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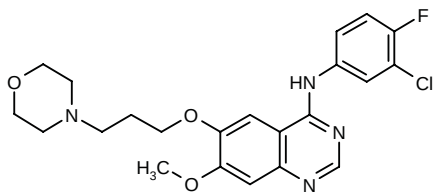
# Iressa™

*Oncolytic*
*EGF Receptor Tyrosine Kinase Inhibitor*

Gefitinib (Prop INN)
ZD-1839

4-(3-Chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazoline




$C_{22}H_{24}ClFN_4O_3$
Mol wt: 446.9076
CAS: 184475-35-2
CAS: 184475-56-7 (as dihydrochloride)
CAS: 184475-55-6 (as monohydrochloride)
EN: 233069

**Abstract**

Iressa is a novel addition to the arsenal of antitumor agents, especially the epidermal growth factor receptor-tyrosine kinase inhibitors, that has shown promising results in preclinical and clinical trials. Current and growing knowledge of the molecular basis of its antitumor activity has provoked interest in its potential for clinical application in the treatment of a variety of solid tumors, especially non-small cell lung cancer and hematological malignancies. The safety and oral bioavailability of this drug is encouraging especially for future use in combination therapy with cytotoxic agents.

## Synthesis*

Monodemethylation of 6,7-dimethoxyquinazolin-4(3*H*)-one (I) in refluxing methanesulfonic acid in the presence of L-methionine provides 6-hydroxy-7-methoxyquinazolin-4(3*H*)-one (II), which is acetylated with acetic anhydride and pyridine at 100 °C to give the acetate (III). Treatment of compound (III) with refluxing $SOCl_2$ and a catalytic amount of DMF yields chloride (IV), which by condensation with 3-chloro-4-fluoroaniline (V) in boiling isopropanol affords the anilinoquinazoline (VI). Hydrolysis of the acetate group of (VI) by treatment with $NH_4OH$ in refluxing MeOH gives the 6-hydroxyquinazoline derivative (VII), which finally is alkylated with 3-(4-morpholinyl)-propyl chloride (VIII) (1) or 3-(4-morpholinyl)propyl bromide (IX) (2) Scheme 1.

## Introduction

The growing understanding of the molecular nature of the origin, evolution and development of cancer has led to the discovery of newer therapeutic targets with new endpoints for efficacy and toxicity (3). The discovery and identification of intracellular signaling pathway has enabled the design and rational applications of treatments that target steps in the pathways of cellular communication and differentiation. The application of this new knowledge has resulted in the development of several novel cytotoxic agents that achieve cell-kill through different mechanisms than standard chemotherapeutic modalities. One of the agents that has steadily moved through clinical trials and is expected to obtain FDA approval in the near future is Iressa.

The response of cellular proto-oncogenes to the extracellular stimuli is largely determined by various growth factors. These factors bind to specific receptors and initiate a cascade of intracellular events that regulate cell growth, mitogenesis, differentiation, lineage determination, cell migration, extracellular matrix production and apoptosis (4). The new paradigm in understanding neoplastic transformation sees deregulated cell growth, the hallmark of neoplasia, as primarily a function of perturbed signal transduction and response to growth factor, although clearly many other factors modify and affect this

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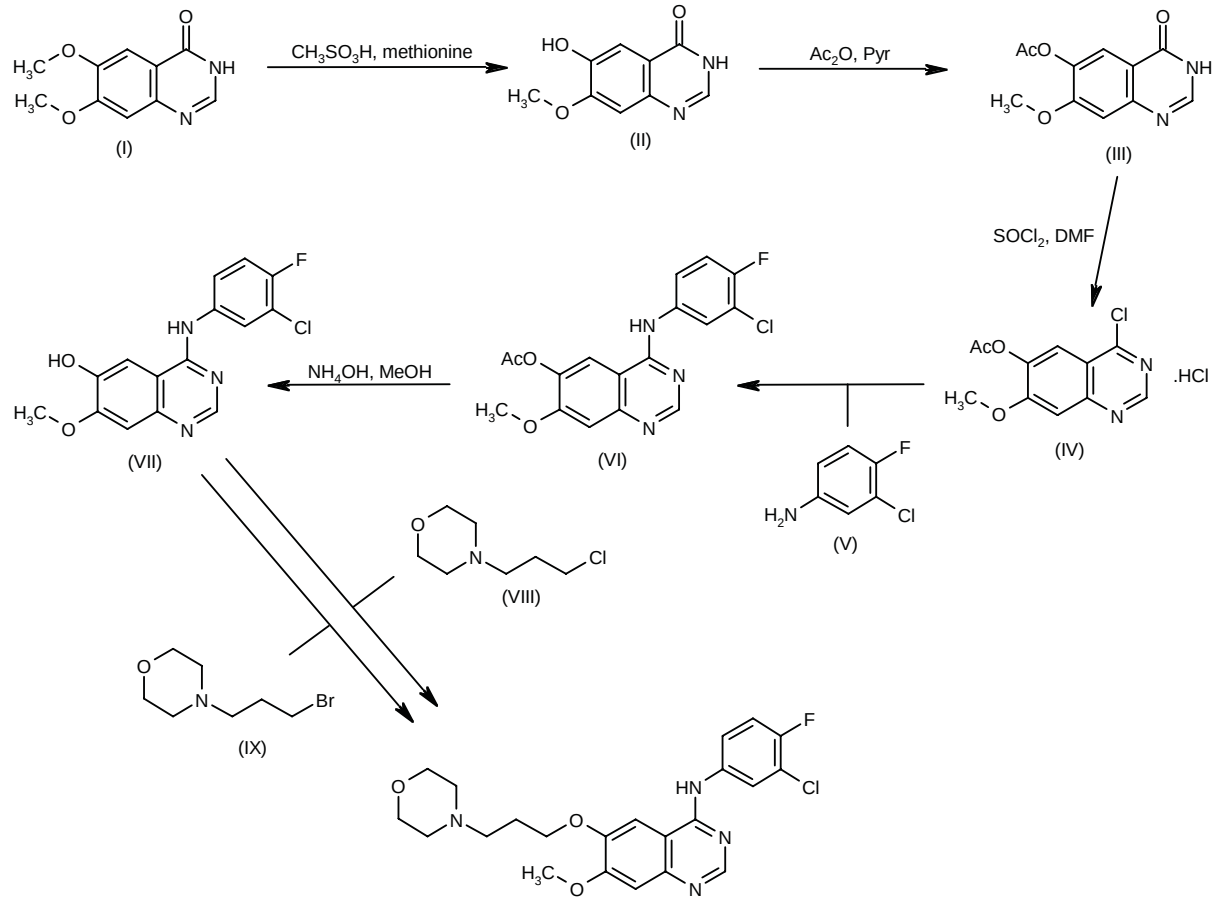
**Scheme 1: Synthesis of Iressa™**




process. Molecular research has shown that mutations or structural alterations in certain classes of signaling proteins such as the receptor protein-tyrosine kinases (RPTKs) are far more frequent than in others, resulting in the generation of potent oncoproteins. Inhibition of these RPTKs can thus slow tumor progression and is currently one of the most active foci for research in tumor therapy (5, 6).

The epidermal growth factor (EGF), discovered in the early 1950s by Levi-Montalcini and Cohen, was one of the first peptide growth factors described. This was followed by the discovery of a 170-kDa transmembrane glycoprotein belonging to the receptor tyrosine kinase family of growth factor receptors, which was named the epidermal growth factor receptor, variously referred to as EGFR, HER1 or erb B-1 (7). Consequently, other members of this family were also identified, namely erbB2/Her2-neu, erbB3/Her3 and erbB4/Her4, although EGFR and HER2-neu have been the most thoroughly studied. Trastuzumab (Herceptin®) is the best known therapeutic agent in wide use, targeting the erB2 receptor and it has been FDA approved in the U.S. for treatment of metastatic breast cancer. EGFR overexpression occurs in a wide variety of human carcinomas, such as breast, bladder, lung, brain and pancreas. Direct evidence of the causal relation between EGFR overexpression and tumorigenesis was demonstrated by a study in a transgenic mouse model, in which epithelial cell transformation was induced by EGFR overexpression (8). In addition, a study of oral small cell carcinoma cell lines suggests that coexpression of EGFR, Her2-neu and Her3 may be a stronger predictor of clinical outcome than expression of any single receptor alone (9). The extracellular region of the EGFR is a specific ligand-binding site for many polypeptide growth factors such as EGF and TGFα, as well as for nonspecific ligands such as amphiregulin, betacellulin, heparin-binding EGF, epiregulin and vaccinia growth factor.

Both EGF and TGFα have a variety of actions that are important to tumor development and progression. In addition, they promote mitogenic activity, in particular angiogenesis, stromal proliferation, extracellular matrix deposition and induction of cytokine release and they achieve these actions via paracrine, autocrine or juxtacrine mechanisms (10, 11). In addition to overexpression of normal EGFR in tumors such as breast cancer where there is an inverse relationship between EGFR positivity and

estrogen and progesterone receptor levels (12), mutations in the EGFR gene lead to formation of truncated receptors, the commonest being the type III EGFR deletion mutant (EGFR vIII) that has been detected in 16% of non-small cell lung cancer (NSCLC) and 78% of breast carcinoma specimens (7).

The discovery of the structure of the EGFR and its ligands, their signal transduction pathways and their role in tumorigenesis has led to a focus on development of potential anticancer therapies that target these pathways. These therapies include anti-receptor monoclonal antibodies as well as a therapeutically lucrative class of compounds known as small-molecule tyrosine kinase inhibitors (TKIs) of EGFR that act by reversibly or irreversibly blocking the tyrosine kinase of EGFR. The premise that EGFR with mutations in the ATP binding site lack tyrosine kinase function and do not display a full range of ligand-induced biochemical responses has also been successfully used to develop anti-receptor molecules that compete for the Mg-ATP binding site of the catalytic domain of EGFR tyrosine kinases (13, 14). Among the latter, Iressa (ZD-1839) – developed by AstraZeneca – has shown the most promising results in preclinical as well as clinical phase I/II studies. In addition, the therapeutic potential of this agent includes favorable interactions with conventional chemotherapeutic drugs, radiotherapy and cytostatic agents (7, 10, 11, 15).

## Biochemistry

Iressa is an orally active, reversible small-molecule EGFR-TKI. Chemically, it is a synthetic anilinoquinazoline that was one of the first identified selective inhibitors of the EGFR kinase. Although theoretically the substrate protein binding site of the EGFR kinase possesses lower homology than the Mg-ATP binding site, 4-anilinoquinazolines such as Iressa are potent and selective inhibitors despite competitive binding to the ATP site. Like other compounds in this group, Iressa has a clearly defined mode of binding, as suggested by its tight structure-activity pattern where the quinazoline ring binds in the adenine pocket and the aniline ring binds in an adjacent, unique lipophilic pocket (16, 17). Iressa blocks the EGFR kinase *in vitro* with an $IC_{50}$ of 0.023 nm and this EGFR specificity is in contrast to the 100-fold higher concentrations required to block other kinases. In intact cancer cells, however, the higher concentrations of ATP necessitate a higher concentration of these inhibitors to block the EGFR for prolonged durations (17).

## Pharmacokinetics

A series of 3 recently concluded clinical trials conducted in healthy human volunteers investigated the pharmacokinetics and tolerability of Iressa when taken orally as a single dose ranging from 1-75 mg, as 3 daily doses of 100 mg or a single daily dose in combination with food. The agent is bioavailable when orally administered as tablets; even low doses produce plasma concentrations of the drug of the same order of magnitude as those demonstrated to have antiproliferative effects in EGFR-expressing human cancer cells *in vitro* (11, 18). Iressa is absorbed moderately slowly with a $C_{max}$ of 3-7 h after administration, with a subsequent slow, biphasic decline in plasma concentration ($t_{1/2}$ = 12-58 h, mean = 28 h) and demonstrates dose-dependent pharmacokinetics as reflected by the proportional increase in AUC and $C_{max}$ with multiple dosing. When taken with food, however, there was a clinically nonsignificant reduction in $C_{max}$ and AUC presumed to be due to a decrease in the rate and/or extent of absorption but no change in the $t_{1/2}$. In animals, the drug is metabolized in the liver and excreted mainly through the biliary route, with less than 0.5% of the administered dose found in the urine after 24 h (18).

A low incidence of adverse events, most commonly mild and transient headache was seen in studies in healthy volunteers. There was no adverse effects in EGFR-dependent areas, such as the eye where EGFR is involved in the development of epidermis, and there were no clinically significant effects in laboratory safety parameters (18, 19). In a phase I dose-escalation trial in patients with solid malignant tumors that express or overexpress EGFR, the commonest NCI-CTC grade 1-2 adverse events were diarrhea and acneiform skin rash; grade 3-4 adverse events were rare and usually related to disease progression (20, 21).

## Pharmacodynamics and Antitumor Activity

The antiproliferative effects of Iressa are linked to its selective inhibition of the HER/erbB receptors, including the EGFR. Blockade of these receptors inhibits the network of signaling pathways that regulate cell cycle progression and obviates proapoptotic molecules, thus promoting deregulated cell growth and increased tumor cell survival (17). Evidence of the role of EGFR in the development of hair follicles and skin was suggested in a study determining the pharmacodynamic effects of Iressa in human skin in cancer patients (22, 23). In addition to EGFR inhibition by suppression of EGFR phosphorylation, Iressa was also found to inhibit downstream receptor-dependent processes, in particular inhibition of MAPK (mitogen-activated protein kinase) activation, reduction of keratinocyte proliferation index, changes in skin maturation markers, phosphorylation of STAT-3 (signal transducer and activator of transcription), increased expression of the cyclin-dependent kinase (Cdk) inhibitor p27kip1 and increased apoptosis. In addition, all these anti-EGFR effects were profound at all dose levels, even at doses well below those associated with toxicity (24). It has been hypothesized that only tumors with with normal levels of p27, cyclin D1 and normal Rb function are responsive to anti-EGFR therapies (17). Using these surrogate markers of EGF receptor signaling, studies have been carried out in a range of tumor cell

types and human tumor xenografts. In human head and neck squamous carcinoma specimens, Iressa inhibited ERK 1/2 (extracellular signal-regulated kinases/ MAPK) at concentrations that inhibited autocrine cell proliferation (25). *In vitro* studies with tamoxifen-resistant MCF7, a malignant breast cell line expressing EGFR, have shown a marked decrease in proliferative activity on treatment with Iressa (26).

Ductal carcinoma in situ (DCIS) cells are associated with a high rate of EGFR and HER2/erbB-2 expression. This dependence on EGFR-mediated tumor growth is borne out in a study demonstrating the increase in apoptosis induced by exposure of tissue samples obtained from women with DCIS to Iressa (27). However, the observation that despite high *in vitro* $IC_{50}$ values against HER2, much lower concentrations of Iressa are needed to inhibit certain human breast cancer cells that overexpress HER2 and only moderately express EGFR, suggests an additional mechanism of antitumor action. In this cohort of cells that coexpress HER2 and EGFR, HER2 is transactivated via ligand-activated EGFR (28). Tumor types that overexpress HER-2 are especially sensitive to Iressa and growth inhibition in these cell lines is associated with dephosphorylation of EGFR, HER-2 and HER-3 accompanied by loss of association of HER-3 with phosphatidylinositol 3-kinase and downregulation of Akt activity (29). Cancer cells secrete other growth factors such as VEGF, TGFα and bFGF, which play a key role in tumor angiogenesis, a vital mechanism that sustains cancer cells and increases their survival. Data from a study evaluating the antitumor activity of Iressa in human colon (GEO, SW480, CaCo2), breast (ZR-75-1, MCF-7 ADR), ovarian (OVCAR-3) and gastric (KATO III, N87) cancer cells that coexpress TGFα and EGFR demonstrated a significant dose-dependent reduction of VEGF, bFGF and TGFα expression by immunohistochemical analysis accompanied by a decrease in tumor growth and neoangiogenesis. These results suggest antiangiogenesis as yet another mechanism that explains the antitumor effects of Iressa (30). Furthermore, in studies in nude mice bearing the GEO colon cancer xenografts, survival benefit was most marked in animals cotreated with paclitaxel and Iressa, consistent with the hypothesis that chemotherapy-induced cell damage can convert EGFR ligands from growth factors into survival factors, and that blockade of EGFR with concomitant cytotoxic therapy induces apoptosis (30, 31).

**Preclinical Studies**

In preclinical studies, Iressa produced reversible growth inhibition and growth delay in a wide range of tumor cell lines as well as human tumor xenografts (32). Continuous culture of MCF7 breast cancer cells in a steroid-depleted, ICI-182780-supplemented medium resulted in development of an antiestrogen resistant cohort of cells (FASMCF) that, unlike wild-type cells, are highly sensitive to growth inhibition by Iressa with no reversal of this effect observed after short-term withdrawal of Iressa. Although longer withdrawal periods of about 10 weeks produced a partial reversal of the cellular phenotype, with increase in estrogen receptor and decrease in EGFR levels, even wild-type cells maintained in a combination of TKI and ICI-182780 remained growth arrested for more than 6 months (33).

In animal studies conducted in nude mice bearing GEO colon cancer xenografts, a complete inhibitory effect on tumor growth was observed at a dose of 5 mg/day that, despite being cytostatic in nature, was associated with improved survival in animals treated with Iressa. In addition, a significant antitumor effect with minimal toxicity was observed with the use of a fixed dose (2.5 mg) of Iressa in combination with 4 weeks of maximally tolerated doses of the conventional chemotherapeutic agents paclitaxel, topotecan or raltitrexed (17, 30).

Iressa potentiates antitumor activity of a wide variety of cytotoxic agents including cisplatin, carboplatin, docetaxel, paclitaxel, doxorubicin, gemcitabine, vinorelbine and edatrexate, in several human tumor xenografts irrespective of their EGFR status but at doses above the usual single-agent maximum tolerated dose for Iressa. Oral Iressa (5 times daily for 2 days) and cytotoxic agents (i.p every 3-4 days for 4 days) were administered to mice with human vulvar (A431), lung (A549, SKLC-16 and LX-1) and prostate (PC-3 and TSU-PR1) cancers. All of these cell lines differ in their levels of EGFR expression. The maximum tolerated dose (150 mg/kg) of Iressa induced partial regression of A431 which expresses high levels of EGFR, 70-80% inhibition of A549, SKLC-16, TSU-PR1 and PC-3 which have low but highly variable EGFR expression and 50-55% inhibition of LX-1 that has very low EGFR expression. However, in combination with Iressa, doxorubicin induced a 99% inhibition against A549, edetrexate resulted in partial or complete inhibition of A549, LX-1 and TSU-PR1, and paclitaxel produced marked regression of A431.Combined therapy with gemcitabine was neither additive nor antagonistic, but a combination with vinorelbine was not effective (17, 34).

The fact that HER-2 is transactivated by ligand-activated EGFR has been used as the molecular rationale behind the use of TKIs in the treatment of certain breast tumor xenografts. The addition of Iressa to trastuzumab was found to induce a 5-fold increase in apoptosis in a HER-2 overexpressing and HER-1 coexpressing breast cancer cell line (BT-474). This finding was the basis of a recent experiment conducted by the Department of Hematology/Oncology at Vanderbilt-Ingram Cancer Center in Nashville, where addition of Iressa to trastuzumab in the treatment of established BT-474 tumors in nude mice produced marked reduction in tumor size that was statistically significant when compared with tumor reduction achieved with trastuzumab alone (28, 35). Applying this rationale to treatment of SKBR-3s murine xenograft breast cancer cell line that also overexpresses HER-2, while coexpressing HER-1 with a combination of Iressa and trastuzumab or the individual agent alone, a substantial tumor regression was evident with

the combination in comparison with monotherapy. Flow cytometric studies to detect apoptotic cells in SKBR-3s xenografts demonstrated 0.56% apoptotic cells in untreated cells, 1.06% in cells treated with Iressa, 1.52% in cells treated with trastuzumab and 5.26% in cells treated with a combination of Iressa and trastuzumab. Analysis of the effect of these agents on harvested breast cancer tumors showed 29% of controls to be in the S phase as compared to 14% with Iressa, 22% with trastuzumab and 10.4% with the combination ($p = 0.001$, compared with trastuzumab alone or controls) (36).

## Clinical Studies

Promising data from phase I trials in patients with a wide variety of tumor types was presented at the American Society of Clinical Oncology 2001 meeting. Results that indicate the clinical efficacy and good tolerability of Iressa, especially in the treatment of NSCLC, have resulted in the acceleration of the drug from phase I to phase II and III trials (32, 37). One phase I trial (38) enrolled 64 patients with a median age of 54 years and a wide variety of solid tumors, including NSCLC, ovarian cancer, breast cancer, head and neck cancers and prostate cancer. Participants were given a single dose of 50 mg/day of Iressa and were observed for 6 days.Pharmacokinetic measurements were drawn followed by escalating doses for 14 days every 28 days until a maximum of 925 mg/day was reached or dose-limiting toxicity or significant corneal damage was observed. In these patients, at drug doses equal to or greater than 100 mg/day, the plasma concentration of Iresssa exceeded the $IC_{90}$ for *in vitro* growth inhibition. In 14 patients, stable disease was observed for 4 months and 4 of 16 patients with advanced NSCLC who had received prior cisplatin or carboplatin had partial or major response. Follow-up revealed that approximately 10% of patients in phase I monotherapy trials remained on the study for 6 or more months and 8 patients have remained on treatment for 1-2 years (37, 38).

Another phase I study was conducted in 31 Japanese patients (23 of whom had NSCLC) with advanced solid tumors who had received intensive prior chemotherapy, using intermittent dosing with dose escalation. Participants were given a single dose of Iressa starting with 50 mg orally and observed for 7-10 days and retreated with the same dose for 14 days followed by a 14-day rest period. Five of the 23 patients with NSCLC achieved a partial remission and 16 of these patents who had received prior platinum-based therapy had sustained responses for up to 11 months (17, 37, 39). Additional trials reporting similar clinical efficacy in breast and colorectal cancer and hormone refractory prostate cancer have also been reported (37, 40, 41).

None of these phase I studies enrolled patients based on prescreening EGFR expression/overexpression, although the solid tumors that were treated are known to express EGFR. Dose-limiting toxicity in these trials was grade 3 diarrhea at 700 mg/day. There were very few additional adverse events, mostly acneiform rash, anorexia, nausea and no significant myelosuppression was noted (17, 37-39).

A phase II trial evaluating the safety and efficacy of Iressa in combination with carboplatin and paclitaxel in the treatment of previously untreated advanced NCSLC has been recently concluded. Twenty five patients were randomized to two dose levels of Iressa (250 or 500 mg/day) and to one of two schedules: Iresssa given on days 1-14 with the cytotoxic agents given on days 8 and 36 or Iressa on days 22-35 and cytotoxic therapy on days 1 and 29. No novel toxicities were seen except for 1 patient with dose-limiting grade 3 rash. On day 56, the overall response rate was 25% among the remaining 24 participants. Partial remission was maintained for 1-12.4 months, while 1 patient maintained complete remission for 8+ months. The efficacy and tolerability of full active doses of Iressa with standard doses of cytotoxic agents was an encouraging result prompting phase III trials with this combination of drugs. Phase II monotherapy trials in breast, prostate and gastric cancer are also under way (17, 36, 37, 42).

Results from two global, randomized, double-blind, placebo-controlled, multicenter phase III trials in chemotherapy-naive patients with advanced NSCLC are being eagerly awaited. In both these trials, patients were randomized to one of three treatment arms: chemotherapy alone with carboplatin and paclitaxel, cisplatin and gemcitabine or chemotherapy in combination with Iressa at either 250 or 500 mg/day. In addition, the National Cancer Institute and other oncology cooperative groups are enrolling patients into clinical trials of Iressa in renal cell, bladder, glioblastoma and brain cancers. Another trial, in which patients with Stage III NSCLC are given chemoradiation for 4 months followed by docetaxel for 3 cycles and then randomized to Iressa versus a placebo, has recently begun (17, 36, 37, 43).

## Source

AstraZeneca plc (GB).

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