Gefitinib

(Brand names: Iressa®)

For curing lung cancers

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1.18 million people die of Lung cancer each year
Introduction:

• Treat cancer
• Inhibitor of *EGFR* (epidermal growth factor receptor) tyrosine kinase activity
• binds to the *ATP* (adenosine triphosphate)
  » initiates a signal » influence *tumor cell biology*
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

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

- Drug design

- Fluoro-substituent blocks para-hydroxylation

- Fluorine similar in size to hydrogen - no steric effect

- Methyl group replaced by chloro substituent - similar sizes and lipophilicities

- Chlorine acts as a bio-isotere

- 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 ring increases water solubility

- Morpholine nitrogen allows generation of water soluble amine salts

- Spacer allows morpholine to protrude out of the active site
Synthesis of gefitinib and analogues

1. Methionine
   - Methionine
   - Methionine
   - Methionine
   - Methionine

2. Phenol
   - Phenol
   - Phenol
   - Phenol
   - Phenol

3. Pyridine
   - Pyridine
   - Pyridine
   - Pyridine
   - Pyridine

4. Protecting group
   - Protecting group
   - Protecting group
   - Protecting group
   - Protecting group

5. Aniline substituent
   - Aniline substituent
   - Aniline substituent
   - Aniline substituent
   - Aniline substituent

6. R₂N(CH₂)ₙBr
   - R₂N(CH₂)ₙBr
   - R₂N(CH₂)ₙBr
   - R₂N(CH₂)ₙBr
   - R₂N(CH₂)ₙBr
Formuation development

• Dosage Form:
  - oral tablets
  - each tablet : 250mg
• absorbed slowly
  - mean bioavailability : 60%
  - elimination : by metabolism and excretion in faeces
  - elimination half-life : 48 hours
  - daily oral administration : 2-fold accumulation
• Steady state plasma concentrations are achieved within 10 days.
Safety tests and human trials:

- **Asia** in patients with locally advanced or metastatic cancer
- **Ex-light smokers** or **never smokers**.
- **1217 patients** from **87 centres** in **China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand** were studied.
- Progression-free survival (PFS)
- Overall survival (OS)
- Objective tumour response rate (ORR)
- Quality of life (QoL)
- Symptom improvement
- Has not been studied in patients with severely **reduced kidney function**
Approval for marketing:

- "Product Monograph" published
- IRESSA was approved for sale in Canada
- Prescribed by a health care professional
- Should not be used in patients with EGFR mutation negative tumours
- Not recommended for use in patients under 16
Side Effects:

- Diarrhea, nausea, vomiting, stomatitis (red and sore mouth)
- Loss of appetite
- **Skin reactions** (rash, itching dry skin and redness)
- Nosebleed or blood in the urine
- **Protein in urine**
- Nail problems
- **Loss of hair**
- **Eye problems** (dry, red, itchy eye or red and sore eyelid)
- **Fever**
- Bleeding from the lungs