Drug chosen: Gefitinib (Brand names: Iressa®)

Proposed Indication

IRESSA™ is indicated for the treatment of patients with locally advanced or metastatic轉移性的/新陳代謝的/變形的non-small cell lung cancer who have previously received platinum-based chemotherapy.

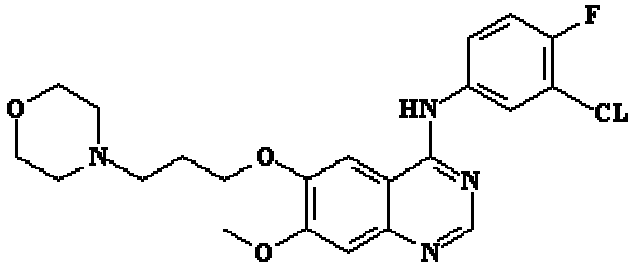
Drug Class

ZD1839 (IRESSA™) is an anilinoquinazoline with the chemical formula N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoline-4-amine and the molecular structure shown below.

The compound is a white powder with a molecular formula of C22H24ClFN403 and molecular weight of 446.9.

Gefitinib

$C_{22}H_{24}CLFN_4O_3$



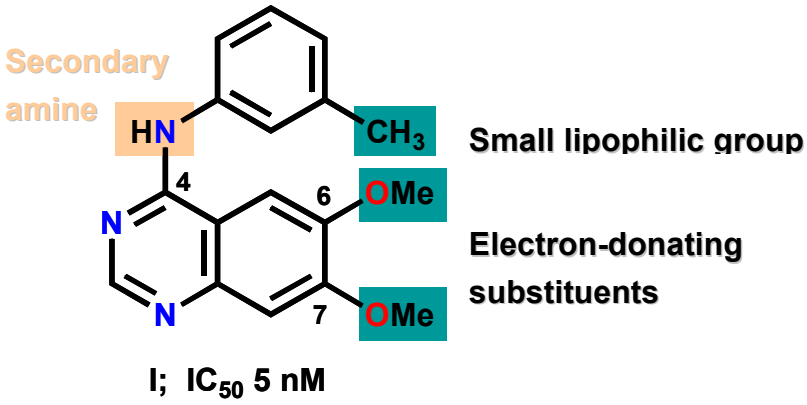
ZD1839 mechanism of action - EGFR inhibitor which interrupts a growth factor in cancer cells

ZD1839 is an inhibitor of epidermal growth factor receptor tyrosine kinase activity that completely blocks EGFR autophosphorylation with resultant complete blockade of signal transduction from the EGFR in lung and breast cancers, EGFR is overexpressed in the cells of certain types of human cancers. This leads to inappropriate activation of the anti-apoptotic Ras signalling cascade, eventually leading to uncontrolled cell proliferation.

Gefitinib binds to the adenosine triphosphate (ATP)-binding site of the enzyme, initiates a signal that can influence many aspects of tumor cell biology including growth, survival, metastasis, and angiogenesis, as well as tumor cell sensitivity to chemotherapy and radiation therapy.

(I) Lead compound discovery

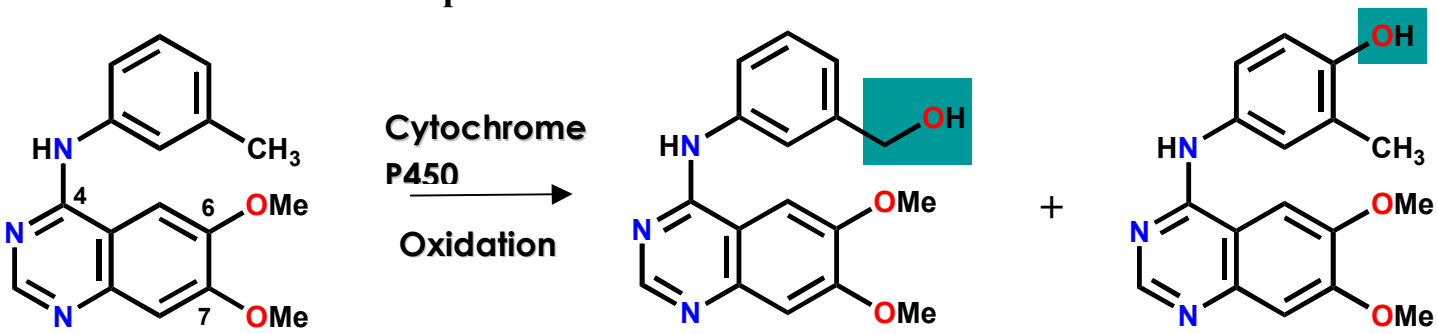
Lead compound:



I; IC_{50} 5 nM

The secondary amine, electron-donating substituents and small lipophilic group are all important for activity. Useful *in vitro* activity, lower *in vivo* activity due to rapid metabolism. It is metabolised by cytochrome P450 enzymes.

Metabolism of the lead compound:

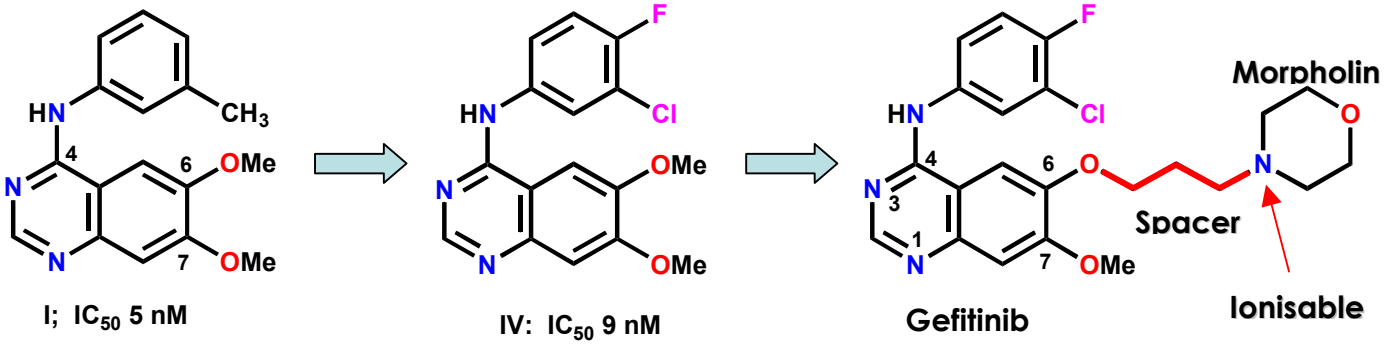


I; IC_{50} 5 nM II III

Methyl group and *para*-position of aromatic ring are susceptible positions.
Blocking metabolism should improve the half life of the drug.

(II) Molecular modification

Drug design:



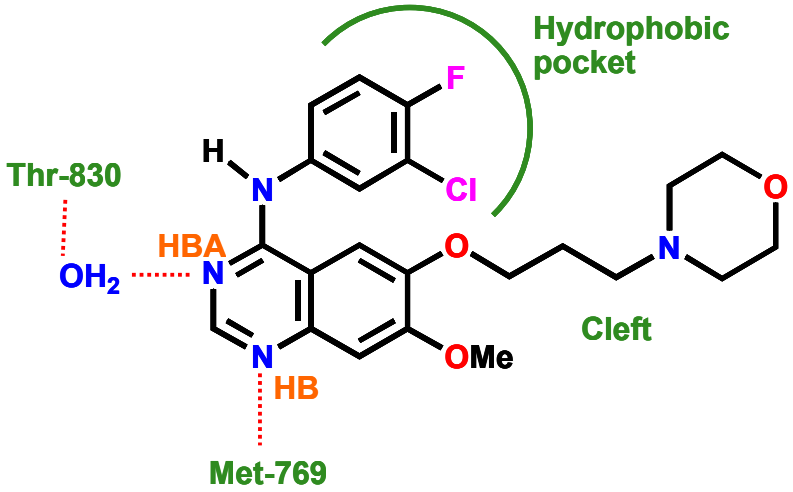
I; IC_{50} 5 nM IV: IC_{50} 9 nM Gefitinib

Fluoro-substituent blocks *para*-hydroxylation of the aromatic ring
Fluorine is similar in size to hydrogen and has no steric effect
Methyl group is replaced by a chloro substituent
Chlorine and methyl group have similar sizes and lipophilicities

Chlorine acts as a bio-isotere for the methyl group
Chlorine is resistant to oxidation
Compound is less active *in vitro*, but more active *in vivo*
(* bioisosteres are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound. In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.)

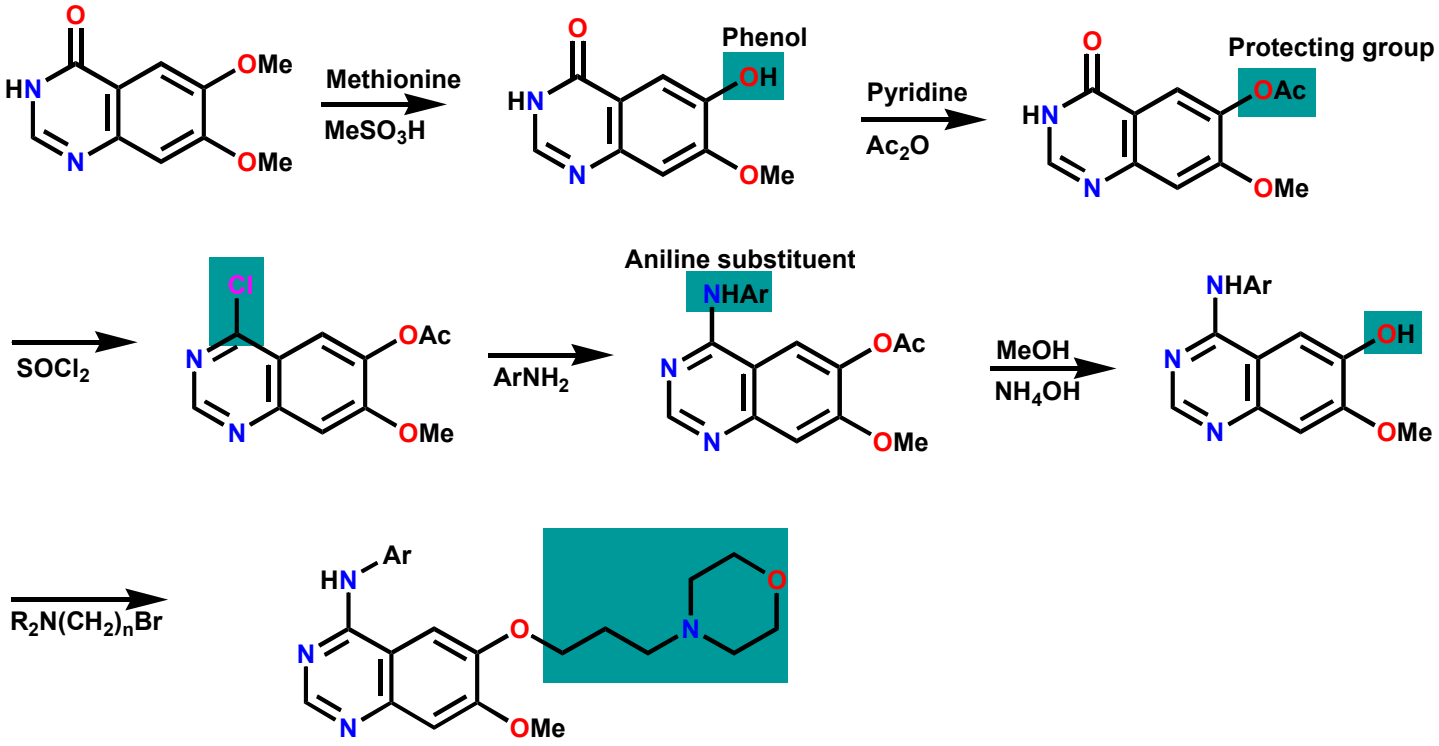
Morpholine 嗎啉 ring increases water solubility
Morpholine nitrogen allows generation of water soluble amine salts
Spacer allows morpholine to protrude out of the active site
Remains solvated when the drug is bound
Avoids a desolvation penalty

Binding interactions:



Identified by a molecular modelling experiment
Gefitinib is docked with a model binding site
Binds to the ATP binding site
Aniline ring occupies the normally vacant hydrophobic pocket opposite the ribose binding pocket
Quinazoline binds to the same region as the purine ring of ATP

Synthesis of gefitinib and analogues:



(III) Formulation development

Dosage Form: Gefitinib is available as oral tablets. Each tablet contains 250mg of Gefitinib.

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%.Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 hours. Daily oral administration of gefitinib to cancer patients resulted in a 2-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days.

Adverse effects:

As gefitinib is a selective chemotherapeutic agent, its tolerability profile is far superior to previous cytotoxic agents. Adverse drug reactions (ADRs) do still occur however, but may be preferable to the fatal consequences of not taking the therapy.

Acne is reported very commonly. Other common adverse effects (≥1% of patients) include: diarrhoea, nausea, vomiting, anorexia, stomatitis, dehydration, skin reactions, paronychia, asymptomatic elevations of liver enzymes, asthenia, conjunctivitis, blepharitis.[7]

Infrequent adverse effects (0.1–1% of patients) include: interstitial lung disease, corneal erosion, aberrant eyelash and hair growth.[7]

(IV) Safety tests and human trials

The efficacy and safety of IRESSA was demonstrated in a randomized, open-label, multicentre, Phase III trial versus carboplatin/paclitaxel doublet chemotherapy in the first line setting (IPASS).

This study was conducted in Asia in patients with locally advanced or metastatic (Stage IIIB or IV) NSCLC of adenocarcinoma histology who were ex-light smokers (ceased smoking ≥15 years ago and smoked ≤10 pack years) or never smokers. A total of 1217 patients from 87 centres in China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand were studied.

The primary efficacy endpointwas progression-free survival (PFS). Secondary endpoints were overall survival (OS),objective tumour response rate (ORR), safety, quality of life (QoL) and symptom improvement.

Demographic and baseline characteristics were well balanced between the two treatment groups.

(V)Approval for marketing

"Product Monograph" published when IRESSA was approved for sale in Canada and is designed specifically for consumers.

Serious Warnings and Precautions

IRESSA should be prescribed by a health care professional experienced in the treatment and management of patients with cancer. IRESSA should not be used in patients with EGFR mutation negative tumours. IRESSA has not been studied in patients with severely reduced kidney function.

BEFORE you use IRESSA, talk to your doctor or pharmacist if:

. You have, or have had, lung diseases other than lung cancer. Some of them may worsen during treatment with IRESSA.
. You are pregnant, or plan to become pregnant.
. You are breastfeeding.
. You have a disorder affecting the liver.
. You have eye problems or wear contact lenses.
. You have kidney problems.

Bleeding has been reported with the use of IRESSA suchas nosebleed, blood in the urine, coughing up of blood and bleeding from the lungs.

IRESSA is not expected to impair your ability to drive or use machines. However, some patients may occasionally feel weak. If this happens, you should not drive or operate machinery.

IRESSA is not recommended for use in patients under 16years of age.

Proper use of IRESSA

Usual dose:

Take one 250 mg tablet, once a day, every day, at about the same time. You can take IRESSA with or without food. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Overdose:

If you take more IRESSA than you should, talk to your doctor, pharmacist or regional poison control centre or go to your nearest hospital emergency department immediately.

Missed Dose:

If you forget to take a dose, take the last missed dose as soon as you remember, as long as it is at least 12 hours before the next dose is due. If it is less than 12 hours until the next dose, do not take the dose you have missed

Side Effects and what to do about the

Like all medicines, IRESSA can have side effects. These are usually mild to moderate in intensity, and reversible. Side effects often start during the first month of taking IRESSA.

Talk to your doctor if any of the following happens to you.
You may need further examinations or treatment:

Very common side effects (Greater than or equal to 10 of every 100 patients):

- Diarrhea, nausea, vomiting, stomatitis (red and sore mouth)
- Loss of appetite
- Skin reactions such as rash, itching dry skin and redness
- Weakness (asthenia)

Common side effects (Greater than or equal to 1 every 100 patients, but less than 10 of every 100 patients):

- Dry mouth
- Nosebleed or blood in the urine
- Protein in your urine (shown in a urine test)
- Nail problems
- Loss of hair
- Eye problems (dry, red, itchy eye or red and sore eyelid)
- Fever

Uncommon side effects (Greater than or equal to 1 of every 1000 patients, but less than 1 of every 100 patients):

Unexpected bleeding if you are taking warfarin.
The following side effects can also occur with IRESSA, and they are seen when a blood test is taken:

Very common (Greater than or equal to 10 of every 100 patients):
Changes to the level of one liver enzyme known as alanine aminotransferase (ALT).

Common (Greater than or equal to 1 every 100 patients, but less than 10 of every 100 patients):
Changes to the level of bilirubin and the other liver enzyme known as aspartate aminotransferase(AST).
Changes to the level of creatinine in your blood, which shows how well your kidneys are working.This is often a consequence of diarrhea or vomiting, which may lead to severe dehydration.

Uncommon (Greater than or equal to 1 of every 1000 patients, but less than 1 of every 100 patients):
Changes to the way your blood clots, if you are taking warfarin (medicine to prevent bloodclotting).

How to store IRESSA:
Keep out of the reach and sight of children.
Store at room temperature, 15 to 30°C.
Keep IRESSA in the original package in order to protect it from moisture.
Do not use IRESSA after the expiry date on the blister pack.

END OF REPORT