772_G773 insert YVMA	1/188 (0.5)	Serous carcinoma	Lassus et al., 2006
c.2327 G>T	p.G776V	1/6 (17)	Ovarian cell lines	Ikediobi et al., 2006
c.2570 A>G	p.N857S	1/27 (4)	Serous carcinoma	Stephens et al., 2004
c.2539 C>G	p.I767M	1/58 (2)	Serous carcinoma	Kan et al., 2010

bp, base pairs; NK, not known.

Table 2. *HER2* mutations in ovarian tumors and cell lines.

Ligand-dependent signaling via HER2–HER3 or HER2–EGFR dimers may also be important in ovarian cancer (Amler, 2010; Campiglio et al., 1999; Lewis et al., 1996). To investigate this hypothesis, Gordon et al. measured activated phosphorylated (p)HER2 by enzyme-linked immunosorbent assay and *HER2* gene amplification by FISH in 20 fresh ovarian tumor biopsies. They found that while only two tumors had *HER2* gene amplification (10%), pHER2 was detected in 45% of tumors (Gordon et al., 2006), indicating that activation of HER2 signaling probably occurs independently of gene amplification.

2.3 Biomarkers to identify HER2 activated or dependent ovarian tumors

Cumulative evidence over the past decade has demonstrated that in most cases, tumors from the same anatomic site of origin can be sub-classified into distinct molecular subsets driven by different underlying biological mechanisms and with distinct prognoses. This is best exemplified in breast cancer, where at least four distinct subtypes have been identified (Onitilo et al., 2009). Biomarkers that can differentiate between these distinct biological subsets of tumors can be used to predict the prognosis of a patient and potentially identify those who will derive the most benefit from targeted therapies (Carden et al., 2009). In breast cancer, such relevant biomarkers include measuring the expression of estrogen receptor α and the progesterone receptor to identify patients who would be sensitive to hormonal therapies, and HER2 to identify patients who would benefit from treatment with HER2-targeted therapies (Labuhn et al., 2006). Likewise, biomarkers are also used to determine the best course of treatment in a variety of other cancers. For example, patients with NSCLC or colorectal cancer (CRC) are screened for mutations in *EGFR* and *KRAS*, respectively, to determine whether they would benefit from EGFR inhibitors (Catenacci et al., 2011; Domingo et al., 2010). Mutations in both of these oncogenes are likely representative of distinct biological subsets of disease. For example, patients whose tumors harbor EGFR mutations are typically non-smokers, often female and of Asian ethnicity, and generally have a better prognosis than non-EGFR mutant NSCLC (Coate et al., 2009).

The identification of patients with ovarian tumors that express either high levels of HER2, HER2 with activating mutations, or biomarkers that indicate activated HER2 signaling, such as pHER2, could enable the patients who would derive the greatest therapeutic benefit to receive HER2-targeted therapies. Measuring the expression status of genes regulated by HER2 signaling could also identify tumors with activated HER2 signaling.

The importance of HER2–HER3 heterodimers in the HER2 signaling pathway has led to the investigation of HER3 as a prognostic biomarker in ovarian cancer (Amler, 2010). In one study of patients with ovarian cancer, those with high (≥ median; n=62) expression of HER3 protein had significantly decreased survival compared with those with low (< median; n=54) expression levels (1.80 versus 3.31 years; p=0.0034) following surgery and chemotherapy. In multivariate analysis, high HER3 expression significantly increased the risk of mortality compared with low HER3 expression (p=0.018) (Tanner et al., 2006). In contrast, patients with ovarian cancer receiving gemcitabine who had low HER3 mRNA expression (< median; n=35) had a significantly decreased progression-free survival (p=0.0002) and overall survival (p=0.003) than patients with high HER3 (≥ median; n= 24) mRNA levels. These data suggest that HER3 may be a prognostic biomarker in ovarian cancer (Makhija et al., 2010).

Interestingly, two separate studies have demonstrated that HER3 mRNA and protein levels in ovarian cancer cell lines were reduced on addition of heregulin, a ligand for HER3 (Makhija et al., 2010; Nagumo et al., 2009). The modulation of HER3 mRNA levels was

found to be inversely proportional to activation of the downstream signaling molecules Akt and ERK1/2, critical components of the PI3K–Akt pathway (Nagumo et al., 2009). This suggests that low HER3 mRNA levels in HER2-positive tumors are associated with a high level of HER2–HER3 signaling. Overall these results point to a negative feedback loop that responds to the activation of HER3 by downregulation of HER3 mRNA expression (Makhija et al., 2010; Nagumo et al., 2009), and suggests that HER3 protein or mRNA levels may be a useful prognostic biomarker in patients with ovarian cancer.

3. HER2 as a drug target in human cancer

3.1 Clinical evidence for HER2 as a drug target in solid tumors

Trastuzumab (Herceptin) is a monoclonal antibody that binds to HER2 in the juxtamembrane region of the extracellular domain (Cho et al., 2003). Trastuzumab is licensed for use as a first-line treatment in combination with other chemotherapeutic agents in patients with HER2-positive breast cancer or gastric cancer in the USA and Europe. It has also been licensed for use as a single agent in patients with breast cancer who have not responded to previous chemotherapy (Genentech Inc., 2011). A trial of trastuzumab in combination with other chemotherapies in 3351 patients with breast cancer demonstrated significant improvements in disease-free survival ($p<0.0001$) and overall survival ($p=0.015$) compared with patients receiving chemotherapeutic agents alone (Romond et al., 2005). Patients who received trastuzumab after chemotherapy also exhibited a significant improvement in disease-free survival compared with those who did not ($p<0.0001$) (Piccart-Gebhart et al., 2005). In a Phase III trial of 584 patients with gastric cancer, the addition of trastuzumab to other chemotherapeutic agents significantly improved survival versus chemotherapy alone ($p=0.0046$) (Bang et al., 2010).

Lapatinib (Tyverb/Tykerb) is a small molecule inhibitor that targets the tyrosine kinase domain of HER2 and EGFR, thereby inhibiting downstream signaling from both receptors. In a Phase III trial, lapatinib increased the time to disease progression from 4.4 months in patients on capecitabine monotherapy ($n=161$) to 8.4 months in patients on a combination of the two drugs ($n=163$; $p<0.001$) (Geyer et al., 2006). The addition of lapatinib to letrozole also significantly reduced the risk of disease progression versus letrozole monotherapy ($p=0.019$) in 219 patients with HER2-positive breast tumors (Johnston et al., 2009). Following these trials, lapatinib was licensed for use in combination with letrozole as a first-line treatment for HER2-positive breast cancer, and in combination with capecitabine as a second-line treatment for breast cancer in the USA and Europe (GlaxoSmithKline, 2011).

A third agent targeting the HER2 signaling pathway, pertuzumab, is another monoclonal antibody that binds to the extracellular domain of HER2 and inhibits HER2 dimerization. The clinical development of pertuzumab is most advanced in breast cancer. In a Phase II trial of 66 patients with HER2-positive advanced breast cancer whose disease had progressed while on trastuzumab monotherapy, pertuzumab in combination with trastuzumab resulted in a complete response for 6% of patients. An additional 18% of patients had a partial response to therapy and 26% achieved stable disease for ≥6 months. Overall, 50% of patients benefited from the pertuzumab–trastuzumab combination (Baselga et al., 2010). Pertuzumab is currently undergoing several clinical trials for the treatment of HER2-positive breast cancer in combination with various other agents including trastuzumab (clinicaltrials.gov; Baselga & Swain, 2010).

Other HER2-targeted therapies in development for cancer are shown in Table 3.

HER2-targeting agent	Mechanism of action	Clinical stage	Cancer type	Clinicaltrials.gov identifier
Neratinib	TKI Dual HER2/EGFR inhibitor	Phase III	Breast	NCT00878709 NCT00915018
Afatinib	TKI Dual HER2/EGFR inhibitor	Phase III	Breast NSCLC	NCT01125566 NCT01121393
		Phase II	CRC Prostate Glioma Head and neck	NCT01152437 NCT01320280 NCT00727506 NCT00514943
		Phase I	Advanced solid tumors	NCT01206816
Varlitinib	TKI Triple HER2/EGFR/ HER4 inhibitor	Phase I/II	Advanced solid tumors	NCT00862524
MGAH22	HER2 mAb	Phase I	NSCLC Prostate Bladder Ovarian Breast	NCT01195935 NCT01148849

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2/4, human epidermal growth factor receptor 2/4; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Table 3. HER2-targeted therapies in clinical testing for the treatment of cancer (data from clinicaltrials.gov).

3.2 Preclinical evidence for HER2 as a target in ovarian cancer

Trastuzumab, pertuzumab, and lapatinib have all been studied in cell and animal models of ovarian cancer, demonstrating the potential use of these therapies to treat patients.

For example, in SKOV3 cells, a cell line derived from the ascites of an ovarian adenocarcinoma, trastuzumab has been shown to reduce pHER2 and pAkt levels, indicating that trastuzumab reduced the activation of HER2 signaling pathways (Larbouret et al., 2007). Moreover, both trastuzumab and lapatinib have been shown to reduce the ability of SKOV3 cells to form spheres in a dose-dependent manner, suggesting that both agents have an effect on the growth or viability of ovarian cancer cells (Magnifico et al., 2009). Pertuzumab and trastuzumab have been shown to reduce HER2–EGFR dimerization in SKOV3 cells by 24% and 44%, respectively, while lapatinib had little effect on dimerization (Gaborit et al., 2011). Finally, trastuzumab was shown to reduce tumor progression of SKOV3 xenografts in mice (Larbouret et al., 2007; Magnifico et al., 2009).

A number of studies have also investigated the effect of HER2 inhibitors on ligand-dependent signaling. Pertuzumab has been shown to reverse ligand-stimulated growth by inhibiting the phosphorylation of HER2 and subsequent activation of downstream signaling pathways (Mullen et al., 2007). Makhija et al. showed that HER3 mRNA expression was reduced by ligand stimulation in six of the eight ovarian cell lines tested. This effect was reversed by the

addition of pertuzumab, small interfering RNAs (siRNAs) targeting the HER2 transcript, or inhibition of PI3K activity using a small molecule inhibitor. In contrast, siRNAs targeting the EGFR transcript, or a MEK inhibitor were not able to suppress ligand stimulation, indicating that pertuzumab inhibits HER2–HER3 signaling (Makhija et al., 2010). In a separate study, down-regulation of HER3 mRNA by heregulin-dependent activation of HER3 was reversed by pertuzumab. These authors also demonstrated that a change in HER3 mRNA levels was accompanied by changes in Akt and ERK signaling (Nagumo et al., 2009).
Other preclinical studies have suggested that levels of the HER2 extracellular domain may be a biomarker of response or resistance to some therapies used to treat ovarian cancer (Vazquez-Martin et al., 2011).

3.3 Clinical evidence for HER2 as a target in ovarian cancer

Trastuzumab, pertuzumab and lapatinib have also been studied in a number of clinical trials of ovarian cancer (Table 4).

Drug	Combination	No. pts	Clinical stage	Reference
Trastuzumab	Monotherapy	41	Phase II	Bookman et al., 2003
Lapatinib	Carboplatin	11	Phase I	Kimball et al., 2008
	Carboplatin and paclitaxel	21	Phase I/II	Rivkin et al., 2008
	Topotecan	18	Phase II	Weroha et al., 2011
Pertuzumab	Monotherapy	117	Phase II	Gordon et al., 2006
	Carboplatin with gemcitabine or paclitaxel	84		Kaye et al., 2008
	Gemcitabine	130		Makhija et al., 2010

Table 4. A summary of completed clinical trials of trastuzumab, lapatinib, and pertuzumab in HER2-positive ovarian cancer.

3.3.1 Trastuzumab

In HER2-positive ovarian cancer (2+/3+ staining by IHC), a Phase II trial of trastuzumab in 41 patients demonstrated an overall response rate of 7% (3 patients). One patient had a complete response to trastuzumab, and two patients had partial responses to treatment, while a further 16 patients (39%) achieved stable disease (Bookman et al., 2003). There are no reports of further development of trastuzumab for the treatment of ovarian cancer.

3.3.2 Lapatinib

Although studies of lapatinib for the treatment of ovarian cancer are at a relatively early stage, available evidence suggests that lapatinib may be effective in some patients with ovarian cancer. Of 11 patients with platinum-sensitive ovarian cancer receiving lapatinib

plus carboplatin in a Phase Ib trial, three (27%) had a partial response to treatment and a further three patients achieved stable disease (Kimball et al., 2008). Rivkin et al. reported preliminary results from a Phase I/II study of lapatinib in combination with carboplatin and paclitaxel in 21 patients with ovarian cancer. Complete responses were observed in 21% of patients, with a further 29% of patients experiencing a partial response and 29% achieving stable disease (Rivkin et al., 2008). Lapatinib has also been studied in ovarian cancer in combination with topotecan. Results from this Phase II trial with 18 patients showed that four patients (22%) experienced clinical benefit from the combination (one partial response and three patients who achieved stable disease) (Weroha et al., 2011). In terms of further development, a Phase I trial is underway of lapatinib in combination with paclitaxel in patients with advanced solid tumors including ovarian tumors (clinicaltrials.gov identifier NCT00313599).

3.3.3 Pertuzumab

Pertuzumab has been more extensively studied in patients with ovarian cancer than other HER2-targeted agents. Studies have included trials of pertuzumab monotherapy as well as trials of pertuzumab in combination with other agents (Langdon et al., 2010). In a Phase II trial of pertuzumab alone, a partial response was observed in 4% of patients with a further 7% achieving stable disease for ≥6 months. Interestingly, patients with tumors that had a detectable level of HER2 phosphorylation (eight out of 28 tumors tested), had longer progression-free survival following pertuzumab treatment than those who did not express pHER2 (20.9 vs 5.8 weeks), although this difference was not statistically significant (p=0.14) (Gordon et al., 2006). These results, while very preliminary, suggest that pHER2 may indicate active HER2 signaling in these tumors and thus benefit from HER2 targeted therapy.

In trials of pertuzumab in combination with carboplatin, gemcitabine, or paclitaxel, patients with platinum-sensitive ovarian cancer achieved a 64% response rate compared with 52% for patients receiving chemotherapy alone (Kaye et al., 2008; Langdon et al., 2010). Pertuzumab has also been tested in combination with gemcitabine versus gemcitabine alone in 130 patients with ovarian cancer. A partial response was observed in 14% of patients receiving the combination therapy versus 5% receiving gemcitabine alone (Makhija et al., 2010).

Exploratory biomarker analyses in the Makhija and Kaye studies demonstrated that patients with ovarian tumors that express a low level of HER3 mRNA have a better response to pertuzumab than those with higher HER3 mRNA levels. Makhija et al. observed that patients with low (< median) HER3 mRNA levels receiving pertuzumab and gemcitabine demonstrated better response rates than those receiving gemcitabine alone (p=0.0002) (Makhija et al., 2010). Kaye et al. reported that in patients with tumors expressing a low level of HER3 mRNA who had a treatment-free interval of 6–12 months, those receiving pertuzumab had a longer progression-free survival time compared with those who received chemotherapy alone; however, this difference was not statistically significant (hazard ratio 0.55; p=0.16) (Amler, 2010; Kaye et al., 2008).

3.4 Summary

Preclinical data demonstrate that HER2 inhibitors reduce tumor cell signaling via HER2 in ovarian cancer cells and tumor models. In the clinic, a subset of patients with HER2-positive

ovarian tumors responds to HER2-targeted treatment. Studies by Makhija et al. and Kaye et al. suggest that measuring the HER3 mRNA level may help to identify a subset of patients with ligand-dependent activation of HER2 signaling pathways who may benefit from treatment with a combination of pertuzumab and chemotherapy.

4. The future of the HER family as targets in oncology

Clinical validation of HER2 as a relevant target in ovarian cancer opens up several possibilities for therapeutic development in this area. These include the use of HER family antibody conjugates, bispecific antibodies, and novel targeted combinations, all of which are likely to require advanced and clinically integrated biomarker strategies to identify appropriate patient subsets for treatment.

HER2 antibodies can be conjugated with other anticancer drugs or radioactive entities to target chemotherapy and radiotherapy to cancerous cells that express HER2. Radiolabeled trastuzumab and pertuzumab have both been shown to delay tumor progression in mice with SKOV3 xenografts (Palm et al., 2007; Persson et al., 2007) and reduce the growth of SKOV3 cells in vitro (Heyerdahl et al., 2011), while trastuzumab–platinum (II) conjugates have been shown to increase SKOV3 cell death in vitro (Gao et al., 2008). Trastuzumab–DM1 (T-DM1) conjugates enable the targeted delivery of the antimicrotubule agent DM1 to cancer cells overexpressing HER2. In a single-arm Phase II study of T-DM1 therapy, a response rate of 26% was observed in 112 patients with HER2-positive metastatic breast cancer (Burris et al., 2011).

The bispecific, trifunctional antibody ertumaxomab, targets HER2 expressed on cancer cells and CD3 on T cells, and binds to Fcγ type I/III receptors via its Fc portion. In this way, ertumaxomab brings HER2-expressing cells into close contact with T cells and macrophages, facilitating antibody-dependent cellular cytotoxicity (ADCC) (Kiewe et al., 2006). In vitro studies have also demonstrated that ertumaxomab is able to kill cell lines with low HER2 expression derived from breast, lung, and colorectal cancers, whereas trastuzumab had no cytotoxic effect in these cells (Jager et al., 2009). In a Phase I trial of ertumaxomab in patients with HER2-positive metastatic breast cancer, five of 15 patients experienced an antitumor response (Kiewe et al., 2006).

Tumor cells commonly develop resistance to single-agent targeted therapies, thus combinations of agents that target different mechanisms of cell proliferation and survival often improve response compared with monotherapy alone. For example, the combination of trastuzumab with chA21 significantly reduced tumor size in mice with SKOV3 xenografts compared with antibody monotherapy ($p<0.05$) (A. Zhang et al., 2010). Similar results were observed with pertuzumab–trastuzumab combinations (Faratian et al., 2011) that have shown promise in the clinic (see Section 3.1) (Baselga et al., 2010). However, early clinical results for lapatinib and trastuzumab are not as promising. In a clinical trial of 282 patients with breast cancer, the combination of 1000 mg lapatinib with trastuzumab did not improve progression-free survival compared with 1500 mg lapatinib alone (16.3 versus 12.3 weeks; $p=0.18$) (Wu et al., 2011). Clinical trials of trastuzumab combined with pertuzumab (Baselga & Swain, 2010) and T-DM1 combined with pertuzumab (clinicaltrials.gov identifier NCT01120184) are ongoing in breast cancer.

Therapies targeting HER2 can also be combined with EGFR inhibitors in order to block multiple signaling pathways. Addition of matuzumab, an EGFR inhibitor, to trastuzumab

was shown to reduce tumor progression in mice with SKOV3 xenografts to a greater extent than either antibody alone (Larbouret et al., 2007). The combination of trastuzumab or pertuzumab with another EGFR inhibitor, cetuximab, significantly inhibited cell growth in OVCAR-3 and IGROV-1 cells, although this effect was not observed in SKOV3 cells, possibly because of high basal levels of pERK and pAkt (Bijman et al., 2009). A combination of cetuximab and trastuzumab has also been shown to inhibit HER2–EGFR dimerization in SKOV3 cells, and this effect was shown to improve median survival and the percentage of tumor-free animals in a mouse model of ovarian cancer (Gaborit et al., 2011).

To date, clinical trials of anti-HER2/EGFR combinations have only been performed in non-ovarian cancer. Trastuzumab has been studies in breast cancer in combination with the EGFR inhibitors, gefitinib (Arteaga et al., 2008) and erlotinib (Britten et al., 2009). However, the trial of trastuzumab with erlotinib was terminated early, and the study with gefitinib showed increased toxicity with no apparent increase in the expected clinical benefit with trastuzumab monotherapy. Currently, there is one ongoing Phase I trial of trastuzumab with cetuximab in breast cancer (clinicaltrials.gov identifier NCT00367250). Trials are also underway to evaluate pertuzumab in combination with erlotinib or cetuximab in several types of cancer (clinicaltrials.gov identifiers NCT00947167, NCT01108458, NCT00855894, NCT00551421) and patients with CRC are being recruited for a trial of lapatinib in combination with cetuximab (clinicaltrials.gov identifier NCT01184482).

Combining agents that target HER2 with inhibitors of downstream signaling pathway components, such as PI3K, mTOR, or MEK, may also lead to increased clinical activity. A preclinical study investigating the PI3K inhibitor PKI-587 demonstrated tumor regression in xenograft models of breast cancer, which was enhanced when PKI-587 was combined with the dual HER2/EGFR tyrosine kinase inhibitor neratinib or a MEK inhibitor, PD0325901 (Mallon et al., 2011). A number of clinical trials are underway in breast cancer to investigate the efficacy of combining trastuzumab with PI3K inhibitors, including BKM120 (clinicaltrials.gov identifier NCT01132664) and XL-147 (clinicaltrials.gov identifier NCT01042925), as well as the combination of neratinib and temsirolimus, an allosteric mTOR inhibitor (clinicaltrials.gov identifier NCT01111825).

Preclinical and early clinical data suggest that targeting HER3 directly may also be therapeutically relevant in several types of cancer, including ovarian. The HER3 monoclonal antibody MM-121 has been shown to inhibit ovarian tumor growth in vivo (Sheng et al., 2010) and in vitro studies of another antibody, MM-111, have demonstrated that it inhibits cell growth alone and in combination with lapatinib (Oyama et al., 2010) and trastuzumab (Huhalov et al., 2010). A Phase I trial of U3-1287 in 31 patients with solid tumors, including one patient with ovarian cancer, showed that 26% of patients achieved stable disease for ≥70 days (Berlin et al., 2011). These antibodies are undergoing early-stage clinical testing in combination with other agents including HER2 and EGFR inhibitors (clinicaltrials.gov). MEHD7945A a dual-specific antibody targeting HER3 and EGFR has also shown in vivo activity in an ovarian xenograft model suggesting a potential benefit of combined inhibition of ErbB members (Schaefer et al., 2011).

4.1 The future use of biomarkers in ovarian cancer

Preclinical and clinical data suggest that amplification and overexpression of HER2 protein or mRNA, while infrequent, clearly exists in some ovarian tumors. Treatment with trastuzumab or a HER2 antibody–drug conjugate could be a potential option for these

patients. Rare mutations in the *HER2* gene may be of particular relevance in ovarian LMP tumors where mutations in the *BRAF* and *KRAS* oncogenes are also common (see Section 2.2) (Anglesio et al., 2008). LMP tumors are usually treated successfully with surgery; however treatment options are limited in patients who relapse following surgery as this tumor type does not respond well to currently available chemotherapy. Further clinical evaluation with agents that inhibit HER2 signaling, such as lapatinib or trastuzumab, are warranted to determine the benefit of these agents to patients with progressed LMP lesions.
Based on the available data, it appears that ligand-dependent activation of HER2 signaling could be a more important mechanism for HER2 oncogenesis in ovarian cancer. Expression of pHER2 or HER3 may also be biomarkers that could identify tumors with oncogenic ligand-dependent HER2-activation. Further studies with inhibitors of HER2 dimerization, such as pertuzumab, will be useful in assessing their clinical potential in patients with ligand-dependent activation of the pathway.

5. Conclusion

Targeting HER2 with trastuzumab and lapatinib has proven successful in treating HER2-positive breast cancer. Other molecules, such as pertuzumab, are in advanced clinical development for the treatment of this indication, further validating the clinical relevance and importance of this target. In contrast to breast cancer, in which HER2 is overexpressed in up to 30% of cases, a much lower proportion of ovarian tumors show activation of HER2 by this mechanism. Nonetheless, trials of HER2-targeted agents in patients identified with HER2-positive ovarian tumors have shown improved progression-free survival and overall survival in a small proportion of patients.
Importantly, there are patients with ovarian tumors with no evidence of HER2 amplification or overexpression, but in whom HER2-targted therapeutics appear to be beneficial. In these patients, activating mutations in *HER2* or high levels of ligand-dependent activation of HER2/HER3 signaling may play a more important role in mediating HER2 oncogenesis. Identifying these patients through the use of novel biomarkers, such as assessment of HER3 mRNA levels, could significantly improve the clinical benefit of HER2-targeted therapies in this setting.
In conclusion, the use of targeted HER2 therapies in ovarian cancer warrants further investigation, particularly with regard to the development and validation of appropriate diagnostic tests.

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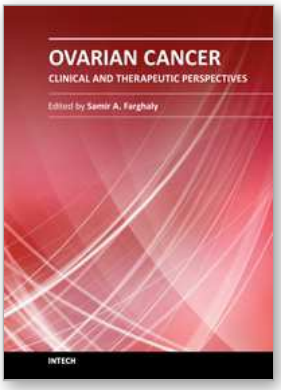

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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