Lapatinib

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Contents

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Abstract

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases plays an important role in the biology of many cancers. In breast and gastrointestinal cancer, and at lower rates also in additional tumor types, HER2 and its homo- or heterodimerization with HER1 or HER3 are essential for cancer cell growth and survival. Breast cancer patients overexpressing HER2 have a more aggressive course of their disease. The poor prognosis associated with HER2 overexpression can be substantially improved by adding HER2-targeted therapy to standard of care using the monoclonal antibody trastuzumab. Lapatinib, an oral dual tyrosine kinase inhibitor, blocks HER1 and HER2 tyrosine kinase activity by binding to the ATP-binding site of the receptor's intracellular domain, resulting in inhibition of tumor cell growth. Lapatinib is generally well tolerated with diarrhea being the most common adverse effect. However, although being mainly of mild to moderate severity, interruption or discontinuation of treatment has been reported in a substantial proportion of patients in clinical trials. In 2007, lapatinib has been approved in combination with capecitabine in patients with advanced HER2-positive breast cancer upon progressive disease following standard therapy with anthracyclines, taxanes, and trastuzumab. In 2013, the approval was extended to a chemotherapy-free combination with trastuzumab for patients with metastatic HER2-positive, hormone receptor-negative breast cancer progressing on prior trastuzumab and chemotherapy. Since 2010, lapatinib is approved in combination with letrozole in the treatment of postmenopausal women with advanced HER2- and hormone receptor-positive breast cancer. In contrast, in first-line cytotoxic-based therapy of both early and advanced HER2-positive breast cancer, data from clinical trials did not provide evidence of additional benefit of lapatinib compared to trastuzumab. Moreover, over the past few years, novel HER2-targeted drugs, either alone or as a combined anti-HER2 approach, have been extensively evaluated, demonstrating a more favorable outcome. Also, neither in first- nor second-line treatment of advanced gastric cancer, lapatinib has been proven to be superior compared to trastuzumab as hitherto standard of care HER2 blockade. Therefore, lapatinib has become somewhat less important in patients with HER2-positive breast cancer during the past 10 years since its first introduction. Nevertheless, consideration of treatment with lapatinib appears to be reasonable in selected patients not only in the approved applications but also beyond, and further indications such as HER2-positive refractory metastatic colorectal cancer may arise in future. Also, lapatinib may have distinct advantages over antibodies in targeting truncated HER2 and crossing the blood–brain barrier. Finally, the favorable cardiac toxicity profile of lapatinib makes it an attractive alternative to trastuzumab-based regimens in patients at risk for cardiac events.

Keywords

Lapatinib · HER2 · Tyrosine kinase inhibitor · Breast cancer · Gastric cancer

1 Introduction

1.1 The Epidermal Growth Factor Receptor Family of Tyrosine Kinases

The human epidermal growth factor receptor family (HER, EGFR, ErbB) comprises four receptor tyrosine kinases (RTKs): HER1 (=EGFR1 or ErbB1), HER2 (=HER2/c-neu or ErbB2), HER3 (=ErbB3), and HER4 (=ErbB4) (Citri and Yarden 2006; Lemmon and Schlessinger 2010). RTKs consist of an extracellular ligand-binding domain with specific docking sites for various adapter proteins and ligands, a transmembrane domain and an intracellular cytoplasmic domain containing the tyrosine kinase catalytic site. Upon ligand binding, various downstream signaling pathways which are linked to cell proliferation, survival, and apoptosis are activated (Wee and Wang 2017). The receptors are not fixed in the lipid bilayer of the plasma membrane. Therefore, dimerization can and does occur upon ligand binding to the extracellular domain. Such dimers can be homodimers or heterodimers comprised of two different members of the same RTK family (Fig. 1) (Mendelsohn and Baselga 2003). While a large number of ligands for HER1, 3, and 4 have been discovered in the past, no direct ligand for HER2 has been identified so

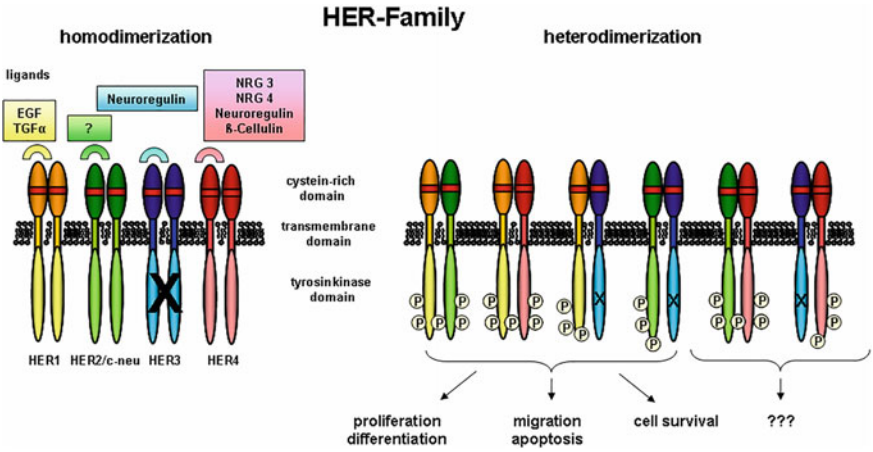

Fig. 1 Organizational principle of the epidermal growth factor receptor family and some dimerization possibilities with corresponding downstream biological events. The left half panel shows the names of the HER family members, depicted as homodimers. The right panel shows heterodimers and downstream effects upon dimerization. P symbolizes phosphorylation. Ligands are shown as semicircles (names in rectangles) and in the color corresponding to the suitable receptor. Note that HER2 does not have a known ligand, it presumably acts mostly as a combination partner for heterodimers. Also, note that HER3 homodimers lack tyrosine kinase activity (indicated by X), but upon ligand binding, the receptor can initiate signal transduction as heterodimer (mainly with the preferred dimerization partner HER2) through the other HER family member's intracellular domain, resulting in multiple downstream effects influencing cell growth and survival

far. However, with its dimerization arm constitutively exposed, HER2 primarily functions as a co-receptor for each of the other ligand-activated EGF receptors (Maruyama 2014). In fact, HER2 is the preferred dimerization partner for all members of the HER family (Graus-Porta et al. 1997), and in contrast to homodimers which are either inactive (like HER3 homodimers) or provide only weak signaling, HER2-containing heterodimers have attributes that prolong and enhance downstream signaling (Tomas et al. 2014).

1.2 Human Epidermal Growth Factor Receptors and Their Inhibition in Cancer

Numerous in vitro and in vivo studies have indicated the functional importance of the HER family in a wide range of cancers as they are often overexpressed and constitutively activated in tumor cells resulting in promotion of their cell proliferation (Hynes and Lane 2005). Hence, development of agents that target these receptors, including monoclonal antibodies like cetuximab, or small molecule inhibitors of the receptor tyrosine kinase (TKIs) such as erlotinib and gefitinib was prompted (Rivera et al. 2008; Kohler and Schuler 2013).

In breast cancer, overexpression of HER1 and HER2, each present in up to 30% of patients is clearly associated with poor prognosis (Ross and Fletcher 1998; Witton et al. 2003, Ansquer et al. 2005). However, the outcome of early and advanced HER2-positive breast cancer patients has been substantially improved upon the addition of trastuzumab, a monoclonal antibody binding to the extracellular domain of HER2, thus inhibiting heterodimerization of HER2 with subsequent activation signals in cancer cells (Slamon et al. 2001; Piccart-Gebhart et al. 2005).

HER2-overexpression also plays a substantial role in gastroesophageal cancer in which about 20% of patients can be identified as HER2-positive (Abrahao-Machado and Scapulatempo-Neto 2016). While previous studies yielded inconsistent findings regarding its prognostic relevance in this entity, a recent meta-analysis demonstrated a significant relation between high HER2 expression and poor prognosis (Zhang et al. 2017). Like in breast cancer, a survival benefit has been achieved by adding trastuzumab to standard first-line chemotherapy in HER2-positive advanced gastroesophageal cancer (Bang et al. 2010).

2 Structure and Mechanism of Action

Lapatinib ditosylate (Fig. 2) is an orally applicable, dual receptor TKI targeting two members of the HER family receptors: HER1 (EGFR1/ErbB1) and HER2/c-neu (ErbB2) (Nelson and Dolder 2006; Medina and Goodin 2008).

Lapatinib interacts intracellularly by reversibly binding to the cytoplasmic ATP-binding site of the tyrosine kinase domain (Fig. 3). Subsequently, phosphorylation and, therefore, activation of the receptor is blocked, resulting in the

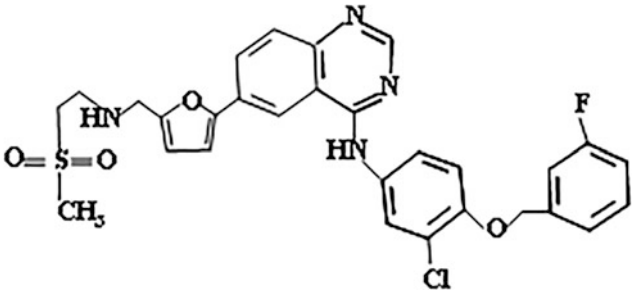

Fig. 2 Chemical structure of lapatinib. Lapatinib is a 4-anilinoquinazoline derivative, distinguishing it from the small head group quinazolines tyrosine kinase inhibitors such as erlotinib and gefitinib

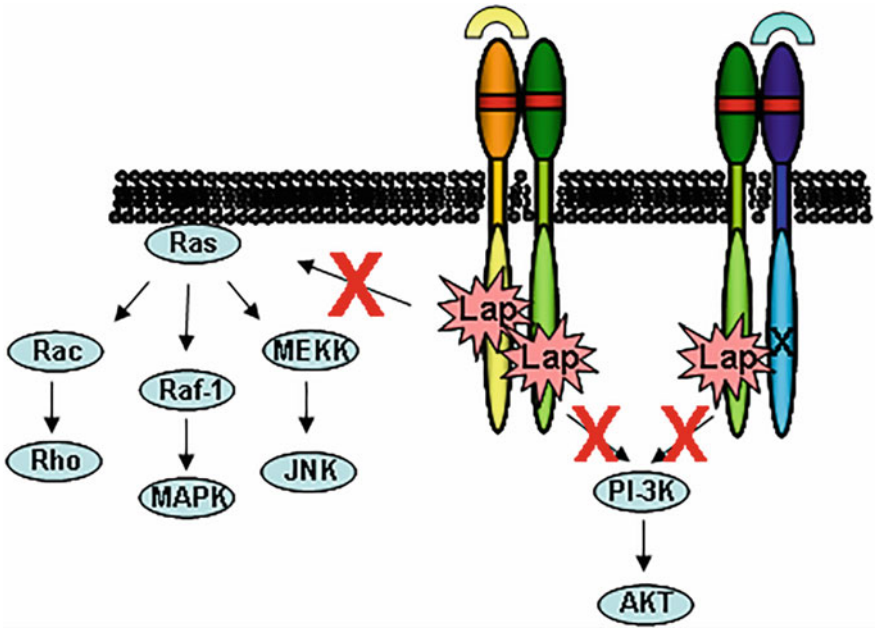

Fig. 3 Intracellular action of lapatinib. Lapatinib binds to the tyrosine kinase domain of HER1 and HER2, blocking the ATP-binding site, and thus preventing (symbolized by "X") the activation of downstream cascades. HER1 is depicted in yellow, HER2 in green, HER3 in blue. Ligands are shown as semicircles in corresponding color. Abbreviations: *Lap* lapatinib; *JNK* Jun-N-terminal kinase; *MAPK* mitogen-activated protein kinase; *MEKK* MAPK/extracellular signal-related kinase (ERK) kinase; *PI3K* phosphatidyl-inositol-3-kinase

inhibition of various downstream signaling cascades such as the extracellular signal-related kinase1/2 (ERK1/2) and the phosphatidylinositol 3′-kinase (PI3K)/AKT pathway, both involved in cell proliferation and apoptosis (Lackey 2006).

By binding the inactive conformation of EGFR, lapatinib differs from other EGFR TKIs such as erlotinib or gefitinib. Furthermore, lapatinib has a slower dissociation rate from HER1 and HER2 than other TKIs. Both could contribute to a greater duration of effect at the target site (Wood et al. 2004).

There are several theoretical advantages of small molecules, inhibiting the tyrosine kinase activity of HER1 and HER2 over monoclonal antibodies such as cetuximab and trastuzumab, targeting the extracellular domain of HER1 or HER2, respectively. In cancer, HER1 and HER2 receptors can be truncated. While still exhibiting tyrosine kinase activity, these truncated forms lack the extracellular domain of the receptors. They are necessarily resistant to the treatment with antibodies binding the extracellular HER domain. Yet, truncated HER2 is still sensitive to the TKI lapatinib (Xia et al. 2004). Another distinctive feature of lapatinib compared to antibody-based anti-HER strategies is its biodistribution. Lapatinib is the first approved small molecule inhibitor with the ability to cross the blood–brain barrier making it suitable for targeting brain metastases (Gril et al. 2008).

In view of the downstream signaling characteristics within the HER family, it is reasonable to assume that agents affecting more than one member of the HER family may suppress cancer cell growth and survival more effectively. First, simultaneous inhibition of HER1 and HER2 may overcome escape mechanisms mediated by redundancy in cell signaling pathways, a form of resistance observed in single tyrosine kinase inhibition, in which upregulation of other members of the HER family occurs (Lin and Winer 2004; Stern 2012). Second, synergistic inhibition of cancer cell growth has been demonstrated upon simultaneous targeting of HER1 and HER2, resulting in a more potent repression of cell growth or greater apoptotic effect compared with inhibiting either HER1 or HER2 alone (Burris 2004). Third, a dual HER1/HER2 TKI may be a useful substrate in a wider range of patients, with regard to the impact of heterodimerization in the progression of a variety of cancer types (Olayioye et al. 2000).

Therefore, the dual HER TKI lapatinib was expected to overcome resistance to monoclonal anti-HER2 antibodies and have superior activity compared to mono-target TKIs. Furthermore, albeit primarily developed for and evaluated in breast cancer, the potential of lapatinib was assumed to reach beyond this disease.

3 Clinical Application

3.1 Pharmacology

Since lapatinib is administered orally, intestinal resorption rates may vary. Intake together with food, particularly high-fat meals, greatly increases its bioavailability (Ratain and Cohen 2007; Devriese et al. 2014). To minimize variability in plasma concentrations, lapatinib intake is recommended under fasting conditions, i.e., no less than 1 h before or at least 1 h after a meal. Following resorption, lapatinib is largely bound to proteins, mainly albumin and acidic alpha1 glycoprotein with peak

plasma levels achieved 3–6 h after administration (Medina and Goodin 2008). With a half-life of approximately 17–24 h when given repeatedly, the drug is administered at a once-daily schedule. Lapatinib is eliminated by hepatic metabolism, primarily through cytochrome P450 isoenzyme, CYP3A4, and biliary excretion. Therefore, inducers or inhibitors of CYP3A4 may alter the metabolism of lapatinib and, vice versa, lapatinib may increase the level of other CYP3A4 substrates (e.g., benzodiazepines and calcium channel blockers) as well as CYP2C8 substrates (e.g., amiodarone and pioglitazone) (GlaxoSmithKline 2007; Medina and Goodin 2008). Furthermore, administration of the drug in patients with impaired liver function, e.g., due to diffuse hepatic metastases, has to be done—if at all—with particular care in a dose-reduced schedule, even though it has not been systemically investigated in this setting so far. The recommended single daily dose of lapatinib is 1250 mg in combination with capecitabine in patients with advanced HER2-positive breast cancer progressing upon therapy with anthracyclines, taxanes, and trastuzumab, 1000 mg in combination with trastuzumab in patients with metastatic HER2-positive, hormone receptor-negative breast cancer upon progression on trastuzumab- and chemotherapy-containing regimens and 1500 mg in combination with hormone therapy for postmenopausal patients with advanced hormone receptor- and HER2-positive breast cancer, respectively (Geyer et al. 2006; Johnston et al. 2009; Blackwell et al. 2010).

4 Results from Clinical Trials

4.1 Efficacy in Breast Cancer

Several preclinical data provided the biological rationale to evaluate lapatinib in patients with HER2-positive breast cancer (Konecny et al. 2006; Nelson and Dolder 2006). A number of phase I–III clinical trials have been conducted in breast cancer at different stages, evaluating lapatinib as a single agent or in combination with other therapeutics including chemotherapy, hormone therapy, or monoclonal anti-HER2 antibodies (Table 1). Phase I clinical trials suggested a favorable side effect profile of lapatinib, revealing good tolerability for the majority of trial participants (Bence et al. 2005; Burris et al. 2005; Chu et al. 2007, 2008). Phase II and III studies demonstrated substantial clinical activity of lapatinib in HER2-positive breast cancer patients, as discussed below.

4.1.1 Second-Line Treatment and Beyond in Advanced Breast Cancer

Based on the results of the pivotal EGF100151 trial, lapatinib was first approved in 2007 by the FDA and in 2008 by the EMA for its combined use with capecitabine in patients with advanced HER2-positive breast cancer after progression upon therapy with anthracyclines, taxanes, and trastuzumab (Geyer et al. 2006). In this open-label phase III trial, patients were randomized to either receive capecitabine

Table 1 Lapatinib in phase I–III clinical trials

Indication	Treatment	Patients (*n*)	Phase	Response (%)			Reference
				CR	PR	SD	
Healthy volunteers	L[1a]	47	I	NA	NA	NA	Bence et al. (2005)
Various solid tumors	L[2b]	59	I	0	7	41◇	Burris et al. (2005)
	X + L[3b]	45	I	2	7	49	Chu et al. (2007)
Breast, ovarian, endometrial cancer	Let + L[3b]	39	I	0	6	59	Chu et al. (2008)
Metastatic breast cancer (second line)	L[4b]	36	II	0	8	14	Blackwell et al. (2004)
	a: X + L[5b]	163	III	<1	21	5◇	Geyer et al. (2006)
	b: X	161		0	14	4◇	
	L[6c]	237	II	0*	6*	37*	Lin et al. (2009)
	a: X + L[5b]	13	II	0*	38*	46*	Lin et al. (2011)
	b: Top + L[5b]	9		0*	0*	33*	
	a: L[4b]	145	III	2	5	28◇	Blackwell et al. (2010)
	b: T + L[7b]	146		1	9	39◇	
	a: X + L[5b]	389	III	0.5	30	d.n.a.	Verma et al. (2012)
	b: T-DM1	397		1	43	d.n.a.	
	a: X + L[5b]	116	II	4	36	23◇	Martin et al. (2013)
	b: N	117		2	27	15◇	
	X + L[5b]	44	II	0*	66*	18*	Bachelot et al. (2013)
	a: X + L[5b]	271	III	3	24	14◇	Pivot et al. (2015)
	b: X + T	269		4	27	12◇	
Metastatic breast cancer (first-line)	*a*: L[4b]	69	II	0	22	58◇	Gomez et al. (2008)
	b: L[8c]	69		0	26	45◇	
	a: P + L[4b]	291	III	5	30	33◇	Di Leo et al. (2008)
	a: P + T + L[7b]	288		2	23	43◇	
	a: Let + Plac	642	III	4	27	25◇	Johnston et al. (2009)
	b: Let + L[4b]	644		5	28	26◇	

(continued)

Table 1 (continued)

Indication	Treatment	Patients (*n*)	Phase	Response (%)			Reference
				CR	PR	SD	
	a: P + T + L^{7b}	29	III	3	76	10◇	Esteva et al. (2013)
	b: P + T + L^{7b}	14		7	64	7◇	
	c: P + T + L^{6b}	20		5	65	10◇	
	a: P + L^{4b}	222	III	7	62	5◇	Guan et al. (2013)
	a: P + Plac	222		3	46	6◇	
	a: Tax + L^{5b}	312	III	54¥	54¥	22◇	Gelmon et al. (2015)
	b: Tax + T	317		55¥	55¥	21◇	
Breast cancer (adjuvant)	*a*: L^{4b}	1,571	III	NA	NA	NA	TEACH (Goss et al. 2012)
	b: Plac	1,576					
	a: T	2,097	III	NA	NA	NA	ALTTO (Piccart-Gebhart et al. 2016)
	b: $L^{4b‡}$	2,100		NA	NA	NA	
	c: T followed by L^{4b}	2,091		NA	NA	NA	
	d: T + $L^{7b‡}$	2,093		NA	NA	NA	
Breast cancer (neoadjuvant)	*a:* P + L^{4b}	154	III	25**	NA	NA	NeoALTTO (Baselga et al. 2012)
	b: P + T	149		30**	NA	NA	
	c: P + T + L^{7b}	152		51**	NA	NA	
	a: EC + D + T	307	III	30**	NA	NA	GeparQuinto (Untch et al. 2012)
	b: EC + D + L^{5b}	308		21**	NA	NA	
	a: P + FEC + T	36	IIb	25**	NA	NA	CHER-LOB (Guarneri et al. 2012)
	b: P + FEC + L^{4b}	38		26**	NA	NA	
	c: P + FEC + T + L^{7b}	45		47**	NA	NA	
	a: Let + L^{4b}	43	IIb	12***	58	23◇	LETLOB (Guarneri et al. 2014)
	b: Let + Plac	49		2***	61	29◇	
	a: P + T	177	III	53**	NA	NA	NSABP (B-41) (Robidoux et al. 2013)
	b: P + L^{5b}	171		53**	NA	NA	

(continued)

Table 1 (continued)

Indication	Treatment	Patients (*n*)	Phase	Response (%)			Reference
				CR	PR	SD	
	c: P + T + L[6b]	171		62**	NA	NA	
	a: P + T	118	III	46**	NA	NA	CALGB 40601 (Carey et al. 2016)
	b: P + L[4b]	64		32**	NA	NA	
	c: P + T + L[7b†]	117		56**	NA	NA	
Advanced gastroesophageal cancer	*a:* P + L[4b]	132	III	27[¥]	27[¥]	d.n.a.	TyTAN (Satoh et al. 2014)
(second-line)	*b:* P	129		9[¥]	9[¥]	d.n.a.	
Advanced gastroesophageal cancer	*a:* XelOX + L[5b]	249	III	2	50	27	LOGiC (Hecht et al. 2016)
(first-line)	*b:* XelOX + Plac	238		2	37	40	
Advanced colorectal cancer	T + L[7b]	27	II	4	26	30	HERACLES (Sartore-Bianchi et al. 2016)
Advanced pancreatic cancer	Gem + L[4b]	29	II	0	10	NA	Safran et al. (2011)
	X + L[5b]	17	II	0	0	35	Wu et al. (2015)

CR complete response; *PR* partial response; *SD* stable disease; *NA* not applicable; *d.n.a* data not available; *a* cohort A; *b* cohort B; *c* cohort C; *d* cohort D
A Doxorubicin; *C* Cyclophosphamide; *D* Docetaxel; *E* Epirubicin; *F* Fluoruracil; *FOLFOX* Oxaliplatin, Folinic acid, Fluoruracil; Gem Gemcitabine; *L* Lapatinib; *Let* Letrozole; *N* Neratinib; *P* Paclitaxel; *Plac* Placebo; *T* Trastuzumab; *Tax* Taxane; *Top* Topotecan; *X* Capecitabine; *XelOX* Capecitabine and oxaliplatin
[a]single and multiple doses, [b]once daily, [c]twice a day
[1]10–175 mg; [2]500–600 mg; [3]1250–1500 mg; [4]1500 mg; [5]1250 mg; [6]750 mg; [7]1000 mg; [8]500 mg
*Data refer to the CNS objective response rate
**Data refer to pathological complete response
***No patient achieved pathological complete response. Data refer to clinical response assessed by ultrasonography, mammography and/or palpation
◇Stable disease for at least 6 months
¥Data refer to overall response rate including patients with complete and partial response
‡During concomitant chemotherapy, lapatinib dosage was reduced to 750 mg once daily
†Due to emerging data regarding exceeding diarrhea, lapatinib was reduced to 750 mg once daily after accrual of 34 patients

alone (201 patients) or a reduced dose of capecitabine and lapatinib (198 patients). Time to disease progression (TTP) was the primary endpoint of this study. A planned interims analysis (Geyer et al. 2006a) revealed 49 disease-progression events in the lapatinib group versus 72 events in the control group, resulting in a 51% risk reduction in time to progression. Based on these data, randomization within this trial was stopped and patients in the control arm could also receive lapatinib in addition to capecitabine. An updated analysis of the trial confirmed the positive results of the interims analysis with TTP improvement from 4.3 to 6.2 months upon addition of lapatinib (hazard ratio (HR) = 0.57, 95% confidence interval (CI) 0.43–0.77, $P < 0.01$) (Cameron et al. 2008). Since premature enrollment termination with subsequent crossover resulted in an insufficient statistical power, exploratory analyses demonstrated only a trend toward a survival advantage with combination therapy (Cameron et al. 2010).

A few years later, the randomized phase III EMILIA trial compared the combination of lapatinib and capecitabine with the novel antibody-drug conjugate trastuzumab emtansine (T-DM1) in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane (Verma et al. 2012; Dieras et al. 2017). With a significantly prolonged progression-free survival (PFS) as well as overall survival (OS) and less toxicity in the experimental arm, T-DM1 was subsequently approved in 2013 for its use in HER2-positive advanced breast cancer, progressing following treatment with trastuzumab and a taxane. Therefore, in patients with uncontrolled HER2-positive advanced breast cancer upon therapy with trastuzumab regimens, current guidelines recommend lapatinib in combination with capecitabine as a therapeutic option in third- and further-line rather than second-line treatment in trastuzumab-resistant HER2-positive breast cancer (Giordano et al. 2014; Cardoso et al. 2017; Thill et al. 2017).

Combination therapy of lapatinib and capecitabine was also compared to neratinib, an irreversible pan-TKI of HER1, HER2, and HER4, in patients with HER2-positive advanced breast cancer following prior trastuzumab-containing regimens (Martin et al. 2013). In this randomized phase II trial, patients receiving lapatinib with capecitabine showed a nonsignificant prolongation of PFS (6.8 months) as well as OS (23.6 months) compared to patients treated with neratinib (4.5 months, HR 1.19, 95% CI 0.89–1.60 and 19.7 months, HR 1.25, 95% CI 0.83–1.86, respectively). Currently, the phase III NALA trial investigates the efficacy and safety of lapatinib and neratinib each in combination with capecitabine in the metastatic setting of HER2-positive breast cancer following at least two prior HER2-directed regimens (NCT01808573).

A pertinent question concerns the benefit of combining anti-HER2 targeted drugs, whether different monoclonal anti-HER2 antibodies with each other or in addition to a HER TKI. Based on preclinical models of dual anti-HER2 therapy with trastuzumab and lapatinib, an enhanced blockade of HER2 signaling by synergistic interaction and their partly nonoverlapping mechanisms of action was proposed (Konecny et al. 2006; Scaltriti et al. 2009). In the pivotal EGF104900 phase III trial, 291 patients with HER2-positive metastatic breast cancer progressing on a trastuzumab-containing regimen were randomly assigned to receive treatment

with either lapatinib alone or in combination with trastuzumab (Blackwell et al. 2010). With prior anthracycline- and taxane-based chemotherapy as further inclusion criteria and a median of three preceding trastuzumab-containing regimens, patients were heavily pretreated and the majority of patients (73%) had visceral disease. In the final analysis, PFS as the primary endpoint of this study was modestly, yet significantly longer in patients treated with the combination therapy (11.1 weeks) compared to those receiving single-agent lapatinib (8.1 weeks, HR 0.74, 95% CI 0.58—0.94, $P = 0.01$). Further, OS was significantly improved with 14 versus 9.5 months (HR 0.74, 95% CI 0.57–0.96, $P = 0.03$) (Blackwell et al. 2012). Patients with estrogen receptor-positive breast cancer did not have an OS benefit from the combination therapy. In contrast, within the cohort of 163 patients with HER2-positive and hormone receptor-negative breast cancer, an even increased magnitude of effect of the combination therapy was demonstrated compared with lapatinib alone (median OS 16.5 vs. 8.9 months, respectively, HR 0.68; 95% CI 0.47–0.98, $P = 0.12$). Based on these results, in 2013, the EMA extended the approved indication for lapatinib to include its use in the chemotherapy-free combination with trastuzumab in patients with HER2-positive metastatic breast cancer that has recently progressed on trastuzumab-containing regimens. However, due to the lack of comparative data with endocrine-based therapy, thus questioning the benefit in patients with hormone receptor-positive breast cancer, the indication is restricted to patients with hormone receptor-negative tumors.

HER2-overexpression itself is a predictive factor for the development of brain metastases in patients with breast cancer. Yet, trastuzumab does not cross the blood–brain barrier. Therefore, cerebral metastases represent a major problem among patients treated with trastuzumab for metastatic HER2-positive breast cancer, with incidence rates of up to 43% in this group (Clayton et al. 2004; Leyland-Jones 2009). The efficacy of lapatinib in combination with capecitabine in HER2-positive breast cancer patients with previously untreated brain metastases (i.e., not having received lapatinib, capecitabine or whole brain radiotherapy) was first demonstrated in the phase II LANDSCAPE study (Bachelot et al. 2013). Twenty-nine of 44 patients (65.9%) showed an objective CNS response and median overall survival was 17.0 months. In contrast, in patients with prior whole brain radiation therapy and trastuzumab, treatment with single-agent lapatinib resulted in an only moderate clinical benefit with 15 of 237 (6%) patients achieving an objective response and 88 patients (37%) showing stable disease (Lin et al. 2009). However, these results have to be seen in view of a group of patients with very little treatment options and an extremely high risk of disease progression. Moreover, in these extensively pretreated patients, lapatinib given in combination with capecitabine may further increase the objective response rate of brain metastases to about 30%, as shown in a recent meta-analysis (Petrelli et al. 2017). Therefore, lapatinib in combination with capecitabine is a reasonable approach in HER2-positive breast cancer patients with brain metastases not suitable for (re)irradiation therapy (Ramakrishna et al. 2014). In terms of prevention of brain metastases, the randomized phase III CEREBEL study was conducted, comparing the incidence of brain metastases as the first site of relapse in a total of 540 patients with

HER2-positive metastatic breast cancer receiving capecitabine in combination with either lapatinib or trastuzumab (Pivot et al. 2015). Albeit underpowered for its primary endpoint, incidence of new brain metastases did not differ between the lapatinib and trastuzumab arm (3 vs. 5%, $P = 0.36$). However, patients receiving the trastuzumab-regimen showed a significant prolongation of PFS (HR 1.30; 95% CI 1.04–1.64) and a trend toward longer OS time (HR 1.34, 95% CI 0.95–1.90).

4.1.2 First-Line Treatment in Advanced Breast Cancer

In 2010, Lapatinib was approved for first-line treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor and for whom hormonal therapy is indicated. This approval was based on the EGF30008 phase III trial, in which 1286 postmenopausal women with hormone receptor-positive metastatic breast cancer, irrespective of HER2 expression status, were randomized to receive either the aromatase inhibitor letrozole alone or in combination with lapatinib (Johnston et al. 2009). In HER2-positive patients ($n = 219$), the addition of lapatinib increased PFS from 3.0 to 8.2 months (HR 0.71, 95% CI 0.53–0.96, $P = 0.02$), while HER2-negative patients ($n = 952$) showed no improvement in PFS. Similar results, albeit slightly less improvement in PFS for HER2-/hormone receptor-copositive metastatic breast cancer patients, could be achieved with the combination of trastuzumab and the aromatase inhibitor anastrozole compared to endocrine therapy alone (Kaufman et al. 2009). Since, however, no direct comparison between the two anti-HER2 drugs in combination with hormone therapy has been performed, it remains unclear, which HER-inhibiting combination partner for endocrine therapy is better. Toward this end, it is also important to note the recently published results of the phase II PERTAIN trial, evaluating a dual anti-HER2 approach with trastuzumab and pertuzumab, a monoclonal antibody inhibiting the dimerization of HER2 with other HER receptors, in addition to hormone therapy (Arpino et al. 2016). Yet, results of an ongoing phase III trial (NCT02344472), further evaluating this therapeutic regimen have to be awaited.

In patients with HER2-positive advanced breast cancer for whom chemotherapy is indicated, lapatinib in combination with taxane-based treatment has been proven to be effective as first-line treatment in several placebo-controlled phase III studies (Di Leo et al. 2008, Guan et al. 2013). Subsequently, a direct comparison of lapatinib and trastuzumab as the hitherto standard combination partner for first-line chemotherapy has been performed in a phase III trial (Gelmon et al. 2015). Therapy-naïve patients ($n = 636$) with HER2-positive metastatic breast cancer were randomized to receive a taxane-based chemotherapy with either lapatinib or trastuzumab, each for 24 weeks, following anti-HER2 monotherapy for 4 years or until progressive disease. After a median follow-up of 21.5 months, patients receiving trastuzumab had a significantly longer PFS (11.3 months) than patients receiving lapatinib (9.0 months; HR 1.37, 95% CI 1.13–1.65, $P < 0.01$). Hence, in patients with HER2-positive metastatic breast cancer, priority as anti-HER2 combination partner to first-line chemotherapy is clearly given to trastuzumab over lapatinib, at least if HER2-targeted treatment is confined to one agent and if there is no

trastuzumab contraindication such as severe cardiac disease. In first-line therapy of HER2-positive breast cancer, the recent randomized phase III CLEOPATRA trial demonstrated a clear improvement in PFS and OS by adding pertuzumab to trastuzumab and docetaxel without further increase of toxicity (Swain et al. 2015). As a result, international guidelines currently recommend this triple therapy regimen as first-line treatment in patients with HER2-positive metastatic breast cancer (Giordano et al. 2014; Gradishar and Salerno 2016; Cardoso et al. 2017). Still, the efficacy and safety of a dual anti-HER2 inhibition with lapatinib and trastuzumab in addition to a taxane-based chemotherapy is evaluated as first-line treatment in HER2-positive metastatic breast cancer in an ongoing randomized, double-blind, placebo-controlled phase III study (NCT00272987). Before initiation of this trial, a safety study with three different dose regimens of paclitaxel, trastuzumab, and lapatinib was conducted in 63 patients with HER2-positive advanced breast cancer, revealing higher rates of severe diarrhea in patients receiving standard doses of lapatinib (Esteva et al. 2013). Therefore, it remains uncertain whether this triple combination offers a manageable safety profile with superior efficacy compared to trastuzumab in combination with pertuzumab and docetaxel in the first-line treatment of HER2-positive advanced breast cancer.

4.1.3 Neoadjuvant Treatment in Early Breast Cancer

Following encouraging first data of lapatinib in the metastatic therapy of breast cancer, a number of trials investigated its role in the neoadjuvant setting.

The randomized phase III GeparQuinto trial evaluated potential benefits of either lapatinib or trastuzumab, each combined with epirubicin and cyclophosphamide followed by docetaxel as chemotherapy backbone prior to surgical removal of the primary tumor in the breast (Untch et al. 2012). Of 309 patients assigned to chemotherapy plus trastuzumab, 30.3% showed pathological complete response (pCR), defined as absence of invasive tumor cells in the breast at the time of surgery. In contrast, only 22.7% of 311 patients receiving chemotherapy with lapatinib showed pCR (OR 0.68, 95% CI 0.47–0.97, $P = 0.04$).

The combination of the two drugs in the neoadjuvant setting was assessed in the open-label, multicenter phase III NeoALTTO study (Baselga et al. 2012). 455 women with HER2-positive early breast cancer were randomly assigned to receive either trastuzumab and lapatinib or each drug individually, both in combination with paclitaxel chemotherapy. The rate of pCR was significantly higher in the cohort with combined anti-HER2 therapy (51.3%) than in the group given trastuzumab alone (29.5%; difference 21.1%, $P < 0.01$) with no significant difference between the trastuzumab and lapatinib group (24.7%, $P = 0.34$). However, although not powered to detect significant differences in terms of survival outcomes, neither 3-year event-free survival nor 3-year OS significantly differed between patients treated with combination therapy (84% and 95%, respectively) and those assigned to trastuzumab mono (76% and 90%, respectively) (de Azambuja et al. 2014).

Further, evidence of superior efficacy of a neoadjuvant dual anti-HER2 treatment approach with trastuzumab and lapatinib was provided by the randomized phase IIb

CHER-LOB (Guarneri et al. 2012) as well as phase III NSABP B-41 (Robidoux et al. 2013) and the CALGB 40601 trials (Carey et al. 2016).

Finally, in a recent meta-analysis, including 1155 patients with HER2-positive breast cancer from a total of six randomized trials, neoadjuvant chemotherapy combined with trastuzumab and lapatinib as dual HER2 blockade was associated with a significant 13% increase in pCR rate compared to chemotherapy with trastuzumab alone (Clavarezza et al. 2016). Interestingly, similar to the pivotal EGF104900 trial, a greater benefit was seen in patients with hormone receptor-negative breast cancer compared to those with hormone receptor-positive status, indicating an inhibitory cross talk between endocrine and HER2 pathways (Li et al. 2015).

In conclusion, dual inhibition of HER2 seems to be a valid approach to neoadjuvant treatment of HER2-positive breast cancer. However, concurrently to lapatinib, efficacy and safety of pertuzumab as further HER2-targeting combination partner to trastuzumab was investigated in the neoadjuvant treatment of HER2-positive breast cancer too. Largely based on the phase II NeoSphere trial (Gianni et al. 2012) demonstrating a significant increase in complete response rate, current guidelines recommend consideration of dual HER2 blockade with trastuzumab and pertuzumab together with chemotherapy for neoadjuvant treatment of HER2-positive breast in patients with locally advanced breast cancer (Senkus et al. 2015; Gradishar and Salerno 2016; Liedtke et al. 2017). Dual anti-HER2 therapy with lapatinib in the preoperative setting of HER2-positive breast cancer should be restricted to highly selected cases only (e.g., contraindication to trastuzumab).

4.1.4 Adjuvant Treatment in Early Breast Cancer

To address the role of lapatinib in the adjuvant setting, the TEACH trial, a large randomized phase III study, has been performed (Goss et al. 2012). A total of 3147 women with HER2-positive early breast cancer who had completed trastuzumab-free adjuvant chemotherapy and had no evidence of disease were randomly assigned to receive daily lapatinib or placebo for up to 12 months. After a median follow-up of 4 years, disease-free survival (DFS) events occurred in 13% in the lapatinib group and 17% in the placebo group (HR 0.83, 95% CI 0.70–1.00, $P = 0.053$), thus very closely not meeting the prespecified criteria for statistical significance. Exploratory analyses restricted to patients with centrally confirmed HER2-positive status (78% in the lapatinib group and 80% in the placebo group) indicated a significant, though marginal benefit for patients receiving lapatinib (HR 0.82, 95% CI 0.67–1.00, $P = 0.04$). In terms of therapy onset, subgroup analyses showed a slight improvement in DFS in patients starting lapatinib treatment within 1 year of initial diagnosis (HR 0.70, 95% CI 0.50–0.99, $P = 0.04$).

Efficacy and safety of adjuvant treatment with lapatinib has also been evaluated as part of a dual anti-HER2 blockade with trastuzumab in the phase III ALTTO-study (Tomasello et al. 2008). A total of 8381 patients with HER2-positive early breast cancer were randomly assigned to either receive one year of adjuvant trastuzumab alone, lapatinib alone or the combination of both drugs, simultaneously as well as in sequential order. Based on a preplanned interim analysis in 2011

failing to demonstrate non-inferiority of single-agent therapy with lapatinib in terms of DFS as primary end point, lapatinib monotherapy was discontinued early. In 2015, final results with a median follow-up of 4.5 years were published (Piccart-Gebhart et al. 2016). Compared to standard therapy with trastuzumab alone, dual anti-HER2 treatment, either concurrently or sequentially given, did not result in a significant improvement of DFS (HR 0.84, 95% CI 0.70–1.02, $P = 0.05$ and HR 0.96, 95% CI 0.80–1.15, $P = 0.61$, respectively).

As a result, lapatinib, neither as single-agent nor in combination with trastuzumab can be recommended in the adjuvant treatment of HER2-positive early breast cancer (Senkus et al. 2015; Liedtke et al. 2017).

4.2 Efficacy in Gastrointestinal Cancer

Preclinical and early clinical evidence showed promising activity of lapatinib not only in breast cancer but also in HER 2-overexpressing gastroesophageal cancer cell lines (Kim et al. 2008; Wainberg et al. 2010). In contrast, clinical trials revealed only limited efficacy of lapatinib in patients with gastric cancer (Table 1). The Asian randomized phase III clinical trial TyTAN evaluated the benefit of adding lapatinib to paclitaxel as second-line therapy in patients with advanced gastric cancer who were HER2-positive by fluorescence in situ hybridization (FISH) (Satoh et al. 2014). In the intent-to-treat population ($n = 261$), median overall survival was superior upon combined treatment compared to paclitaxel alone (11 vs. 8.9 months) but this was only significant in the subgroup of patients with HER2 immunohistochemistry (IHC) 3+ (14 vs. 7.6 months, HR 0.59, 95% CI 0.37–0.93, $P = 0.02$). Moreover, lapatinib was also evaluated in the first-line treatment of HER2-positive advanced esophagogastric cancer. In the phase III LOGiC trial, a total of 545 patients were randomized to receive capecitabine and oxaliplatin in combination with lapatinib or chemotherapy alone (Hecht et al. 2016). With a median overall survival of 12.2 months in the lapatinib arm compared to 10.5 months in patients treated with chemotherapy only, there was no significant improvement in overall survival (HR 0.91, 95% CI 0.73–1.12, $P = 0.35$). However, overall response rate was significantly higher in the lapatinib cohort (53 vs. 39%, $P < 0.01$). In conclusion, in HER2-positive metastatic gastric cancer, lapatinib does not seem to generally provide additional value over current standard of care with chemotherapy and trastuzumab. Yet, a small subset of patients may benefit from lapatinib, albeit valid biomarkers are mandatorily needed for further identification of these patients.

Besides its clinical impact in esophagogastric cancer, there are interesting data from preclinical investigations on dual HER2 inhibition in colorectal cancer. The combination of lapatinib with trastuzumab led to sustained inhibition of tumor growth in patient-derived cetuximab-resistant xenografts of HER2-positive metastatic colorectal cancers (Bertotti et al. 2011). Consequently, clinical investigation of this dual anti-HER2 blockade was performed within the phase II HERACLES study, recruiting patients with KRAS exon 2 wild-type, HER2-positive metastatic

colorectal cancer refractory to standard of care including cetuximab or panitumumab (Sartore-Bianchi et al. 2016). Forty-eight of 914 patients (5%) were found to be HER2-positive with 27 of them finally enrolled. At a median follow-up of 94 weeks, 8 patients (30%) achieved an overall response rate and 12 patients (44%) showed stable disease. Combination therapy was generally well tolerated with maximum grade 3 adverse events in six patients (22%). Thus, although eligible for only a minor subgroup of metastatic colorectal cancer patients, combination therapy of lapatinib and trastuzumab may be an effective therapeutic option in these heavily pretreated patients.

HER2 overexpression can also be demonstrated in about 20% of patients with pancreatic adenocarcinoma. However, in a phase II trial evaluating lapatinib in combination with gemcitabine in metastatic pancreatic cancer, a planned six months analysis showed only minor clinical benefits with solely three of 29 patients (10%) achieving partial response (Safran et al. 2011). Furthermore, in a cohort of 17 patients with gemcitabine-refractory metastatic pancreatic cancer, receiving second-line treatment with capecitabine and lapatinib within a phase II trial, none of the patients attained a response and only six patients (35%) showed stable disease (Wu et al. 2015). In terms of the minor clinical benefits and the limited number of study participants so far, there is currently no indication of lapatinib in the treatment of metastatic pancreatic cancer.

4.3 Tolerability

In healthy volunteers, oral administration of lapatinib revealed good tolerability (Bence et al. 2005). Commonly reported side effects included diarrhea, skin rash, and headache. In a phase I, dose escalation study of 67 heavily pretreated HER2-positive cancer patients, the main toxicity was grade 1 and 2 diarrhea (Burris et al. 2005). With linear relation to the dosage of lapatinib over the 500–1600 mg range, but not to serum concentration, diarrhea may rather evolve from direct toxic effects on the intestinal epithelium.

In the pivotal EGF100151 trial, diarrhea, dyspepsia, and skin rash, the most common adverse events occurred significantly more frequently in patients receiving capecitabine plus lapatinib than capecitabine alone (Geyer et al. 2006). However, these differences were largely due to an increase in grade 1 events and adverse event-related discontinuation of therapy was similar in both treatment arms (13% in the combination arm vs. 12% in the monotherapy group).

In the approval trial for postmenopausal women with hormone receptor-positive metastatic breast cancer, the combination of lapatinib and letrozole caused grade 3 and 4 diarrhea in 10% of patients compared to 1% of patients receiving letrozole alone, resulting in discontinuation (15%) or interruption of therapy (36%), dose reduction (19%), or supportive treatment without dose adjustments (31%) (Johnston et al. 2009).

In the EGF104900 trial, 41% of patients receiving single-agent lapatinib and 60% of those treated with the combination of lapatinib and trastuzumab

experienced grade 1 or 2 diarrhea, while the incidence of diarrhea grade 3 or higher was similar with 7% in both groups. Besides, all other adverse events including those reported in $\geq 10\%$ of patients such as rash, nausea, and fatigue did not differ between single- and combined HER2-therapy. Adverse events led to permanent discontinuation of treatment in 11% of patients receiving the combination regimen compared to 6% treated with single-agent lapatinib.

In all phase III trials evaluating lapatinib in the neoadjuvant setting of breast cancer, grade 3 adverse events, mainly diarrhea, with subsequent discontinuation of therapy were more common in patients receiving lapatinib with or without trastuzumab than in patients receiving trastuzumab alone (Baselga et al. 2012; Guarneri et al. 2012; Untch et al. 2012; Robidoux et al. 2013; Carey et al. 2016). Further, in the phase III ALTTO trial, all lapatinib-containing adjuvant treatment arms were associated with more adverse events compared to trastuzumab monotherapy. The most common side effects of lapatinib resulting in dose modification or interruption were diarrhea, rash, and neutropenia.

Taken together, diarrhea is a frequent problem upon therapy with lapatinib, although symptoms appear to be mostly manageable. However, particularly in combination with chemotherapy, more severe diarrhea may result in treatment limitations.

Therapy with lapatinib is less frequently associated with cardiac failure than treatment with trastuzumab, in which reduction in left ventricular output has been a significant concern, prevents simultaneous treatment with anthracyclines, and excludes patients with coexisting cardiac failure (Xin et al. 2016; Choi and Chang 2017). Still, because cardiac events were slightly more common in patients receiving lapatinib than in patients in control arms, routine evaluation of cardiac function is usually recommended before initiating treatment with lapatinib (Dias et al. 2016).

Additionally, quite infrequently reported adverse events upon treatment with lapatinib were hepatotoxicity and interstitial pneumonitis (GlaxoSmithKline 2007; Guarneri et al. 2012). Therefore, routine laboratory evaluation of liver function and clinical observation of pulmonary function are recommended before and during treatment with lapatinib.

However, altogether, life-threatening events (grade 4) or death (grade 5) attributable to lapatinib treatment seem to be very rare (Moy and Goss 2007).

5 Biomarkers

Accurate assessment of HER2 status is mandatory to predict a potential response to anti-HER2 treatment. To define HER2 positivity, either HER2 protein overexpression or gene amplification has to be determined by IHC or (F)ISH, respectively.

In terms of IHC, results of HER2 testing are categorized in a four scale score (range, 0 through 3+), based on the percentage of positive tumor cells and staining intensity. According to the ASCO/CAPs guidelines, a HER2 IHC score of 0 to 1+ is

considered as HER2-negative, while all patients with a score of 3+ should be determined as HER2-positive. Patients with a IHC score of 2+ are regarded equivocal, demanding further assessment by (F)ISH (Wolff et al. 2014). Since HER2 expression essentially differs between breast and gastric cancer with regard to membranous distribution of the antibody and intratumoral heterogeneity, different IHC scoring systems have been proposed (Hofmann et al. 2008).

Generally, high concordance exists between both methods (Bahreini et al. 2015). However, in breast cancer patients with dissenting HER2 test results, HER2 amplification by FISH seems to characterize HER2 status more accurately compared to at least some frequently used IHC assays and may predict benefit from lapatinib treatment more precisely than IHC-defined HER2 protein overexpression (Press et al. 2002, 2008). Conversely, in gastric cancer, patients not only showing HER2 amplification by FISH but also high HER2 protein expression (i.e., IHC3+) seem to benefit most from anti-HER2 treatment (Bang et al. 2010; Satoh et al. 2014).

However, even in precise assessment of HER2 status by (F)ISH and IHC, HER2 amplification and overexpression appear to be necessary, yet not always sufficient for response to anti-HER2 drugs. Therefore, additional biomarkers are urgently needed to increase the positive predictive value of HER2. In this regard, continuous quantitative measurement of HER2 protein expression may be more useful for accurate stratification of patients with respect to response to (dual) HER2-targeted treatment approaches than semiquantitative protein measurements by IHC (Scaltriti et al. 2015). In addition, assessment of serum HER2 extracellular domain levels (ECD) may not only be useful as an overall prognosis tool at diagnosis of HER2-positive breast cancer but also in monitoring the efficacy of anti-HER2 treatment, as previously shown in the neoadjuvant setting with trastuzumab (Reix et al. 2016). Moreover, somatic HER2 mutations should be further explored as predictors of response or resistance to specific HER2-targeted drugs (Bose et al. 2013).

6 Conclusion and Future Perspectives

Patients with HER2-positive breast cancer have a high risk of disease progression upon treatment with conventional chemotherapeutic drugs but benefit enormously of the additional HER2-targeted therapy with trastuzumab. In the past, failure to respond to trastuzumab-containing regimens has posed a therapeutic dilemma to patients and clinicians. Lapatinib in combination with capecitabine was the first alternate anti-HER2 treatment approach to demonstrate further efficacy in patients with advanced HER2-positive but trastuzumab-resistant breast cancer. Moreover, dual anti-HER2 blockade with continuation of trastuzumab and lapatinib offers a significant survival benefit in trastuzumab-pretreated patients with uncontrolled metastatic HER2-positive, hormone receptor-negative breast cancer. In addition, lapatinib is an effective combination partner with hormonal therapy in postmenopausal women with advanced, triple-positive breast cancer.

However, there also have been major drawbacks in the evaluation of the efficacy of lapatinib; In first-line therapy of breast cancer, single-agent lapatinib in combination with standard chemotherapy did not show superiority over trastuzumab-containing regimens in both, early and advanced HER2-positive breast cancer, but resulted in higher toxicity with subsequent treatment interruption in, an albeit, small proportion of patients. Furthermore, favorable data with novel anti-HER2 antibodies, antibody-drug conjugates, and second-generation irreversible HER TKIs such as pertuzumab, T-DM1, and neratinib, respectively, have recently emerged, postponing lapatinib to third line and beyond rather than first or second line in the treatment of HER2-positive breast cancer. In the treatment of advanced HER2-positive gastric cancer, lapatinib showed only minor benefit compared to trastuzumab.

Despite some restrictions, one may speculate about the future role of lapatinib in the treatment of HER2-positive cancer as some open questions remain. These include: (i) with ongoing evaluation of modern anti-HER2 drugs in the treatment of early and advanced HER2-positive breast cancer, which position will lapatinib adopt in the sequence of therapeutic options?, (ii) is lapatinib plus capecitabine an equal or even more efficient alternative to trastuzumab in the special setting of patients with HER2-positive breast cancer and brain metastases?, (iii) in advanced triple-positive breast cancer, is lapatinib in combination with letrozole inferior to dual anti-HER2 therapy with trastuzumab and pertuzumab together with endocrine therapy?, (iv) does the benefit outweigh the risks of dual anti-HER2 therapy with trastuzumab and lapatinib in combination with chemotherapy in the treatment of advanced HER2-positive breast cancer?, (v) what is the role of a potential triple HER2-targeted therapy using lapatinib, trastuzumab, and pertuzumab with or without concomitant chemotherapy?, (vi) will lapatinib become an effective treatment approach in HER2-positive advanced colorectal cancer progressing upon standard of care including anti-EGFR antibodies?, and (vii) which biomarkers can accurately predict response to HER2-targeted therapies?

Many of these topics will be addressed in ongoing or future clinical trials. The results are eagerly awaited, but may not be available for quite some time. Until then, the combination of lapatinib with capecitabine or trastuzumab in HER2-positive (and hormone receptor-negative, respectively) advanced breast cancer, progressing upon treatment with trastuzumab, as well as the combination of lapatinib with letrozole as first-line therapy in triple-positive breast cancer are the only approved, but probably not the only effective applications of this agent.

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