The ErbB Family

1. What role does the ErbB Family play in cancer?
2. Blockade of the ErbB Family
3. The importance of mutation testing in advanced NSCLC

1. THE ErbB FAMILY

- The ErbB Family of receptors are involved in processes in the body which help cells to grow and divide.
- The ErbB Family consists of four related enzymes which are called tyrosine kinases: EGFR (epidermal growth factor receptor, ErbB1), HER2 (human epidermal growth factor receptor 2, ErbB2), ErbB3 and ErbB4.
- These different homo- and heterodimers create the potential for multiple intracellular pathways to be activated.

2. WHAT ROLE DOES THE ErbB FAMILY PLAY IN CANCER?

- The ErbB Family of receptors are often dysregulated (i.e. they are uncontrolled, therefore too many are produced) or mutated (i.e. they are hyperactive) in many types of cancer. More than 90% of all solid tumours overexpress at least one ErbB Family receptor.¹
- Overactivation of the ErbB receptor tyrosine kinases leads to uncontrolled cell growth, inhibits programmed cell death (known as apoptosis) and promotes tumour growth and spread.² ³

3. BLOCKADE OF THE ErbB FAMILY

- Inhibition of one ErbB receptor type alone may not always be sufficient to reduce tumour cell growth and survival. However, it is hypothesised that inhibition of all ErbB receptors can provide a complete block of ErbB Family signalling - by blocking the signals that tell cancer cells to grow and divide.
- There is a need for new, effective therapies with acceptable safety and tolerability profiles for patients with ErbB-driven cancers.
- Ongoing research is driving a new generation of treatments that recognise specific targets in cancer cells. These targeted therapies may hold the promise of improved efficacy and fewer side effects for cancer patients.
- One such targeted therapy is GIOTRIF® (afatinib*) - an irreversible ErbB Family Blocker, approved in a number of markets including the EU, Japan, Taiwan and Canada and in the U.S, under the brand name GILOTRIF®, for use in patients with distinct types of EGFR mutation-positive non-small cell lung cancer (NSCLC), a distinct subtype of NSCLC.

*Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada under the brand name GIOTRIF® and in the U.S. under the brand name GILOTRIF® for use in patients with distinct types of EGFR mutation-positive NSCLC. Afatinib is under regulatory review by health authorities in other countries worldwide.
Afatinib® blocks the signalling of all ErbB Family receptors, therefore blocking the key pathways involved in cell growth.

The signalling of ErbB3 is blocked indirectly through blocking of transphosphorylation.

### 4. THE IMPORTANCE OF MUTATION TESTING IN ADVANCED NSCLC

- **EGFR (ErbB1)** mutation-positive NSCLC is a genetically distinct subtype of lung cancer that requires a specific treatment approach.
- There are different types of EGFR mutations in lung cancer, the most common, which account for 90% of all EGFR mutations being del19 (50%) and L858R (39%).
- EGFR mutations are very common in Asian NSCLC patients, detected in approximately 40% of patients. Within the Caucasian NSCLC patient population, 10-15% are identified as EGFR mutation positive.
- Early mutation testing of the EGFR status is extremely important so that patients have the opportunity to receive the most suitable, targeted therapy from the start.
- Clinical and pathological characteristics such as adenocarcinoma (both the most common type of lung cancer and the most common form of NSCLC), female gender and a non-smoking status are frequently linked to EGFR mutations, but do not confirm the presence of an EGFR mutation.
- Testing for mutations in EGFR is strongly recommended by most international and European oncology organisations including the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer (IASLC), the National Comprehensive Cancer Network (NCCN), the College of American Pathologists and the Association for Molecular Pathology.
- EGFR mutation testing should be standard in all NSCLC patients. This requires close coordination between all physicians involved in the care of the patients, from those taking a biopsy (the removal of cells or tissues for examination by a pathologist) such as interventional radiotherapists or pulmonologists, to pathologists and cancer treating specialists.

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REFERENCES