RELEVANCE OF THE ErbB FAMILY TO THE TREATMENT OF ADVANCED NSCLC

B A C K G R O U N D E R

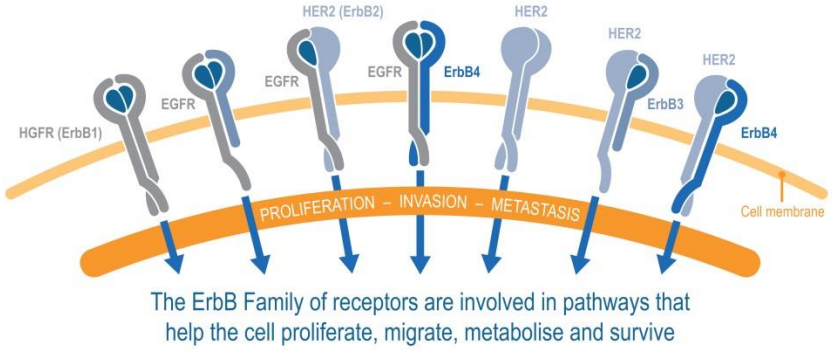
1. **The ErbB Family**
2. **Role of the ErbB Family in cancer**
3. **Blockade of the ErbB Family**
4. **Role of mutation testing for first-line therapy against advanced NSCLC**
5. **Quality criteria for a mutation test**

1. THE ErbB FAMILY

- The ErbB Family of receptors includes epidermal growth factor receptor (EGFR), ErbB2, ErbB3 and ErbB4; these are expressed ubiquitously in epithelial, mesenchymal, cardiac and neuronal cells[1,2]
- The ErbB Family of receptors is involved in various cellular processes including proliferation, survival, angiogenesis and metastasis of many cancers[1,2]
- An active ErbB receptor is formed by dimerisation, either between identical receptors e.g. ErbB1 and ErbB1 (homodimers) or different receptors e.g. ErbB1 and ErbB2 (heterodimers)[1]
- These different homodimers and heterodimers create the potential for multiple intracellular pathways to be activated[1]

*Afatinib is approved in more than 70 markets including the EU, Japan, Taiwan, and Canada under the brand name GIOTRIF®, in the US under the brand name GILOTRIF® and in India under the brand name Xovoltib®; for the full list please see here.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK). Afatinib is subject to country-specific regulations and the approved product label may vary from country to country.
Information on this website is derived from the approved European Summary of Product Characteristics. Please refer to your local product label for full details.

Figure 1. Ligand-induced ErbB Family receptor signalling.



Reproduced from: Lynch TG, *et al Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib.* NEJM 2004;350(21)2129–139; Hynes NE, *et al ERBB Receptors and Cancer: The Complexity of Targeted Inhibitors.* Nat Rev Cancer 2005;5:341–54.

2. ROLE OF THE ErbB FAMILY IN CANCER

- The ErbB Family of receptors are often overexpressed or mutated in many types of cancer including lung, head and neck, bladder, pancreatic and colorectal cancers[3,4]
- More than 90% of all solid tumours express at least one receptor from the ErbB Family[2]
- Dysregulation of ErbB signalling by overexpression or constitutive activation of ErbB Family receptors plays a critical role in the growth and spread of many pervasive and deadly cancers[5,6]
- Overactivation of the ErbB receptor tyrosine kinases leads to uncontrolled cell proliferation, inhibits apoptosis (programmed cell death), and promotes tumour growth and spread[7,8]

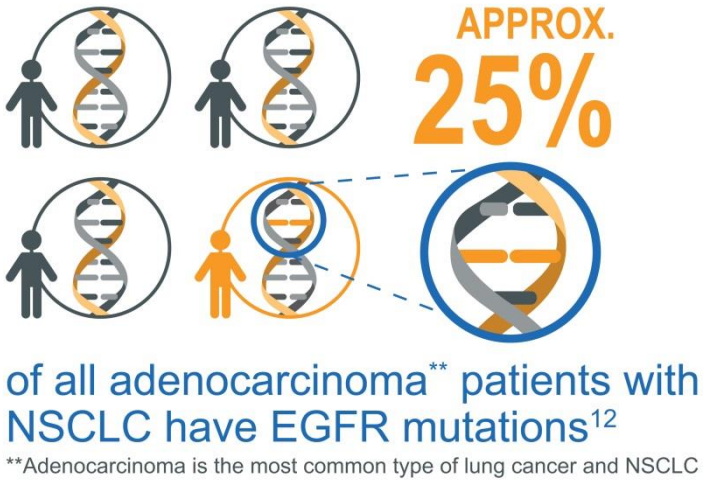
3. BLOCKADE OF THE ErbB FAMILY

- Since ErbB-mediated signalling can be initiated by a variety of homodimers and heterodimers, inhibition of one receptor type alone may not be sufficient for optimal inhibition of tumour cell proliferation and survival. Inhibition of all ErbB receptors, however, may provide a complete block of ErbB Family signalling[9]
- There is an unmet clinical need for new therapies with improved efficacy and acceptable safety and tolerability profiles for patients with ErbB-driven cancers such as non-small cell lung cancer (NSCLC) and head and neck cancer[10]
- The complexity and interdependency of ErbB Family signalling limits the effectiveness of some EGFR inhibitors, as they fail to block all dimerisation partners in an active receptor complex[5]

- Afatinib* is the first irreversible ErbB Family Blocker that inhibits signalling from all ErbB Family receptors
    - Afatinib is approved for use in patients with locally advanced or metastatic NSCLC with activating *EGFR* mutation(s) and in patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy[11]

4. ROLE OF MUTATION TESTING FOR FIRST-LINE THERAPY AGAINST ADVANCED NSCLC

Figure 2. Frequency of *EGFR* mutations in patients with NSCLC adenocarcinoma.



- The prevalence of *EGFR* mutations is approximately 40% among Asians and 10–15% among Caucasians with NSCLC[13]
- NSCLC is a genetically distinct subtype of lung cancer, and requires a specific treatment approach[14,15]
- Early testing for *EGFR* mutation status is important so that patients have the opportunity to receive the appropriate personalised therapy from the start[15,16]
- *EGFR* M+ is a well-established, critical biomarker that predicts significant treatment benefit, particularly from EGFR-targeted therapy[14,15]
- Clinical and pathological characteristics such as adenocarcinoma, female sex and non-smoking status are frequently linked to *EGFR* mutations, but do not confirm the presence of an *EGFR* mutation[16]
- Consequently, testing for mutations in *EGFR* in patients with non-squamous NSCLC is therefore strongly recommended by most international oncology organisations, including the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology

(ASCO), International Association for the Study of Lung Cancer (IASLC), and the College of American Pathologists and Association for Molecular Pathology.[17–19]

5. QUALITY CRITERIA FOR A MUTATION TEST

- *EGFR* mutation testing should be standard for all patients with non-squamous NSCLC. This requires close coordination between the physicians taking the biopsy (such as interventional radiotherapists or pulmonologists) with pathologists and cancer-treating specialists
- A sufficient amount of a reliable tissue sample is required for the test to be conclusive
- As well as biopsy, minimally invasive techniques can be used in patients with advanced NSCLC. These include exfoliative cytology and aspiration cytology[20]
    - In addition, the use of surrogate sources of DNA, such as blood, serum and plasma samples, which often contain circulating free tumour DNA or circulating tumour cells, is emerging as a new strategy for tumour genotyping. This is referred to as liquid biopsy[21]
- A number of different methods are used for mutation testing. Polymerase chain reaction (PCR) and sequencing are the methods recommended by ASCO for *EGFR* mutation analysis[13,18,22]
- However, in patients with advanced lung carcinoma, tumours may be inoperable and may have already metastasised before detection. Patients with such tumours have limited samples (small biopsies or cytology specimens), hence traditional PCR may not be reliable. In these cases, next-generation sequencing can improve detection of *EGFR* mutations[23]
    - Next-generation sequencing methods, also known as massive parallel sequencing, describes the parallel analysis of a very large number of DNA molecules, which is quicker and cheaper than the previously used Sanger sequencing. The ‘catch-all’ term describes a number of different modern sequencing techniques, which greatly improve detection from limited samples[23]

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Abbreviated EU SmPC:

EGFR M+ NSCLC and sqNSCLC

GIOTRIF®: Irreversible ErbB family blocker. **Active substance:** Afatinib. **Indications:** GIOTRIF is indicated as monotherapy for (1) patients with locally advanced or metastatic NSCLC with activating EGFR mutations not previously treated with EGFR TKIs, (2) patients with NSCLC of squamous histology progressing on or after platinum-based chemotherapy. **Posology:** The recommended dose is 40 mg once daily, orally. Not recommended in patients with an eGFR <15ml/min and severe hepatic impairment. **Contraindications:** Hypersensitivity to afatinib or any of the excipients. **Interactions:** Potent P-gp inhibitors may lead to increased afatinib exposure, concomitant treatment with potent P-gp inducers may lead to a reduction in afatinib exposure. Afatinib is not an inhibitor or inducer of CYP enzymes. **Undesirable effects:** Paronychia, cystitis, decreased appetite, dehydration, hypokalaemia, dysgeusia, conjunctivitis, dry eye, epistaxis, rhinorrhoea, diarrhoea, stomatitis, nausea, vomiting, cheilitis, dyspepsia, alanine aminotransferase increased, aspartate aminotransferase increased, rash, acneiform dermatitis, pruritus, dry skin, palmar-plantar erythrodysaesthesia syndrome, nail disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased, interstitial lung disease, keratitis, pancreatitis. **Presentations:** 20 mg, 30 mg, 40 mg, and 50 mg film-coated tablets. For detailed information, please refer to the published Prescribing Information.

Supply classification: POM.

▼This medicine is subject to additional monitoring.

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EGFR M+, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

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