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REVIEW

Lapatinib: A Sword With Two Edges

László Kopper

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Abstract Lapatinib is an oral dual tyrosine kinase inhibitor targeting EGFR1 and EGFR2 (HER2). Phase I trials have shown that lapatinib is well tolerated, with mild diarrhea and skin rush as common adverse effects, and low cardiotoxicity. Phase II and III trials provided evidences on clinical effectiveness in advanced or metastatic breast cancer and potential against brain metastases. Lapatinib is active in combination with trastuzumab and in trastuzumab-resistant patients, moreover it has synergistic action with capecitabine. Several clinical trials are in progress to explore the effectiveness of lapatinib in other combinations and against several tumor types.

Keywords Lapatinib · Targeted therapy · EGFR-inhibition · HER2-inhibition · Trastuzumab resistency · Breast cancer

Introduction

Theoretically, the molecular target-specific drugs have the potential to improve antitumor effectivity while minimizing toxicity to normal host cells. One of the most frequent genetic lesion in epithelial tumors is the overexpression of EGFR family members which can activate different pathways responsible for key cell functions, as survival and proliferation. In certain tumors, such overexpression correlates with a poor clinical outcome, suggesting these genetic changes as useful therapeutic targets. The extracellular domain of tyrosine kinase receptors, including EGFRs, could be targeted by monoclonal antibodies, while the intracellular domain by small molecules competing with ATP for the ATP-binding pocket.

There are rationals to develop dual (or multitargeted) tyrosine kinase inhibitors, specifically which targets EGFR1 and HER2: (a) it is easier to overcome signaling redundancy, a form of resistance observed in single tyrosine kinase inhibition in which other members of EGFR family are upregulated, (b) a dual inhibitor may be useful in more patients due to the role of EGFR1 and HER2 dimers in the progression of various cancer types, (c) and synergistic inhibition of cancer cell growth can be expected. [1]

L. Kopper (✉)
Ist Department of Pathology and Experimental Cancer Research,
Semmelweis University,
Üllői út 26,
1085 Budapest, Hungary
e-mail: kopper@korb1.sote.hu

Drug and Target

Drug

Lapatinib ditosylate monohydrate (GW572016, Tykerb, GlaxoSmith Kline, Research Triangle Park, NC) is an oral 4-anilinoquinazoline derivative that inhibits reversibly phosphorylation of the tyrosine kinase domains in EGFR1 and EGFR2 (HER2) by competing with ATP. It was approved in March 2007 in US to be used in combination with capecitabine (Xeloda, Roche) for the treatment of patients with advanced or metastatic HER2+ breast cancer who have already received previous therapy with anthracyclines, taxanes and trastuzumab.

Target

The epidermal growth factor (EGFR, HER, ErbB) family has four members— EGFR1-4 —all of which bind ligands, except EGFR2 (HER2). Ligand binding of the extracellular domain causes receptor homo- or heterodimerization and

tyrosine kinase phosphorylation (auto-or transphosphorylation), which will activate different pathways for cell survival (against apoptosis), proliferation, as well as progression. There are considerable efforts to block these receptors or stop the receptor activated pathways in tumor cells, what is a great challenge due to the rather frequent overexpression (many times owing to amplification) or mutation of these important regulators. [2] The members of the EGFR family are activated in many epithelial malignancies which is usually associated with poor prognosis, partly by interfering with the inhibitory effect of chemotherapeutic agents.

HER2 is the only member of the family that does not bind known ligand, its main functional role results from recruitment into heterodimeric complexes with the others. The type of partner in dimerization is important because it decides the downstream effect. Being the most common heterodimerization partner of EGFR1, HER2 potentiates its signaling by increasing the binding affinity of the ligands, reducing degradation and predisposing the receptor recycling. Ligand stimulation of EGFR1 leads to activation of HER2 by transduction through heterodimerization. EGFR-specific inhibitors can reduce HER2 signaling and growth of breast cancer cells that overexpress HER2. Thus combined inhibition of both EGFR1 and HER2 may be more effective than targeting just one of them.

Lapatinib binds the inactive form of EGFR1 and differ from other EGFR-inhibitors, which bind the receptor in its active conformation. This explains why lapatinib has a slower dissociation rate compared to other tyrosine kinase inhibitors, resulting in a greater duration of the effect at the target site than that seen either with erlotinib or gefitinib [3].

Preliminary biomarker studies suggest that inhibition of HER2 is more important in the effectiveness of lapatinib than its blockade of EGFR. In a phase III trial all patients had HER2+ disease and was no correlation between the likelihood of response and the level of HER2 overexpression. This suggests that all HER+ cases had a chance to respond. On the contrary EGFR expression level did not correlate with response in either arm of the study. The conclusion was that EGFR is overall not very important in lapatinib efficacy. If this is the case, why does lapatinib work in patients who became resistant to trastuzumab? There is no firm answer just suggestions, e.g. lapatinib is effective against the truncated form of HER2 (where extracellular binding site is missing), but trastuzumab does not. In breast cancer cells truncated but overexpressed and activated form of HER2 ($p95^{erbB2}$ or $p95^{HER2}$) preferentially forms heterodimers with HER3. (The ligand for HER3 is not EGF but heregulin.) Such HER2+ cells were resistant to trastuzumab, but sensitive to lapatinib supporting the lack of cross-resistance [4].

Preclinical and Pharmacokinetic Data

In vitro the 50% inhibitory concentration (IC_{50}) against purified EGFR and HER2 of 10.8 and 9.3 nM, respectively. [5] *In vivo* lapatinib inhibited dose-dependently the growth of human tumor xenografts (BT474 breast cancer, GEO colon cancer, HN5 head and neck cancer). In murine mammary xenografts (estrogen receptor positive, tamoxifen resistant breast tumor) lapatinib restored tamoxifen sensitivity. The combination of lapatinib and tamoxifen showed better antiproliferative effect than either drugs alone [6].

Oral administration of lapatinib to healthy human volunteers and cancerous patients proved the tolerability of lapatinib with no severe adverse effects. Absorption from the GI tract was dose-dependent and constant, serum concentration peaked 3–4 h after the dose. The half-life was ~17 h achieving a steady-state concentration after 6–7 days of o.d. dosing, with elimination via CYP3A4/5. Lapatinib does not appear to be a substrate for P-glycoprotein.

Safety and maximum tolerated dose of lapatinib have been evaluated in several phase I trials (usually in heavily treated patients). In these studies no grade 4 toxic effects occurred. Grade 3 toxicity involved mainly GI tract and the skin. Analysis of dose and concentration relationship with response determined that the majority of the responders were receiving 1200 mg lapatinib per day with a serum through concentration of 0.3–0.6 μg/ml.

According to the phase I studies lapatinib, as single agent in cancer patients, was well tolerated orally up to 1.800 mg once daily until disease progression. Drug-related side effects were rash, diarrhea, nausea, vomiting, constipation, fatigue, anorexia [7].

Clinical Trials

Two nonrandomized, multicenter, phase II (EGF20002, EGF20008) assessed the safety and efficiency of lapatinib monotherapy for metastatic breast cancer resistant to either trastuzumab, or anthracyclines, taxanes and capecitabine. According to the preliminary evaluation 22% and 14% of patients showed clinical response (CR, PR, SD). Concerning biomarkers, ER and PR negativity, EGFR overexpression and intact extracellular domain of HER2 may be related to lapatinib response in tratuzumab pretreated patients [8].

It is generally accepted, that targeted therapy (or therapy with targeting agents) will achieve better clinical activity in combinations than in monotherapy.

In a phase I study 45 patients with previously treated, advanced solid malignancies were enrolled to determine the optimally tolerated regimen (OTR) in a combination of lapatinib and capecitabine. It turned to be 1,250 mg/day (14 days) plus capecitabine 2000 mg/m^2/day (for 14 days in

a 21 day cycle). The majority of side effects were grade 1 or 2 in severity. The most common drug-related toxicities (over 15% of patients) were diarrhea, nausea, rash, palmar–plantar erythrodysesthesia, mucositis, vomiting and stomatitis. There were four responses. The pharmacokinetics of lapatinib and capecitabine plus its metabolites were not significantly changed by the combination [9].

A phase I study was designed to determine the feasibility of a combination with lapatinib and FOLFOX4 (oxaliplatin/leucovorin/5-fluorouracil) in patients with solid tumor. Lapatinib was given once daily during the study. Leucovorin and oxaliplatin was received concurrently over a 2 h infusion, followed by 5-FU in bolus and later as continuous infusion over 22 h on day 1. 5-FU and leucovorin were repeated identically on day 2. Such cycle was administered every 2 weeks. 34 patients were treated and no dose-limiting toxicities were observed. The optimally tolerated regimen was established at 1,500 mg/day lapatinib in combination with the standard FOLFOX4 therapy. The most important hematologic side-effect was neutropenia, the non-hematological mainly nausea, diarrhea, vomiting. Drug–drug interactions were not observed between lapatinib and the FOLFOX4 regimen. Further study was suggested to explore the beneficial antitumor effect of this combination [10].

A phase I trial intended to determine the OTR of oral lapatinib given in combination with i.v. 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) assessing the safety, tolerability and pharmacokinetics of the combination. From 25 patients at solid tumors enrolled into the study 12 was treated at three dose levels to determine OTR, than 13 were treated at OTR to evaluate the phamacokinetics of the combination. The 2-weekly OTR contained 1250 mg/day lapatinib with 108 mg/m^2 (day 1) irinotecan and 200 mg/m^2 leucovorin, 240 mg/m^2 5-FU in bolus and 360 mg/m^2 in infusion (days 1 and 2). In that case the doses of 5-FU and irinotecan were a 40% reduction in dose compared to conventional FOLFIRI. Diarrhoea (grade 3) and neutropenia (grade 4) were dose-limiting toxicities. Of 19 patients evaluable for response four patients had partial response and 9 had stable disease. Concerning colorectal cancers (nine pts) 55% (five pts) showed disease control (PR + SD). Despite the small numbers this trial compares favourably with historical response rates for 5-FU/irinotecan combinations in second-line treatment of advanced colorectal cancer (disease control rate 34%). The results suggest further study in a phase II trial [11].

Breast Cancer

Over a million women are diagnosed with breast cancer yearly and globally, what is 10% of all new cancers and 23% of all female cancer cases. Within, metastatic breast cancer is one of the leading cause of death worldwide among women. It is often associated with overexpression and activation of HER2, which is present in ~20–30% of patients with breast cancer and is associated with increased progression and decreased overall survival [12]. HER2 overexpression in HER2 3+ is usually caused by the gene amplification, but in 2+ carcinomas it is due to an accumulation of the recycled oncoprotein to the cell surface induced by activated PKCα. [13] FDA approved *trastuzumab* (Herceptin), a humanized monoclonal antibody binding to the extracellular part of HER2 to treat breast cancers overexpressing HER2. Trastuzumab in combination with taxane-based therapy is now the standard first–line treatment for HER2+ metastatic breast cancer. Furthermore, in combination with other drugs it can be effective as adjuvant therapy reducing the risk of disease recurrence.

Although trastuzumab is a powerful agent, the objective response rate to its monotherapy is not too high (ranging 10–35% in different studies) [14]. Most patients who respond initially to trastuzumab will show resistance within 1 year. Therefore, identification of novel agents that can inhibit the trastuzumab-resistant cells is very important.

Lapatinib is a small molecule inhibitor of the tyrosine kinase domains in EGFR1 and HER2, with a consequence of blocking the downstream signaling pathways from these receptors (e.g. activity of AKT, S6 kinases and MAPK decrease, $p27^{KIP1}$ increases). The action against survival and proliferation can stimulate apoptosis. In breast cancer cells responsive to lapatinib the expression of AKT and AKT-related genes (MAPK9, HSPCA, IRAK1, CCND1) were strongly down-regulated 7- to 25-fold, while weakly (<fivefold) in non-responsive cell lines. Phosphorylation of FOXO3A, a proapoptotic gene, which is negatively regulated by AKT, was significantly upregulated in responsive cancer cells exposed to lapatinib. Lapatinib also stimulated the expression of estrogen and progesterone receptor and modulated many other genes (in cell cycle control, glycolysis, fatty acid metabolism) [15] In the *cell cycle control* the genes were mainly involved with either G1-S phase transition (such as CDC6, CDK4 and the transcription factor E2F1), or in the prereplication complex machinery (such as MCM2, MCM3, MCM6 and MCM7). Lapatinib may limit the growth capacity of responsive cells by influencing some critical factors in *glycolysis* (e.g. glyceraldehyde-3-phosphate dehydrogenase, enolase 1, pyruvate kinase). Tumor progression is closely linked with increased glycolysis and AKT-mediated resistance to growth factor withdrawal is associated with maintenance of glycolytic rate. This explains why lapatinib treatment results in the suppression of genes related to glycolysis. Besides, in lapatinib treated cells energy is deprived not only via inhibition of glycolysis but also by modulating genes in *energy and fatty acid metabolism*. FASN is required for

carbohydrate to fatty acid conversion, and is highly expressed in breast cancers. One mechanism of FASN-mediated tumorigenic activity could be through modifying the expression, activation and cellular localization of HER2. FASN and other genes in fatty acid and sterol biosynthesis (e.g. δ-9-desaturase, SCD, 7-dehydrocholesterol reductase) was down-regulated by lapatinib to a greater extent in responsive versus non-responsive cell lines [15].

Lapatinib and trastuzumab There are several reasons why lapatinib could be a very useful agent in the treatment of breast cancer. One obvious target is a HER2+ tumor, similarly to trastuzumab. However, they show remarkable differences [16].

Despite the impressive results with trastuzumab in adjuvant therapy of breast cancer, 15% of patients with overexpressed or amplified HER2 will relapse within 3 years. To overcome the resistance new drugs are under development and some are in advanced stage. Although trastuzumab and lapatinib target the same receptor, HER2, their combination could be attractive, since they attack different parts of the receptor: trastuzumab is against the extracellular, lapatinib against the intracellular domains, trastuzumab increases the internalization and degradation of HER2, lapatinib inhibits the tyrosine kinase activity. In combination with trastuzumab in breast cancer cells lapatinib induces apoptosis and inhibits transactivation of EGFR3 (HER3) to a greater extent than either agents alone. This combination in HER2 overexpressing breast cancer cells proved to be more effective than the trastuzumab plus gefitinib (a powerful inhibitor of EGFR1) [17, 18]. Preclinical data indicates that simultaneous administration of lapatinib and trastuzumab have synergistic effect on HER2+ breast cancer cells, moreover, lapatinib showed activity against selected trastuzumab resistant cells indicating the lack of cross resistance [19]. In a phase I study (EGF10023) 54 heavily pretreated, HER2+, trastuzumab resistant patients were given lapatinib and complete or partial responses occurred in eight patients, however the adverse effects were also increased. At higher doses of lapatinib fatigue was the dose-limiting toxicity [20].

Theoretical advantage of dual inhibitors is given in those tumor cells where the extracellular domain of tyrosine kinase receptors (here EGFR1 or 2) is missing (or truncated), because in that case the binding of the monoclonal antibodies (as trastuzumab or pertuzumab) is highly questionable. Truncated form of HER2 (p95) has a higher kinase activity than wild-type HER2. While lapatinib can inhibit baseline $p95^{HER2}$ phosphorylation in BT474 cells and in xenografts, whereas trastuzumab neither binds to or inhibits p95. Therefore, if p95 appears during tumor progression it can be responsible for trastuzumab resistance and an indication to use lapatinib [4].

Brain metastases appear in about 20–30% of metastatic breast cancer and are associated with a very poor outcome. The incidence of brain metastases seems to be higher in HER+ tumors. In an *in vitro* and *in vivo* experimental system lapatinib inhibited the colonization of dual EGFR1-HER2+ breast cancer cells. (MDA-MB-231 cell line over-expressing EGFR was transfected with HER2 cDNA.) [21] Trastuzumab is rather effective against visceral metastases, but it seems to be inactive to prevent or treat brain metastases. Essentially, the brain-blood barrier inhibits *trastuzumab* to reach adequate concentration in the cerebrospinal fluid and in the tumor cells. Lapatinib, as a small molecule may cross this barrier and might be active in the treatment of brain metastasis. As a preliminary result, in a phase III study fewer patients (four pts) had CNS relapse in lapatinib plus capecitabine treated group compared to capecitabine alone (eleven pts), although this difference was not significant. [22] In a small group of patients (38) with brain metastasis and CNS progression, previously exposed to trastuzumab, lapatinib showed a modest but real activity (response rate: 5.1%) [23].

Cardiac toxicity is a known adverse effect in patients on trastuzumab (in ~ 11% of patients). The cardiac functions have been analysed in more than 3.000 patients treated with lapatinib in 18 phase I-III clinical trials [24]. Left ventricular ejection fraction (LVEF) was abnormal in 1.6% of patients who experienced a decrease in LVEF (1.4% was asymptomatic, 0.2% symptomatic). The symptomatic cases reacted promptly to standard cardiac management. All comparisons with matched control cohorts or trastuzumab-treated patients lapatinib seems to be significantly less toxic than trastuzumab.

Lapatinib and capecitabine A phase III trial evaluated capecitabine (Xeloda) with and without lapatinib in the treatment of 321 patients (HER2+, locally advanced or metastatic breast cancer refractory to trastuzumab). (Treatment schedule: lapatinib 1250 mg orally, daily, continuously, capecitanibe 2,000 mg per m^2 per day, when combined, 2,500 mg per m^2 per day, when alone, on days 1–14 every 21 days.) Both treatments were planned to be administered until tumor progression or unacceptable toxicity. The primary end-point was time to progression (TTP), and secondary end-points were overall survival, response rate, clinical benefit response and toxicity. Addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression. Significant improvement in median time to progression was achieved by the combination versus monotherapy (8.4 vs 4.4 month). The overall response was 22% vs 14%, the partial response 21% vs 14%, clinical benefit 27% vs 18%, but the death rate was identical (22%). The most common side effect (above 5% as grade 3 or 4) was diarrhea,

hand-foot syndrome in combination and almost the same in monotherapy with capecitabine. The conclusion was that lapatinib plus capecitabine is superior to capecitabine alone in HER2+ advanced breast cancer that has progressed after treatment with regimens that included anthracycline, taxane and trastuzumab [22].

An updated phase III trial compared lapatinib (1250 mg/day) plus capecitabine (2,000 mg/m2 days 1–14 of a 21 day cycle) versus capecitabine alone (2,500 mg/m2 on the same schedule) in 399 women with HER2+, locally advanced or metastatic breast cancer previously treated with anthracycline-, taxane- and trastuzumab-containing regimens. Addition of lapatinib increased the tumor-free period with a hazard ratio (HR) of 57 (95% CI, 0.43–0.77) and indicated a trend toward improved overall survival (HR: 0.78, CI: 0.55–1.12). and reduced the frequency of brain metastases. Baseline serum level of HER2 extracellular domain did not predict the advantage of lapatinib [25].

Inflammatory breast cancer Lapatinib had remarkable activity in inflammatory breast cancer in two phase II trials, and the effect seemed to be based primarily on HER2 inhibition. In one of the trials patients were divided into two groups according to the expression profile of HER2 and EGFR. Tumors overexpressed HER2 made one group independently of the EGFR status and 16 out of 32 patients had an objective response. On the contrary, in 15 women whose tumor did not overexpress HER2 but did overexpress EGFR only one showed an objective response. Biomarker analysis of the responders showed that almost all had high level of HER2 expression and 80% had activated EGFR. It is indicated that HER2 activation may trigger EGFR activation in these cases, therefore inhibition of both targets by lapatinib could be important [26].

In another phase II trial lapatinib monotherapy was evaluated with relapsed/refractory inflammatory breast cancer. One group (A) was selected upon HER2+ overexpression (IHC, immunohistochemistry, 2/3+, FISH, fluorescent in situ hybridization, +), irrespective from EGFR1 status, while the other group (B) had patients with EGFR+ and HER2- tumors. 34 patients were enrolled and 17 were evaluated. Clinical response (CR/PR) occurred 8/11 in group A, but 0/6 in group B. All responders overexpressed HER2, pHER2 (phosphorylated form, i.e. activated) increased, co-expressed IGF-IR and expressed activated HER3. PTEN status did not affect response to lapatinib. As a conclusion, high HER2, pHER2 and IGF-IR co-expression predict for clinical response to lapatinib monotherapy in patients with relapsed/refractory inflammatory breast cancer [27].

Another trial combined paclitaxel with lapatinib as neoadjuvant therapy in inflammatory breast cancer and reached clinical response in almost all patients (95%, 20/21) [28].

Other mechanisms It has been shown that physical interaction and cross-signaling between HER2 and IGF-I (*insulin-like growth factor I*) contributes to trastuzumab resistance. [29]. Lapatinib can interfere with the phosphorylation of IGF-I receptor and induce apoptosis in trastuzumab-resistant cells. When such cells were co-treated with lapatinib and IGF-I receptor-targeted antibody, αIR3, the cytotoxic effect was increased, strongly supporting that lapatinib alone or in combination may effectively inhibit breast cancers that have progressed on trastuzumab [30] These findings firmly suggest again that there is no cross-resistance between trastuzumab and lapatinib, in contrast to trastuzumab and pertuzumab, because both bind to extracellular HER2 region.

Lapatinib can influence the signaling from *estrogen receptor*, leading to decreased efficacy. [31] That may scale up the members of a combination therapy. In fact, a triple combination (with antagonists of estrogen receptor, HER2 and IGF-I receptor) augmented the apoptotic effect of single agents or dual combinations in ER+, HER2 overexpressing (BT474) or in ER+, IGF-I receptor-elevated (MCF7) breast cancer cells [32].

Proteolytic cleavage of both EGFR ligands and receptors is a critical event in pathway activation. Such cleavage generates soluble, functionally active forms of ligands and in the case of HER2 the result is the shedding of extracellular domain and a membrane bound fragment (p95) containing a kinase domain with significant constitutive activity. The presence of elevated extracellular part of HER2 in the sera of cancer patients has been linked to poor response rates. The cleavage (i.e. proteolysis) can be mediated by the *ADAM* (a disintegrin and metalloprotease) family of zinc-dependent proteases. Combination of lapatinib with the clinical candidate ADAM inhibitor, INCB7839, prevented tumor growth in the BT474-SCI human breast cancer xenografts model [33].

Further trials Because of the good results of lapatinib treatment on advanced breast cancer and the possibility that it is associated with a lower incidence of cardiac problems, there is an intention to test lapatinib in early-stage breast cancer patients. Two such adjuvant trials are in the works. The first is TEACH (Tykerb Evaluation After Chemotherapy) which is designed to test the efficacy of lapatinib in patients with HER2-positive early breast cancer who have already completed chemotherapy. Patients (about 3,000 from 32 countries) will be randomly assigned to 1 year lapatinib or 1 year of a placebo. If lapatinib decreases the rate of recurrence, the placebo arm will be offered a full year of lapatinib (free of charge). The second and larger trial is ALTTO (Adjuvant Lapatinib and/or Trastuzumab Trial Organization), which will include an unusual two independent primary endpoints. Although ALTTO will not answer all questions about the best use of lapatinib and trastuzumab in

early breast cancer patients, but it will whether one agent is better than the other, whether one is safer, and whether the drugs have to be used concurrently, separately or in tandem [34].

A randomised, multicenter phase III study is started comparing the efficacy of neoadjuvant lapatinib plus paclitaxel, versus trastuzumab plus paclitaxel, versus concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment in HER+ primary breast cancer (NeoALTTO). The primary objective is to evaluate and compare the rate of pathological complete response at the time of surgery. The planned total duration of the anti-HER2 therapy will be one year. (The estimated completion date of the study: September 2019.)

The crosstalk between hormone- and EGFR-family pathway is considered a possible cause of hormone-resistance. Nineteen Italian and European centers participates in this ongoing trial. Postmenopausal women with stage II–IIIa, hormone receptor positive and HER2 negative breast cancer patients are randomized to letrozole (2.5 mg/d) plus lapatinib (1500 mg/d) or placebo. Treatment is given continuously for 24 weeks before surgery [35].

Some Other Cancers

Several trials focus on the combination of pazopanib and lapatinib. One of them compares in a phase II trial the combination of these drugs versus monotherapy either with pazopanib or with lapatinib in patients with FIGO stage IVB or recurrent or persistent *cervical cancer* received zero or one prior chemotherapy for advanced/recurrent disease. The primary objective is to measure progression free survival. In another phase I/II trial the safety and tolerability of pazopanib and lapatinib is under study when administered in combination with enzyme-inducing anti-convulsants in patients with recurrent grade III or IV *malignant gliomas*. (http://clinicaltrials.gov).

In human *bladder cancer* cells (with high and low expression of EGFR1 and HER2) the optimal combination was lapatinib before and during gemcitabin/cisplatin treatment suggesting that lapatinib can cooperate with clinically relevant agents [36].

Patients with progressive, recurrent or metastatic *adenoid cystic carcinoma* expressing at least 1+ EGFR and/or 2+ HER2 were treated with lapatinib 1,500 mg daily. Patients with other malignant salivary gland tumors were treated as a separate group. Although no responses were observed, lapatinib was well tolerated, with a prolonged tumor stabilization of at least 6 months in 36% of assessable patients [37].

A randomised, multicentre, global phase III trial is on comparing the effect of adjuvant oral lapatinib versus placebo in high-risk *head and neck cancer* after surgery. Lapatinib and placebo will be given in combination with radiochemotherapy followed by the maintained administration of drugs for 1 year. The primary objective of the study is to evaluate if lapatinib is effective reducing the recurrency rate in these high-risk patients. (Expected completion date: June 2012).

Conclusion

Targeted molecules became very popular in drug design and now many of them are at different stages of clinical trials (Table 1; 38). (Details for ongoing trials: http://clinicaltrials.gov) This approach offers a promise of a new therapeutic tool that can be used alone or in combination with conventional cancer treatment modalities. EGFR signaling inhibition is one of the emerging strategies within this new treatment paradigm. Disruption of EGFR signaling pathway gained strong support in preclinical tumor models and is undergoing extensive clinical testing. Lapatinib, a dual EGFR inhibitor, is one of the most recent drugs in this respect, and already demanded strong clinical intention. Today it is already in the clinical practice, and further trials with lapatinib are underway, in combination with various drugs and besides breast cancer on other tumors as well. Survival data will be crucial to lapatinib's long-term success, both in placing itself in the treatment algorithms and supporting its price on the market.

Table 1 New targeted molecular drugs in breast cancer

Drug	Type	Target
Trastuzumab	moAb	HER2
Cetuximab	moAb	EGFR
Pertuzumab	moAb	HER2
Bevacizumab	moAb	VEGF
Gefitinib	sm	EGFR
Erlotinib	sm	EGFR
Lapatinib	sm	EGFR and HER2 (reversible)
HKI-272	sm	EGFR and HER2 (irreversible)
Canertinib	sm	EGFR
Dasatinib	sm	Src/Abl
Sorafenib	sm (mt)	VEGFR2, -3, PDGFRB, KIT, RAF, FLT3
Sunitinib	sm (mt)	VEGFR, PDGFR, KIT, RET, FLT3
Pazopanib	sm (mt)	VEGFR1, -2, -3, PDGFR
Temsirolimus	rapalog	mTOR
Everolimus	rapalog	mTOR
Bortezomib		proteasome
Lonafarnib		competition with farnesyl transferase
Flavopiridol		CDK
AG-014699		PARP1

moAb Monoclonal antibody, *sm* small molecule, *mt* multitarget, *rapalog* rapamycin analogue, *CDK* cyclin-dependent kinase

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