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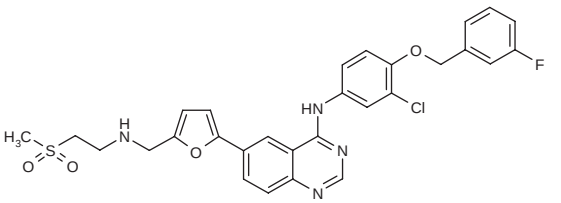
Lapatanib

Prop INN; USAN

Oncolytic
Dual EGFR and erbB-2 Inhibitor

GW-2016
GW-572016
Tykerb

N-[3-Chloro-4-(3-fluorobenzyloxy)phenyl]-6-[5-[2-(methylsulfonyl)ethylaminomethyl]furan-2-yl]quinazolin-4-amine



$C_{29}H_{26}ClFN_4O_4S$ Mol wt: 581.0584

CAS: 231277-92-2

CAS: 388082-78-8 (as tosylate)

EN: 301036

Abstract

Human epidermal growth factor receptor (EGFR) and erbB-2 are subclass I receptor tyrosine kinases that have been linked with a number of cancers, thereby making inhibitors of these proteins attractive targets for drug development. Several signaling cascades are associated with EGFR, which plays a role in mitogenesis, apoptosis, cell migration, differentiation and angiogenesis, all important processes in tumorigenesis. EGFR and its ligands are overexpressed in a number of solid tumors, including pancreatic, lung, ovarian, renal, gastric, hepatic and breast cancer. ErbB-2 overexpression has been found in a wide variety of cancers, including breast, bladder, colorectal, gastric, ovarian, prostate, renal and uterine cancers. Agents that target EGFR and erbB-2 are therefore under development or currently available for a number of cancer indications. One such agent is lapatinib, a potent and reversible dual EGFR and erbB-2 inhibitor that has shown promising pharmacological activity and pharmacokinetics. Lapatinib has been investigated as an anticancer monotherapy, as well as in combination with trastuzumab, capecitabine, letrozole, paclitaxel and FOLFIRI (irinotecan, 5-fluorouracil and leucovorin), in a number of clinical trials. It is currently in phase III testing for the oral treatment of metastatic breast, head and neck, lung, gastric, renal and bladder cancer. Additional trials of lapatinib in patients with brain, gallbladder, prostate, ovarian, endometrial and hepatobiliary cancers are also under way.

Synthesis

Williamson's ether synthesis between 2-chloro-4-nitrophenol (I) and 3-fluorobenzyl bromide (II) by means of K_2CO_3 in acetonitrile affords ether (III), which is reduced to the aniline (IV) by catalytic hydrogenation over Pt/C. Condensation of aniline (IV) with 4-chloro-6-iodoquinazoline (V) in *i*-PrOH furnishes the diaryl amine (VI), which is then submitted to Stille coupling with 5-dioxolanyl-2-(tributylstannyl)furan (VII) by means of $PdCl_2(PPh_3)_2$ and DIEA in DMF to give adduct (VIII). Further acid hydrolysis of the cyclic ketal of compound (VIII) yields aldehyde (IX), which is finally submitted to reductive amination with 2-(methanesulfonyl)ethylamine (X) in the presence of sodium triacetoxyborohydride (1). Scheme 1.

Introduction

Receptor tyrosine kinases (RTKs) constitute a superfamily of proteins with intrinsic protein kinase activity (2). RTKs are involved in the regulation of numerous cell processes, including cell growth, differentiation and metabolic responses. Dysregulated cell signaling associated with RTKs can lead to angiogenesis, cell proliferation, inhibition of apoptosis and finally to malignant neoplasms. Subclass I RTKs consist of the epidermal growth factor receptors (EGFRs) and comprise four members: EGFR (HER1, erbB-1), human epidermal growth factor-like receptor type 2 (HER2/*neu*, erbB-2), HER3 and HER4. EGFR and erbB-2 are particularly important because they have been implicated in a wide variety of human cancers (3).

EGFR is present in epithelial and stromal cells, as well as in glial cells and smooth muscle cells (4). It is considered a pleiotropic effector because of the wide spectrum of responses generated, even in the same cell. In eukaryotes, EGFR plays a critical role in wound healing. This function involves stimulation of mitogenesis, apoptosis, cell migration, differentiation and angiogenesis (5). These

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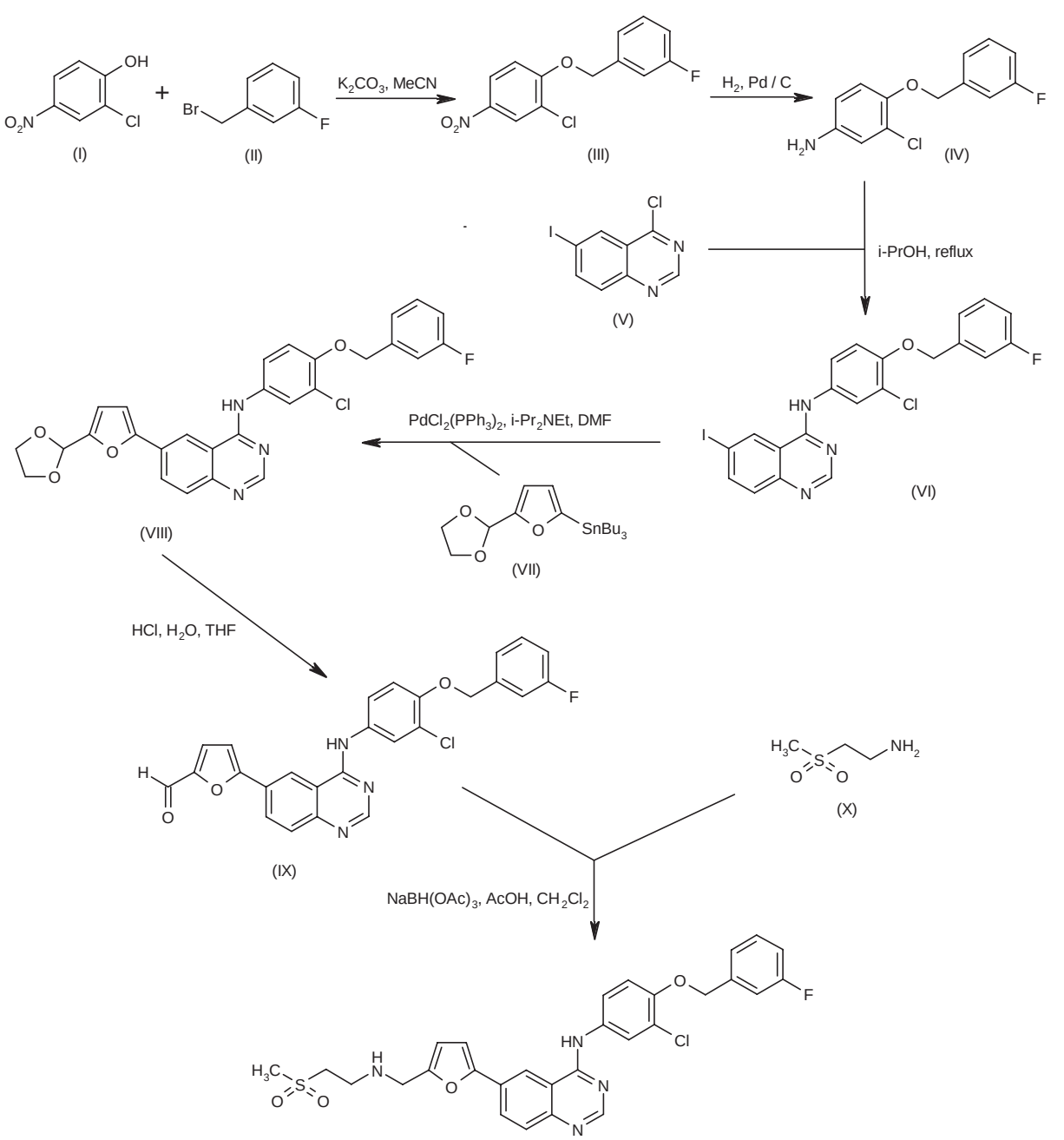
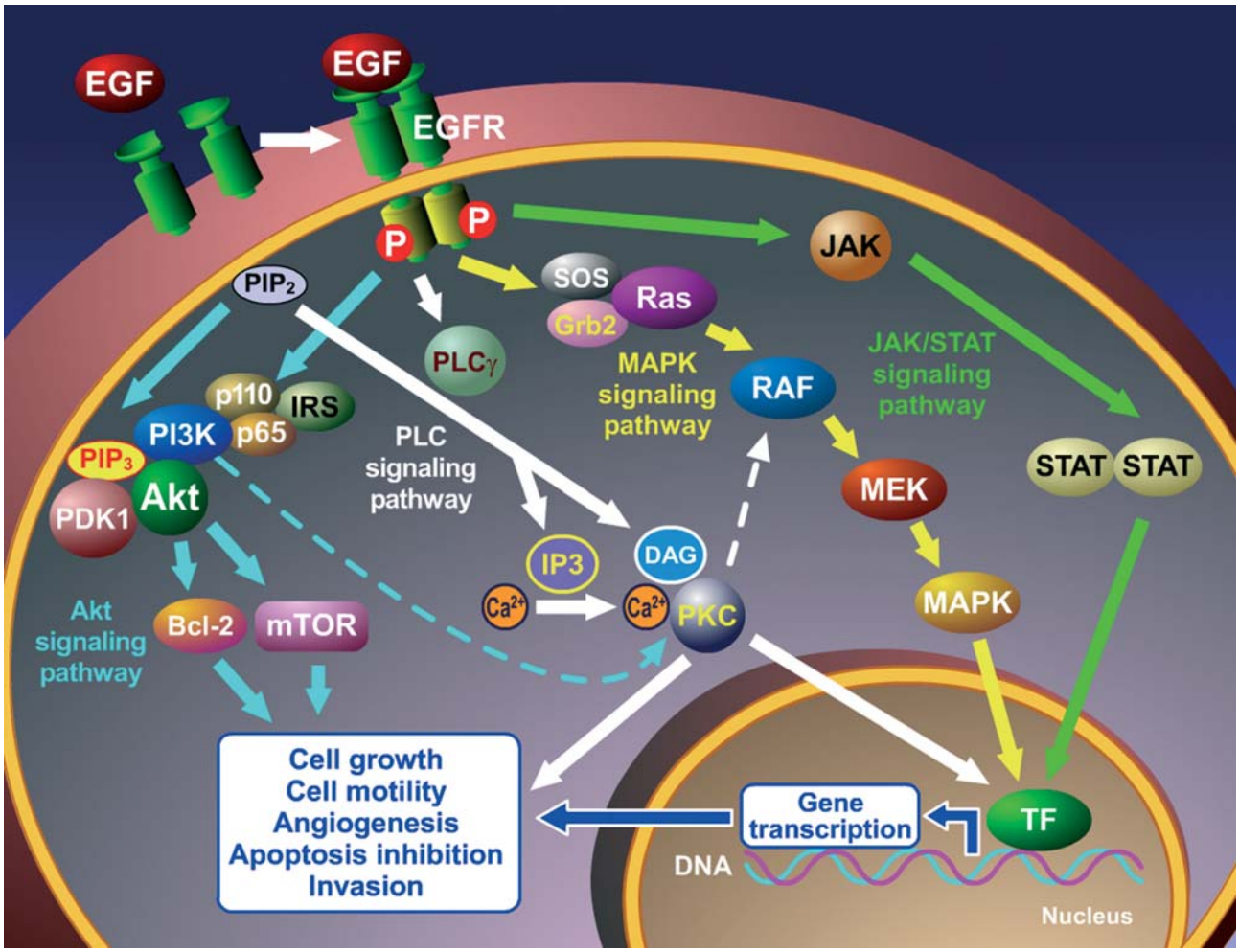
Scheme 1: Synthesis of Lapatinib



processes are also important in tumorigenesis, and several reports have described overexpression and mutations of EGFR in cancer (6, 7).

Ligands able to activate the EGFR are polypeptides known as growth factors, but other molecules, such as membrane proteins and extracellular matrix components, can also activate EGFR. Some known ligands of EGFR are EGF, tumor growth factor-α (TGF-α), amphiregulin, epiregulin and β-cellulin (8). After ligand binding, a conformational change is induced in the protein which causes receptor homo- or heterodimerization. The juxtaposition of the intracellular domains induces a second conformational change that activates the kinase activity of the molecule (9). Crossed autophosphorylation of tyrosine residues takes place, causing a third conformational change that induces specific binding of adaptor proteins, which activate numerous intracellular cascades of signal transduction events, identical for all RTKs (10). The



known signaling cascades associated with EGFR are: the mitogen-activated protein protein kinase (MAPK) pathway (11), the phospholipid pathway (12), the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway (13) and the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway (14). However, cross-talk between the different pathways exists. Figure 1 summarizes the signaling pathways and the cellular responses associated with EGFR activation.

The MAPK cascade is the most important signaling pathway triggered after EGFR activation. Signaling starts with the recruitment of the adaptor proteins growth-factor-receptor-bound protein 2 (Grb2) and son-of-sevenless (SOS) guanine nucleotide exchange factor. Grb2 is phosphorylated and forms a complex with SOS, allowing the recruitment of Ras, a small G-protein that possesses GTPase activity. A key step in the activation of Ras is the attachment of farnesiol from farnesyl pyrophosphate to the molecule, which is necessary for the translocation of the inactive Ras from the cytosol to the membrane. The membrane-bound Ras is then recruited to the Grb2-SOS complex and becomes activated through the release of bound GDP, which allows a GTP molecule to bind in its place. Activated Ras stimulates Raf protein, which in turn activates MAPK/ERK (extracellular signal-regulated protein kinase) kinase (MEK), followed by MAPK phosphorylation. Finally, MAPK translocates to the nucleus to activate transcription factors such as Elk-1, c-Myc or c-Jun, which play a role in the growth, differentiation and survival of cells (11).

Activated RTKs can also trigger the phospholipid pathway through the activation of different phospho-

Table I: EGFR inhibitors launched or under active clinical development.

Phase	Compound	Type	Source
L-2004	Erlotinib (Tarceva)	Small molecule	Roche/Genentech/OSI Pharmaceuticals
L-2003	Cetuximab (Erbitux)	Chimeric MAb	ImClone/Merck KGaA/Bristol-Myers Squibb
L-2002	Gefitinib (Iressa)	Small molecule	AstraZeneca
III	Panitumumab	Human MAb	Abgenix/Amgen
III	Vandetanib	Small molecule	AstraZeneca
II	CP-547632	Small molecule	Pfizer
II	Genistein	Small molecule	National Cancer Institute
II	Matuzumab	Humanized MAb	EMD Pharmaceuticals (Merck KGaA)
II	Nimotuzumab	Humanized MAb	Center of Molecular Immunology/YM BioSciences
I/II	HuMax-EGFr	Human MAb	Genmab
I	Pelitinib	Small molecule	National Cancer Institute
I	IMC-11F8	Human MAb	ImClone
I	INCB-7839	Small molecule	Incyte
I	RadioTheraCIM	Humanized MAb	YM BioSciences

Table II: erbB-2 inhibitors launched or under active clinical development.

Phase	Compound	Type	Source
L-1998	Trastuzumab (Herceptin)	Humanized MAb	Genentech/Roche
II	Pertuzumab	Humanized MAb	Genentech/Roche/National Cancer Institute
I/II	CP-724714	Small molecule	National Cancer Institute
I/II	Ertumaxomab	Chimeric bispecific MAb	Trion Pharma/Fresenius
I	HKI-272	Small molecule	Wyeth

lipases (PLC, PLA_2 or PLD). More precisely, active EGFR phosphorylates phospholipase Cγ (PLCγ), which mediates the elevation of intracellular calcium levels and the activation of protein kinase C (PKC), two key factors in the cytoskeletal rearrangement necessary for cell motility (12).

Alternatively, the PI3-K pathway is triggered when activated EGFR interacts with the proteins p65 and p110. This complex activates PI3-K, which in turn induces Akt-PIP3 (phosphatidylinositol-3,4,5-triphosphate) binding and activation. Activated Akt protein activates mTOR (mammalian target of rapamycin), which unfolds a series of events involving 4E-BP1/PHAS and mTOR, leading to the assembly of the mRNA and the ribosomal complex and to protein synthesis (13). Akt protein is also related to the regulation of the antiapoptotic protein Bcl-2 (15).

Finally, another signaling cascade associated with EGFR is the JAK/STAT pathway. STATs are transcription factors that are phosphorylated by JAK kinases in response to EGFR activation, which then dimerize and move into the nucleus to activate the transcription of responsive genes (14).

ErbB-2 has no known ligand. It can form heterodimers with EGFR and other ligand-bound members of the HER family, and it participates in, and hence amplifies, cell signaling. The structure of erbB-2 is different from the other HER family receptors. It has a fixed conformation that resembles the ligand-bound activated state. This particular structure makes erbB-2 the preferred partner for the other activated family receptors, including EGFR (16).

The cancer-favoring effect of dysfunctional EGFR and erbB-2 HER receptors is based on unbalanced system conditions, such as receptor overexpression, ligand overabundance or attenuated inhibitory control mechanisms. EGFR and its ligands are overexpressed in a number of solid tumors, including pancreatic, lung, ovarian, renal, gastric, hepatic and breast cancer (17). In the majority of epithelial tumors, upregulation of EGFR results from transcriptional activation (18). In some cancers, however, there is a high incidence of EGFR gene amplification, resulting in increased mRNA and protein expression levels (19). ErbB-2 overexpression appears to promote EGFR-mediated tumor progression (20), highlighting the importance of the cross-talk mechanism between the EGFR and erbB-2 receptors. ErbB-2 overexpression has been described in a wide variety of cancers, including breast, bladder, colorectal, gastric, ovarian, prostate, renal and uterine cancers, and others (21, 22). Moreover, a constitutively activated erbB-2 receptor can originate from oncogenic mutations, leading to active signal transduction without receptor dimerization or ligand binding (23).

The appeal of EGFR and erbB-2 as pharmacological targets is obvious. In order to impede receptor activation and the initiation of signal transduction events, several monoclonal antibodies that inhibit the receptor binding site and several small-molecule inhibitors that block the intracellular TK domain have been studied. Table I summarizes the EGFR inhibitors and Table II summarizes the erbB-2 inhibitors that are currently marketed or under active clinical development. However, epidemiological evidence implicates both EGFR and erbB-2 in a variety of tumor types. Moreover, the antitumor activity of EGFR TK inhibitors appears to be less effective in tumor cells that overexpresses EGFR and HER2 than in those that express either receptor alone (24). Thus, there is a rationale for developing multiple HER kinase inhibitors as more effective therapeutic strategies. Table III summa-

Table III: Dual EGFR/erbB-2 inhibitors under active clinical development.

Phase	Compound	Type	Source
III	Lapatinib	Small molecule	GlaxoSmithKline
I/II	AEE-788	Small molecule	Novartis
I	BMS-599626	Small molecule	Bristol-Myers Squibb
I	XL-647	Small molecule	Exelixis
IND filed	ARRY-334543	Small molecule	Array BioPharma

rizes the existing dual EGFR and erbB-2 inhibitors currently under active clinical development. The most advanced, lapatinib (GW-2016, GW-572016), is a potent and reversible inhibitor of both EGFR and erbB-2 tyrosine kinases that was identified and profiled as a potential new anticancer agent and advanced to clinical trials based on its favorable pharmacological and pharmacokinetic profile (25, 26). It is currently undergoing phase III clinical trials for the oral treatment of metastatic breast, head and neck, lung, gastric, renal and bladder cancer. The compound is also being evaluated in the treatment of brain, gallbladder, prostate, ovarian, endometrial and hepatobiliary cancers in collaboration with the National Cancer Institute (NCI). Lapatinib was granted fast track status by the FDA in 2005 for the treatment of refractory advanced or metastatic breast cancer patients who have documented erbB-2 overexpression and who have failed previous therapy (27).

Pharmacological Actions

Using a purified enzyme assay system consisting of recombinant human intracellular domains of each catalytically active erbB family member, it was found that, among a number of molecules tested, lapatinib was unique due to its equivalent potency against EGFR and erbB-2 (estimated K_i = 3 and 9 nM, respectively), as well as its slow off rate ($t_{1/2}$ > 2 h) for both of these tyrosine kinases (28).

The effect of lapatinib was evaluated using a number of normal and tumor-derived human cell lines *in vitro* and *in vivo*. Cell growth assays were performed in EGFR- or erbB-2-overexpressing HN5, A-431 (epidermoid carcinoma), BT-474, Calu-3 and NCI-N87 human tumor cell lines, as well as in normal HFF, nontumorigenic epithelial cells and non-EGFR/erbB-2-overexpressing tumor cells (MCF7 and T-47D). The tumor cell lines overexpressing EGFR and erbB-2 showed an average IC_{50} for growth inhibition of < 0.16 μM after 3 days of exposure to lapatinib. Moreover, lapatinib demonstrated a 100-fold greater average selectivity for tumor cells compared to normal HFF. Western blot analysis confirmed inhibition of EGFR and erbB-2 receptor autophosphorylation and phosphorylation of the downstream modulator Akt in the BT-474 and HN5 cell lines. The results from outgrowth assays involving treatment with lapatinib for 3 days in BT-474 and HN5 cell lines demonstrated that it prevented outgrowth for at least an additional 12 days after removal of the compound. Additional testing using bromodeoxyuridine incorporation and propidium iodide staining also showed growth arrest and cell death. Furthermore, lapatinib treatment at 30 and 100 mg/kg twice daily caused a dose-dependent inhibition of tumor xenograft growth (HN5 and BT-474 cells) in mice, with complete growth inhibition being achieved at the higher dose (29, 30).

Researchers explored the effects of lapatinib on erbB-2 signaling, cell growth and apoptosis in a rat biliary cancer cell line (C611B ChC) that constitutively overexpresses activated erbB-2, with lower expression of erbB-3, weak expression of erbB-1 and no expression of erbB-4. Lapatinib concentration-dependently induced growth arrest and cell death in these cells, and these effects correlated with a selective suppression of erbB-2 tyrosine phosphorylation. The compound also produced downstream effects on the Akt and extracellular signal-regulated kinase ERK1/2 signaling pathways. The apoptotic activity of lapatinib was related to the activation of caspase-3 and cleavage of polyADP-ribose polymerase (31).

The activity of lapatinib was assessed in 10 malignant pleural mesothelioma cell lines. Of these, only two (H2373 and H2452) responded to lapatinib with G1/S cell cycle arrest and growth inhibition. The IC_{50} values were 1.0 and 0.8 μM for the H2373 and H2452 cell lines, respectively. No differences were observed between the responsive and nonresponsive cell lines in terms of the presence or amount of erbB-1, phospho-erbB-1, phospho-erbB-2, erbB-3, erbB-4, phospho-Akt or Akt. Moreover, the ability of lapatinib to inhibit phospho-erbB-1 did not differ between the responsive and nonresponsive cell lines. Lapatinib treatment produced a time-dependent decrease in phospho-Akt and/or ERK1/2, as well as an increase in p27. The sensitive, but not the resistant, cell lines responded to a combination of lapatinib and inhibitors of other signaling pathways (U-0126, LY-294002 or rapamycin) with an increased inhibition of cell growth (32).

The great majority of pancreatic adenocarcinomas express EGFR and its ligands. Therefore, a study was designed to assess the effects of lapatinib in 6 pancreatic cancer cell lines showing variable expression of EGFR, HER2 and HER3 mRNA; HER4 mRNA levels were lower than those of the other EGFR family members. Lapatinib inhibited anchorage-dependent growth with an IC_{50} of 1.7-9.6 μM. Anchorage-independent growth, as determined in soft agar, was strongly inhibited by lapatinib in the 4 pancreatic cancer cell lines known to harbor condon-12 K-*ras* mutations. However, this was not observed in the cell lines with wild-type K-*ras* secondary to an inability to form colonies. The EGF- or heregulin-induced phosphorylation of Akt and p44/42 MAPK was markedly

inhibited by lapatinib, although baseline MAPK phosphorylation did not show a similar response (33).

Experiments using a panel of breast cancer cell lines overexpressing HER2 or EGFR found that lapatinib had especially potent inhibitory effects in the cell lines overexpressing HER2. The effects of lapatinib were examined in the following breast cancer cell lines: MDA-MB-453, MDA-MB-361, SK-BR-3 and BT-474 (which overexpress HER2) and BT-20 and MDA-MB-231 (which overexpress EGFR). The IC_{50} values were 0.27 μM for MDA-MB-453, 0.26 μM for MDA-MB-361, 0.31 μM for SK-BR-3, 0.006 μM for BT-474, 11.4 μM for MDA-MB-231 and 20.9 μM for BT-20. Lapatinib caused a concentration- and time-dependent decrease in basal tyrosine phosphorylation, which was associated with growth inhibition. The maximal growth inhibition produced by lapatinib in HER2-positive breast cancer cell lines was significantly greater than that seen with trastuzumab in these same cell lines. Specifically, the percent inhibitions observed for lapatinib and trastuzumab were: 65% *vs.* 40% for MDA-MB-453; 70% *vs.* 45% for MDA-MB-361; 85% *vs.* 35% for SK-BR-3; and 95% *vs.* 50% for BT-474, respectively. Synergistic interactions at clinically relevant concentrations were seen for lapatinib in combination with carboplatin, docetaxel and trastuzumab in MDA-MB-453, MDA-MB-361 and BT-474 cell lines. The combination of lapatinib with doxorubicin led to additive cytotoxic effects (34).

The results from another study also found lapatinib to be particularly active against HER2-positive breast cancer cells, as well as against trastuzumab-conditioned breast cancer cells. This study tested the effects of lapatinib against a panel of 35 human breast cancer cell lines, including 6 engineered HER2-overexpressing cell lines and 4 trastuzumab-conditioned cell lines. Lapatinib induced a time- and concentration-dependent inhibition of both basal and ligand-stimulated receptor phosphorylation of EGFR, HER2, Akt and ERK. In addition, at nanomolar concentrations it caused growth inhibition in HER2-positive breast cancer cells. In contrast, higher concentrations (1-20 μM) were required to inhibit growth in cell lines with elevated EGFR levels or normal HER2/EGFR expression. Among the 6 cell lines engineered to overexpress HER2, 5 exhibited increased sensitivity to lapatinib as compared to the nonoverexpressing parental controls. In trastuzumab-conditioned breast cancer cell lines (MDA-MB-361 and MCF7/HER2), treatment with lapatinib effectively inhibited cell growth *in vitro* at concentrations comparable to those required to inhibit cells never exposed to trastuzumab (35).

In order to test the hypothesis that blockade of both HER2/*neu* and Bcl-2 might lead to increased apoptosis, researchers studied the effects of combining lapatinib and the Bcl-2 inhibitor HA-14-1 in 3 human breast cancer cell lines. Both lapatinib (1-10 μM) and HA-14-1 (1-10 μM) inhibited cell growth in MCF7 cells, in an HER2/*neu*-transfected MCF7 cell line and in a tamoxifen-resistant MCF7 cell line. Furthermore, combination of both compounds had a synergistic inhibitory effect in all breast cancer cell lines tested (36).

Synergistic apoptotic effects were observed in erbB-2-overexpressing human breast cancer BT-474 and SK-BR-3 cells after the combined use of lapatinib and the anti-erbB-2 antibody trastuzumab or antisera from rabbits vaccinated with a human erbB-2 fusion protein. Following treatment with lapatinib, trastuzumab or the antisera at sublethal concentrations, apoptosis remained relatively unchanged. However, the combination of lapatinib with either trastuzumab or antisera led to a marked downregulation in survivin protein, with a consequent increase in apoptosis (37, 38).

In BT-474 breast cancer cells and tumor xenografts, lapatinib inhibited baseline $p95^{erbB-2}$ phosphorylation. A reduction in downstream phospho-ERK1/2, phospho-Akt and cyclin D steady-state protein levels followed lapatinib-induced inhibition of $p95^{erbB-2}$, $p185^{erbB-2}$ and erbB-1 phosphorylation. Lapatinib also inhibited heregulin-stimulated phosphorylation of $p95^{erbB-2}$ and Akt. Trastuzumab, in contrast, had no inhibitory effects on $p95^{erbB-2}$ phosphorylation or on the expression of downstream phospho-ERK1/2, phospho-Akt or cyclin D (39).

The antiproliferative and radiosensitizing effects of lapatanib were determined in 4 primary human breast cancer cell lines with endogenous EGFR or HER2 overexpression (SUM149, SUM102, SUM225 and SUM185) and in an HER2-transfected cell line (H16N2-HER2). All 5 cell lines exhibited a reduction in constitutive and/or ligand-induced EGFR or HER2 tyrosine phosphorylation after exposure to lapatinib, which correlated with reduced proliferation in 4 of the 5 cell lines tested. In EGFR-overexpressing cell lines, lapatinib produced radiosensitization. HER2-overexpressing cells, however, lost their colony-forming ability after only a brief exposure to lapatinib and could not be tested for radiosensitization. In SUM185 cells, lapatinib inhibited HER2 phosphorylation but it did not inhibit growth or induce radiosensitization. Further testing revealed that downstream ERK and Akt activation was not inhibited by lapatinib in these cells, in contrast to the sensitive HER2-overexpressing cell lines (40).

Further experiments were conducted to investigate the signaling pathways associated with the lapatinib-enhanced radiosensitization of EGFR-overexpressing breast cancer cells. In this study, SUM102 and SUM149 cell lines were exposed to 30 min of lapatinib, U-0126 (an MEK inhibitor) or LY-294002 (a PI3-K inhibitor). Results from this study showed that lapatinib inhibited ERK phosphorylation, EGF-induced but not constitutive STAT-3 phosphorylation and EGF-induced JNK phosphorylation. In contrast, the strong constitutive activation of p38 in SUM149 cells was not greatly affected by lapatinib exposure, and SUM102 cells exhibited minimal EGF-induced p38 phosphorylation. U-0126 produced radiosensitization similar to that produced by lapatinib. However, since U-0126 and lapatinib inhibited both ERK and JNK signaling, it is unclear whether the radiosensitizing effects were due to ERK or JNK inhibition. The PI3-K/Akt pathway did not appear to be involved, as evidenced by the fact that lapatinib did not affect Akt activation and LY-294002-induced PI3-K inhibition did not alter radiosensitivity (41).

Results from other experiments in rat intestinal ephithelial RIE-1 cells indicated that lapatinib may be useful for radiosensitizing tumors where resistance to radiation is mediated by Ras-driven autocrine signaling through the EGFR (42).

The addition of a PI3-K/Akt kinase inhibitor (LY-294002) to lapatinib had synergistic effects on apoptosis in HN5 and a number of other human tumor cell lines (43).

Lapatinib may have potential utility as an adjunct to systemic combination chemotherapy in bladder cancer according to recent studies. RT112 and J82 bladder cancer cells were treated with EGF, heregulin or combined cisplatin, paclitaxel and gemcitabine with or without lapatinib pretreatment. Pretreatment with lapatinib inhibited EGF- and heregulin-induced activation of erbB signaling, as well as combination chemotherapy-induced activation of erbB-1 and erbB-3 in both cell lines. Akt activation in RT112 cells was also inhibited by lapatinib pretreatment, although MAPK activation in J82 cells was unaffected (44).

In similar experiments using RT112 bladder cancer cells, researchers evaluated the effects of treatment with either EGF, lapatinib or lapatinib followed by EGF. The EGF-stimulated activation of erbB-1, erbB-2, p42/44 MAPK and Akt was reduced by lapatinib pretreatment. Lapatinib treatment alone also markedly reduced the activation of these proteins. Thus, this compound may represent a novel tool for improving chemosensitization in advanced bladder cancer (45, 46).

Two studies examined the effects of lapatinib on EGF-induced receptor tyrosine autophosphorylation and downstream signaling pathways *in vitro* and *in vivo*. The effects of lapatinib on tumor cell growth and downstream signaling pathways were studied using a nontransformed human mammary epithelial line (HB4a), HB4a cells transfected with erbB-2 (HB4a-s1 or HB4a-s9), a human tumor cell line overexpressing erbB-2 (BT-474) and a human tumor cell line overexpressing EGFR (HN5). The erbB-2 or EGFR tyrosine autophosphorylation induced by EGF was strongly inhibited by lapatinib in a concentration-dependent manner, which resulted in a concomitant reduction in downstream MAPK and Akt activation. Furthermore, *in vivo* studies involving BT-474 and HN5 tumor xenografts found that lapatinib inhibited both tumor growth and receptor tyrosine autophosphorylation in a dose-dependent, parallel manner. Maximal lapatinib-induced receptor autophosphorylation in these xenografts was associated with the inhibition of MAPK as well (47, 48).

In another study investigating the activity of lapatinib in EGFR- and erbB-2-dependent tumor cell lines, researchers demonstrated that it potently inhibits tyrosine phosphorylation of both EGFR and erbB-2, as well as downstream ERK1/2 and Akt activation. In cells overexpressing erbB-2, complete inhibition of activated erbB-2 was associated with a 23-fold increase in apoptosis as compared to vehicle-treated controls. These inhibitory effects were not reversed by EGF. *In vivo* testing confirmed these results in human tumor xenografts, with lapatinib treatment resulting in inhibition of the activation of EGFR, erbB-2, ERK1/2 and Akt. These findings suggested that ERK1/2 and Akt may serve as biomarkers for determining the clinical efficacy of lapatinib, and also that lapatinib may be useful as monotherapy or as an adjunct to other chemotherapeutic agents in the treatment of EGFR- or erbB-2-dependent tumors (49).

Three xenograft models (BT-474, HN5 and NCI-H322) were used to determine the effects of combination therapy involving lapatinib together with paclitaxel, carboplatin, doxorubicin or vinorelbine. The chemotherapeutic agents were tested at or near the maximum tolerated dose (MTD) and also at reduced dose levels. All three xenograft models responded to treatment with lapatinib, and the combination therapies were generally well tolerated. The fact that the response to lapatinib in combination with any of the agents tested lacked consistency across the panel of tumors studied suggests that any one single model is unlikely to be predictive of clinical therapeutic outcome. The combination of lapatinib with paclitaxel offered the best results, with a significantly improved response compared to either agent alone observed in both the BT-474 and NCI-H322 xenograft models. The lapatinib-vinorelbine combination (with a dose reduction in order to avoid the weight loss observed at higher doses) also produced a favorable response in the BT-474 model relative to either agent alone (50, 51).

Since antiestrogen-resistant breast cancers frequently exhibit increased expression of erbB-1 and erbB-2, researchers designed a study to determine whether the dual inhibitor lapatinib could restore tamoxifen sensitivity in estrogen receptor-positive, tamoxifen-resistant breast cancer models. Single-agent treatment with lapatinib or tamoxifen in MCF7^{pr}, T-47D and ZR-75 cells induced incomplete cell cycle arrest. However, used in combination, the two drugs produced a more rapid and complete cell cycle arrest in all 3 cell lines. Lapatinib inhibited MAPK and protein kinase B (PKB), as well as estrogen-stimulated estrogen receptor transcriptional activity. The combination of tamoxifen and lapatinib led to a more pronounced reduction in cyclin D, a greater increase in p27, a more pronounced inhibition of cyclin E/CDK2 and a greater reduction in estrogen receptor-dependent transcription than either drug used alone (52).

A tamoxifen-resistant tumor xenograft (MCF-TAMR) derived from the human breast cancer MCF7 cell line was used to assess the effects of lapatinib. Following treatment with tamoxifen, nude mice received either vehicle or lapatinib at a dose of 100 mg/kg administered by oral gavage once daily for 60 days. Three (23%) animals from the lapatinib-treated group showed complete tumor regressions, as compared to no animals in the vehicle-treated group. In addition, lapatinib-treated animals showed a significant delay in tumor growth as compared to placebo (time to reach 5 x the initial tumor volume > 34 days *vs.* 25 days) and a significantly smaller increase in tumor volume (4.5% *vs.* 9.9% median volume change). No toxicity was observed. The increased HER2 expression observed

in MCF-TAMR cells was inhibited by lapatinib treatment, as was the activation of downstream survival and/or proliferative pathways such as the ERK1/2 pathway, and VEGF expression (53).

Using the EGFR-positive human head and neck HN5 cancer xenograft model, researchers found that lapatinib exerted strong tumor growth-inhibitory activity. In this study, animals received lapatinib at a dose of 30 or 100 mg/kg b.i.d. for 21 days. Results for the higher dose showed an average 101 ± 20% inhibition in tumor growth, with tumor regression of > 25% occurring in 45% of the treated animals. The lower dose resulted in an average 34 ± 28% growth reduction, with tumor regressions occurring in 18.7% of the study animals. Steady-state plasma concentrations of lapatinib were dose-proportional and associated with antitumor activity, according to results from a parallel pharmacokinetic study. No toxicity was observed at the doses tested. The antitumor activity of lapatinib in HN5 cells appeared to be related to its inhibitory effects on EGFR tyrosine kinase activation (54).

Lapatinib was also found to inhibit tumor growth in the erbB-2-overexpressing ductal breast cancer BT-474 xenograft model. This study also involved treatment with 30 or 100 mg/kg of lapatinib b.i.d. for 21 days. The average inhibition in tumor growth was 94 ± 18% for the high dose and 42 ± 35% for the low dose. Tumors regressed by > 25% in 17.5% of the animals at the higher dose, but no regressions were observed at the lower dose. Lapatinib did not appear to be toxic at the doses tested. The antitumor activity of lapatinib again appeared to be due to inhibition of receptor tyrosine kinase autophosphorylation (55).

Pharmacokinetics

Following oral administration of lapatinib to female SCID mice bearing BT-474 tumors, testing was conducted to determine the compound's pharmacokinetics and pharmacodynamics. The $t_{1/2}$ values after administration of a single dose of lapatinib ranged from 2.1 h in blood to 16 h in liver. Dosing to steady state produced a general increase in $t_{1/2}$ values to 2.9 h in blood and 60 h in liver. Tumor tissue exhibited mean residence time values of 11.4-19.3 h, as compared to values of 3.2-9.8 h in other tissues. AUC and C_{max} values showed an increase that was greater than dose-proportional, and steady-state AUC_{tissue}/AUC_{blood} ratios were 4.4-5.6 for tumor and 7.8-14.1 for liver and kidney. Lapatinib administration produced a dose-dependent decrease in receptor phosphorylation also related to tumor and blood drug concentrations (56).

Two phase I studies assessed the pharmacokinetics of single and multiple oral doses of lapatinib in healthy individuals. The single-dose study examined the safety, tolerability and pharmacokinetics of lapatinib using a randomized, double-blind, placebo-controlled, ascending-dose, crossover study design in 16 healthy volunteers. Lapatinib doses ranged from 10 to 250 mg in this study, and all dose levels were well tolerated. An average lag time of 15 min was observed before lapatinib was absorbed in serum. Peak serum concentrations were achieved at a median of 3 h postdosing and ranged between 11 ng/ml at the dose of 10 mg and 317 ng/ml at the dose of 250 mg. The half-life showed a slight increase from 6 to 9 h with increasing dose, and the serum AUC showed an approximately dose-proportional increase. The multiple-dose study assessed the pharmacokinetics and pharmacodynamics of lapatinib in 27 healthy volunteers who received 8 daily doses of either lapatinib (25, 100 or 175 mg) or placebo. Lapatinib was well tolerated in this randomized, double-blind, parallel, ascending-dose study. Following administration of multiple doses of lapatinib, serum concentrations showed no significant accumulation at the lowest dose. However, a 50% accumulation was observed at the higher doses, with steady state being reached in 6-7 days. In addition, multiple doses of lapatinib also produced a modest time-dependent increase in serum concentrations. An average half-life of 8 h was observed. Based on these phase I results, it was concluded that single and multiple oral doses of lapatinib were associated with dose-related systemic exposure (57-59).

The effects of food on the pharmacokinetics of lapatinib were evaluated in healthy volunteers. In a randomized, crossover study, lapatinib was administered to 19 healthy volunteers after either an overnight fast or a high-fat breakfast. Following food, lapatinib administration was associated with an approximately 60% increase in serum AUC (1136 to 1867 ng.h/ml) and C_{max} (92 to 151 ng/ml). In contrast, median time to achieve peak concentrations (4 h) and geometric mean half-life (10 h) were not altered by food consumption (60).

An ascending-dose phase I study in 39 cancer patients evaluated the pharmacokinetics of lapatinib administered at doses of 175, 375, 675, 900, 1200, 1600 or 1800 mg once daily or 900 mg twice daily for 14 days. Treatment was continued past day 14 until the occurrence of unacceptable toxicity, disease progression or patient/physician request. A dose-proportional increase in serum AUC and C_{max} was observed, and an approximately 60% accumulation in AUC was recorded over the 14 days of continuous dosing. Absorption occurred after a short lag time, and peak plasma concentrations were achieved 4 h after lapatinib administration. Once- and twice-daily dosing produced similar pharmacokinetics. These results were consistent with the findings from previous studies in healthy subjects receiving lower doses of the study drug for a shorter length of time (61).

Clinical Studies

Combination therapy with lapatinib and trastuzumab, two erbB-2-targeted therapies that act at different sites of the receptor and have distinct mechanisms of action, was assessed in an open-label phase I study in heavily pretreated breast cancer patients. In this study, 48 patients were treated with escalating doses of lapatinib (750-1500 mg) and weekly standard doses of trastuzumab (4 mg/kg

loading dose followed by weekly 2 mg/kg infusions). A total of 152 treatment periods lasting 4 weeks each were completed. The most frequent toxicities were grade 1-3 diarrhea, anorexia, fatigue and rash. Assessment of clinical response for the 27 evaluable patients using RECIST (Response Evaluation Criteria in Solid Tumors) criteria showed 1 complete response of 8 months' duration, 5 partial responses of 2-7 months' duration, 10 patients with stable disease of 1-5 months' duration and 11 cases of progressive disease. The researchers selected the dose of 1000 mg of lapatinib plus the standard dose of trastuzumab as the best regimen for patients with erbB-2-overexpressing breast cancer due to its clinical activity and favorable tolerability (62, 63). Results from this and the following clinical studies are shown in Table IV.

A phase I escalating-dose study evaluated the use of lapatinib in patients with solid tumors. Lapatinib was administered at doses of 175-1800 mg once daily or at a dose of 900 mg twice daily. Evaluation was performed monthly and patients were continued on therapy until disease progression or unacceptable toxicity. A total of 45 patients participated in the study. In the cohorts receiving once-daily treatment with lapatinib, the most frequent adverse events were grade 1-2 rash, diarrhea, nausea, vomiting, constipation, fatigue and anorexia, with no grade 3 toxicities being observed. However, 2 of the 6 patients receiving 900 mg of lapatinib twice daily required dose reductions due to grade 3 diarrhea. Disease stabilization of more than 4 months' duration was obtained in 8 patients with a variety of solid tumors, and 2 patients with gefitinib-resistant non-small cell lung cancer had minor responses (64).

Another phase I study in heavily pretreated cancer patients assessed lapatinib's safety, pharmacokinetics and clinical activity. In this study, 67 patients with erbB-1-expressing and/or erbB-2-overexpressing metastatic solid tumors received daily oral dosing with lapatinib. Results showed that lapatinib was well tolerated at once-daily doses of 500-1600 mg/kg. Diarrhea (42%) and rash (31%) were the most frequently reported drug-related adverse effects, with the incidence of diarrhea being correlated with increasing dose and the incidence of rash being independent of dose. No grade 4 adverse events were observed, but 4 patients experienced 5 grade 3

Table IV: Clinical studies of lapatinib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Cancer, breast	Open	Lapatinib, 750 mg/d + Trastuzumab, 4 mg/kg i.v. → 2 mg/kg i.v. 1x/wk Lapatinib, 1000 mg/d + Trastuzumab, 4 mg/kg i.v. → 2 mg/kg i.v. 1x/wk Lapatinib, 1250 mg/d + Trastuzumab, 4 mg/kg i.v. → 2 mg/kg i.v. 1x/wk Lapatinib, 1500 mg/d + Trastuzumab, 4 mg/kg i.v. → 2 mg/kg i.v. 1x/wk	48	The combination of lapatinib plus trastuzumab was well tolerated and induced complete response, partial response or stable disease in 16 of 27 evaluable patients with advanced cancer. The optimal dose was 1000 mg/d of lapatinib plus standard-dose trastuzumab	62, 63
Cancer	Open	Lapatinib, 175 mg p.o. o.d. (n=3) Lapatinib, 375 mg p.o. o.d. (n=3) Lapatinib, 675 mg p.o. o.d. (n=4) Lapatinib, 900 mg p.o. o.d. (n=4) Lapatinib, 1200 mg p.o. o.d. (n=6) Lapatinib, 1600 mg p.o. o.d. (n=4) Lapatinib, 1800 mg p.o. o.d. (n=9) Lapatinib, 900 mg p.o. b.i.d. (n=6)	39	Oral lapatinib administered once daily was well tolerated and showed antitumor activity in heavily pretreated patients with solid tumors	64
Cancer, metastatic	Randomized	Lapatinib, 500 mg p.o. o.d. x 21 d (n=13) Lapatinib, 650 mg p.o. o.d. x 21 d (n=15) Lapatinib, 900 mg p.o. o.d. x 21 d (n=11) Lapatinib, 1000 mg p.o. o.d. x 21 d (n=3) Lapatinib, 1200 mg p.o. o.d. x 21 d (n=12) Lapatinib, 1600 mg p.o. o.d. x 21 d (n=13)	67	Lapatinib was well tolerated at doses up to 1600 mg/d and induced partial responses and prolonged stable disease in 4 and 10 heavily pretreated patients with metastatic solid tumors, respectively, including trastuzumab-resistant metastatic breast cancer. Biological activity was demonstrated by inhibition of activated phospho-Akt and ERK1/2 and cyclin D expression in tumors	65-67
Cancer	Open	Lapatinib, 1250 mg/d p.o. o.d. + Capecitabine, 1500 mg/m2/d b.i.d. x 14 d 1x/21 d Lapatinib, 1250 mg/d p.o. o.d. + Capecitabine, 2000 mg/m2/d b.i.d. x 14 d 1x/21 d Lapatinib, 1500 mg/d p.o. o.d. + Capecitabine, 2000 mg/m2/d b.i.d. x 14 d 1x/21 d	26	The combination of lapatinib plus capecitabine was well tolerated and induced partial responses in 2 patients with gastric carcinoma and squamous cell carcinoma of the skin, a minor response in 1 patient with breast cancer and stable disease in 9 other patients with cancer. The maximum tolerated dose was lapatinib 1250 mg/d p.o. o.d. plus capecitabine 2000 mg/m^2/d b.i.d.	68, 69

continuation

Table IV: Clinical studies of lapatinib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Cancer	Open	Lapatinib, 1250 mg/d + Letrozole, 2.5 mg/d x 4 wks (n=4) Lapatinib, 1500 mg/d + Letrozole, 2.5 mg/d x 4 wks (n=32)	36	The combination of lapatinib plus letrozole was well tolerated and produced stable disease in 4 and a partial response in 1 patient with advanced breast cancer and other tumors	70, 71
Cancer	Open	Lapatinib, 1250 mg p.o. o.d. + Paclitaxel, 135 mg/m2 i.v. 1x/3 wks Lapatinib, 1250 mg p.o. o.d. + Paclitaxel, 175 mg/m2 i.v. 1x/3 wks Lapatinib, 1250 mg p.o. o.d. + Paclitaxel, 200 mg/m2 i.v. 1x/3 wks Lapatinib, 1500 mg/d p.o. + Paclitaxel, 175 mg/m2 1x/3 wks Lapatinib, 1500 mg/d p.o. + Paclitaxel, 225 mg/m2 1x/3 wks Lapatinib, 1500 mg/d p.o. + Paclitaxel, 80 mg/m2 1x/wk x 3 wks 1x/4 wks	48	Lapatinib combined with paclitaxel given once weekly or once every 3 weeks was well tolerated and induced antitumor effects in heavily pretreated patients with cancer, particularly breast cancer	72, 73
Cancer	Open	Lapatinib, 1000 mg p.o. o.d. + 5-Fluorouracil + Leucovorin + Irinotecan 1x/14 d Lapatinib, 1250 mg p.o. o.d. + 5- Fluorouracil + Leucovorin + Irinotecan 1x/14 d	25	The combination of lapatinib plus irinotecan, 5-fluorouracil and leucovorin was well tolerated and effective in inducing partial responses lasting for 1-6 months in 4 patients and stable disease lasting for 1-4 months in 10 patients with cancer	74
Cancer, breast metastatic	Open Multicenter	Lapatinib, 1250 mg p.o. o.d. (n=13) Lapatinib, 1500 mg p.o. o.d. (n=28)	41	Monotherapy with 1500 mg of lapatinib was well tolerated and effective in inducing antitumor effects in patients with metastatic breast cancer overexpressing erbB-2 and unresponsive to trastuzumab-containing regimens	75, 76
Cancer, colorectal metastatic	Open Multicenter	Lapatinib, 1250 mg/d p.o.	86	Lapatinib was generally well tolerated but was not effective as second-line monotherapy in patients with recurrent metastatic colorectal cancer	77, 78
Cancer, transitional cell carcinoma of the urothelial tract	Open Multicenter	Lapatinib, 1250 mg p.o. o.d. until disease progression or withdrawal	59	Lapatinib was generally well tolerated but demonstrated no significant antitumor activity in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract	79, 80
Cancer, breast	Randomized Open	Lapatinib, 500 mg/d p.o. b.i.d. Lapatinib, 1500 mg/d p.o. o.d.	13	Monotherapy with lapatinib induced a partial response in 38% and stable disease for at least 8 weeks in 46.2% of patients with advanced or metastatic breast cancer	81

drug-related gastrointestinal disturbances or rash. Partial responses were reported for 4 patients with trastuzumab-resistant metastatic breast cancer, and disease stabilization occurred in 24 patients with other cancer types. Of the patients experiencing disease stabilization, 10 continued lapatinib therapy for 6 months or more. Tumor cell apoptosis and regression of metastasis were associated with inhibited activation of phospho-Akt within the tumor. Furthermore, clinical response to lapatinib was predictable by measuring the inhibited intratumor expression of activated ERK1/2 and cyclin D protein. The absence of biological response to lapatinib therapy generally correlated with disease progression. Nevertheless, lapatinib-induced changes in phospho-Akt, phospho-ERK1/2 and cyclin D protein only partially correlated with disease regression, a finding which highlights the need to identify other biomarkers of lapatinib activity (65-67).

The safety and tolerability of lapatinib in combination with capecitabine were assessed in a phase I trial. In this study, lapatinib was administered orally once daily and capecitabine was administered twice daily for 14 days every 21 days. After starting doses of 1250 mg/day for lapatinib and 1500 mg/m^2/day for capecitabine, doses were escalated for both drugs and the MTD was determined. At the time of reporting, a total of 26 patients had been enrolled (18 in the dose-escalation study and 8 in the pharmacokinetic study). In the cohort treated with 1250 mg/day lapatinib and 2000 mg/m^2/day capecitabine,

1 of the 8 patients had dose-limiting toxicities consisting of grade 3 mucositis, fatigue and anorexia. Dose-limiting toxicities consisting of grade 3 skin rash and grade 3 diarrhea were observed during the first treatment cycle in 2 of the 7 patients receiving 1500 mg/day lapatinib and 2000 mg/m^2/day capecitabine. Mild to moderate nausea, vomiting, fatigue, anorexia, neutropenia, anemia, elevation in liver enzymes and creatinine, and grade 2 or less hand-foot syndrome were also reported. Based on these results, the MTD of this combination therapy was determined to be 1250 mg/day lapatinib and 2000 mg/m^2/day capecitabine. No additional dose-limiting toxicities were observed in the 8 patients from the pharmacokinetic study receiving this dose. Confirmed partial responses were obtained in 1 patient with gastric carcinoma and 1 patient with squamous cell carcinoma of the skin. In addition, 1 patient with breast cancer had a minor response and 9 patients experienced disease stabilization (68, 69).

The use of lapatinib in combination with letrozole was investigated in an open-label phase I study in patients with estrogen receptor-positive or progesterone receptor-positive advanced breast cancer or other forms of cancer likely to respond to this combination. Lapatinib was administered at escalating doses of 1250 or 1500 mg/day and letrozole was given at 2.5 mg/day. The 36 participants received a total of 123 treatment courses of 4 weeks per course. A single case of grade 3 diarrhea in a patient receiving the higher dose of lapatinib was the only dose-limiting toxicity reported. The most common non-hematological toxicities were grade 1/2 diarrhea, nausea, rash and fatigue. Of the 36 evaluable patients, 2 breast cancer patients and 2 ovarian cancer patients experienced stable disease of > 5 months' duration and 1 endometrial cancer patient had a partial response. The optimally tolerated regimen was established at 1500 mg/day lapatinib and 2.5 mg/day letrozole (70, 71).

Another phase I dose-escalation study assessed the activity of lapatinib in combination with paclitaxel in cancer patients with tumors overexpressing EGFR and/or erbB-2. Initial results were reported from 12 patients who had received a total of over 42 treatment cycles. At dose level 1, paclitaxel was administered at 135 mg/m^2 i.v. on day 1 every 3 weeks, and lapatinib was given at a dose of 1250 mg/day. Treatment at this dose level was administered to a total of 6 patients, 1 of whom experienced disease-related hepatic failure. No other dose-limiting toxicities were observed at this dose level or at doses of 175 or 200 mg/m^2 paclitaxel. Of 3 patients with taxane-resistant metastatic breast cancer, 2 experienced objective responses. In addition, disease stabilization of over 7 months' duration was obtained in a patient with esophageal cancer, and stable disease lasting more than 5 months and more than 3 months was observed in 2 patients with colon cancer. The combination of lapatinib 1500 mg/day and paclitaxel 225 mg/m^2, however, was associated with dose-limiting diarrhea and cumulative neuropathy was reported following multiple doses of paclitaxel of 200 mg/m^2 and above. Therefore, the optimally tolerated regimen was established to be 1500 mg/day lapatinib plus 175 mg/m^2 paclitaxel. The protocol was subsequently amended to include a weekly schedule of paclitaxel (lapatinib 1500 mg/day + paclitaxel 80 mg/m^2/week x 3 weeks). Safety and tolerability data for a total of 48 patients treated with either schedule of paclitaxel revealed no unexpected toxicities. However, the toxicities reported for the combination therapy, including neuropathy, diarrhea, rash and myalgias, were more intense than those reported in other studies involving either lapatinib or paclitaxel alone. Weekly therapy with paclitaxel was also associated with alopecia. Of the 9 heavily pretreated patients with breast cancer enrolled, 6 responses were obtained (72, 73).

Lapatinib was also tested in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (FOLFIRI) in patients with solid tumors. In this phase I study evaluating the safety, tolerability and pharmacokinetics of the combination, a total of 25 patients received lapatinib at 1000 or 1250 mg/day plus FOLFIRI at 80% or 60% of the standard doses every 14 days. The optimally tolerated regimen was found to be lapatinib 1250 mg plus irinotecan 120 mg/m^2, 5-FU 240 mg/m^2 by bolus and 360 mg/m^2 by infusion, and leucovorin 200 mg/m^2 on days 1 and 2, every 14 days. Grade 1 or 2 diarrhea, nausea and vomiting, fatigue, alopecia, anorexia, mucositis, constipation, weight loss and headache were the most common non-hematological toxicities at the optimally tolerated regimen. The combination therapy resulted in a 50% increase in the levels of the SN-38 metabolite of irinotecan, a 30% higher C_{max} and a 14% higher AUC for lapatinib. Partial responses lasting for 1-6 months were obtained in 4 patients, and disease stabilization lasting for 1-4 months was achieved in 10 patients. Based on these results, the researchers concluded that lapatinib can be used in combination with FOLFIRI, but only after dose reductions of both lapatinib and FOLFIRI due to altered pharmacokinetics and toxicity with the combination. Pancreatic and hepatic tumors appeared to be especially responsive to this combination (74).

A multicenter, open-label phase II study revealed that lapatinib, administered at a dose of 1500 mg/day, appeared to have some efficacy in patients with erbB-2-overexpressing metastatic breast cancer refractory to trastuzumab-containing regimens. After 13 initial treatments with a dose of 1250 mg daily, the study was amended and the dose changed to 1500 mg daily. As determined by RECIST criteria, preliminary results on the first 41 patients showed 1 complete response, 3 partial responses and 15 cases of stable disease. The combined efficacy data for these patients yielded a 46.3% response rate for at least the first 8 weeks, and progression-free survival of at least 16 weeks was observed in 12 (29.3%) of these patients. Adverse events reported for the first 41 patients evaluated included rash in 37%, fatigue in 34%, diarrhea in 27%, nausea in 24%, anorexia in 15% and vomiting in 12%. Grade 3-4 toxicities included grade 3 rash in 1 patient, grade 3 fatigue in 2 patients and grade 3 diarrhea in 4 patients. In addition, 1 patient exhibited asymptomatic, transient decrease in cardiac ejection fraction (75, 76).

A multicenter, open-label phase II study was conducted to evaluate the safety and efficacy of oral lapatinib 1250 mg daily in patients with metastatic colorectal cancer that progressed after first-line therapy with 5-FU in combination with irinotecan or oxaliplatin. Safety data reported for the 86 study participants showed the following frequencies for grade 1/2 adverse events: diarrhea (45%), rash (33%), fatigue (27%), nausea (20%), anorexia (16%) and vomiting (14%). Grade 3 diarrhea was reported in 5% of the patients, and grade 3 rash, fatigue and anorexia were each observed in 2% of the participants. One patient experienced grade 3 nausea. Grade 2 treatment-related decreases in left ventricular ejection fraction were also reported in 3 patients, but they were asymptomatic and resolved within 3 weeks after discontinuing treatment. Efficacy results according to RECIST guidelines found 1 confirmed partial response, as well as 5 minor responses with cytoreductions of 20%, 22.4%, 22.8%, 26.8% and 34% at week 8. Stable disease was obtained in 5 patients. Median time to progression was 8 weeks and median overall survival was 42.9 weeks. It was concluded that, despite its generally good tolerability, lapatinib offered limited benefits as a second-line therapy in patients with recurrent metastatic colorectal cancer (77, 78).

Second-line treatment with lapatinib was assessed in a phase II study in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract who had progressed after platinum-based therapy. A total of 59 patients received 1250 mg of lapatinib once daily until disease progression or withdrawal. Visceral metastases were present in 78% of the study participants, and all but 1 had confirmed expression of erbB-1 and/or erbB-2. Objective response rates determined by independent review according to RECIST guidelines showed no complete responses, 1 partial response and 18 cases of stable disease for at least 8 weeks. Median time to progression and overall survival time were 8.6 and 17.8 weeks, respectively. Adverse events included diarrhea in 23 patients, rash in 16, nausea in 16, vomiting in 13, asthenia in 7 and fatigue in 6, with 21 patients reporting WHO grade 3 or 4 toxicity. Clinical response did not appear to be related to tumor erbB-1 or erbB-2 expression. Overall, lapatinib did not appear to have significant activity in this patient population (79, 80).

A randomized phase II trial has been initiated to assess the activity of lapatinib as a first-line treatment for patients with locally advanced or metastatic breast cancer. Lapatinib is administered at doses of 1500 mg once daily or 500 mg twice daily to patients with metastatic breast cancer who have not received previous treatment with any chemotherapeutic agent (including trastuzumab) in the metastatic disease setting. Response rate at 12 weeks is the primary study endpoint and a total enrollment of 130 patients is expected. Preliminary efficacy data for the first 13 patients showed 5 patients with confirmed partial responses, 6 additional patients with stable disease of at least 8 weeks' duration and 2 patients with disease progression. Based on these preliminary results, lapatinib appears to have clinical activity when used as first-line therapy in patients with erbB-2-positive advanced or metastatic breast cancer (81).

Source

GlaxoSmithKline plc. (GB).

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