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## ONCOLOGY | REVIEW ARTICLE

# PI3K/MEK pathway-targeted therapy in non-small cell lung carcinoma

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**Abstract:** Pulmonary carcinogenesis is a chronic process that involves multiple genetic, cellular and tissue alterations, resulting from changes in genes that regulate growth, differentiation and apoptosis, which eventually lead to the development of invasive or metastatic cancer. Lung cancer is divided into two groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC); the latter is more prevalent in the population since it represents approximately 75% of all lung tumours. During the development of NSCLC, different molecular events occur that include the loss of heterozygosity, epigenetic mutations in p53, KRAS and changes in receptor (EGFR), amplification of the cMET epidermal growth factor and microsatellite instability. It is important to note that mutations present in the EGFR are prevalent in adenocarcinomas of non-smoking, whereas in adenocarcinomas of the smokers are mutations in KRAS. Different molecular studies have reported changes in signalling pathways that contribute to lung tumorigenesis. Some of them involve the EGFR and KRAS, cMET AKT proteins. EGFR has been associated with carcinogenesis and progression of the tumour through different mechanisms as the overexpression of the receptor and the ligand, as well as also through various mutations, which are associated with the activation of different signalling pathways.

**Subjects:** Oncology; Pulmonary Medicine; Pulmonary Oncology

**Keywords:** cancer; PI3K/MEK pathway; non-small cell lung carcinoma; target therapy

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### PUBLIC INTEREST STATEMENT

Lung cancer is one of the most common and serious kind of cancers worldwide. Cancers can begin in the lungs or travels to the lungs from other regions of the body. There are various reasons for which this occurs, known as risk factors, which increase the likelihood of an individual to be predisposed to lung cancer. By far, the most common risk factor is smoking. However, other factors can play a role such as old age, genetics, family history, toxic gases and metals such as chromium and others. The treatment of lung cancer depends on multidisciplinary assessment of the patient, and can involve surgery, radiotherapy or chemotherapy or combination of those. Newer medications have now been developed known as targeted therapy. These newer medications have the advantage of less side effects and robust action on cancer cells, with rising hope for better future treatment.

## 1. Epidemiology

Lung cancer is the primary cause of the deaths that are cancer related within the globe. Most of the individuals who are diagnosed with cancer and later succumb to it are faced with the cancer of the lungs. The number of the cases of lung cancer deaths is estimated to be well over that which is occasioned by the combination of breast, prostate and colon cancer (Dogan et al., 2012). The most recent cancer data to have been reviewed indicate just over 239,000 deaths, with up to 161,000 being attributed to lung cancer in the USA. It has been the most frequent cancer world over in the perspective of mortality and incidence.

Based on the data from 38 states and the District of Columbia, the annual incidence for every 100,000 population revealed that the lung cancer incidence varied among ethnic groups in the USA. In African-Americans, Caucasians and American Indians/Alaska Natives, it was 76.1, 69.7 and 48.4, respectively, while the incidences in Asian/Pacific Islanders, Hispanic and Non-Hispanic persons were 38.4, 37.3 and 71.9, respectively (Centers for Disease Control & Prevention [CDC], 2010). In Norway, lung cancer incidence increased from 1988 to 2007 and in women, the age-adjusted annual average saw an increase of 4.9% compared to a smaller increase in men, which was 1.4%. This implies that, of the 64% increase in lung cancer incidence, women were more likely to be diagnosed with localized disease (Jia et al., 2013). In 2011, Lung cancer was the leading cause of death related to cancer in both female and male sexes (National Cancer Registry Ireland, [NCRI], 2014).

Lung cancer rates have been decreasing in men and plateauing in women of USA, the UK, Canada and Australia (Jemal et al., 2008; Peto, Lopez, Boreham, & Thun, 2006). This has led to a fall in the incidence and numbers for squamous carcinoma. As a matter of fact, the age-standardized incidence rate for squamous carcinoma has witnessed an annual decline of 2.8% since 1994, and the major part of this decrease was experienced between 1994 and 2001. However, there has been little change in the rates since that period. In men, the incidence rate of adenocarcinoma of the lung has witnessed a 3.5% increase per annum, though in the incidence of small cell carcinoma, there has been little change. On the other hand, there has been a 1.3% annual increase in the incidence of small cell carcinomas in women and a 6.5% annual increase in the incidence of adenocarcinoma; however, the incidence of small cell carcinoma has not witnessed any significant change (NCIR, 2014).

Cumulative exposures to ambient air pollution and carcinogenic substances put individuals at a higher risk of developing lung cancer (Timofeeva et al., 2012). Also, carriers of the TP53 genes also have an increased risk of having lung cancers whether they smoke or not, though the risk is higher if they smoked.

In men, the age-adjusted incidence of lung cancer is 84.9 for every 100,000 men and this varied with ethnicity from 48 for every 100,000 Hispanic men to 103.5 for every 100,000 African-Americans. Regarding lung cancer deaths, the age-adjusted incidence is 68.8 for every 100,000 men, and this also varied from 32.5 for every 100,000 Hispanic men to 87.5 for every 100,000 African-Americans. In women, the age-adjusted incidence is 55.6 for every 100,000 women and it varied with ethnicity from 27.1 per 100,000 Hispanic women to 57.9 for every 100,000 non-Hispanic women, while the age-adjusted lung cancer deaths' incidence is 40.6 for every 100,000 women, which also varied with ethnicity from 14.4 for every 100,000 Hispanic women to 42.6 for every 100,000 non-Hispanic women (Brenner et al., 2013).

Physical activities and exercises have proven to be very effective in the reduction of the risk of having lung cancer and mortality related to it among heavy smokers (Timofeeva et al., 2012).

In a prospective cohort study with 463,837 men and women that were aged between 50 and 71 years in the USA, the age-standardized incidence rates for current smokers that smoked more than two packs per day are 1,249.2 in every 100,000 person years in men, and 1,308.9 in every 100,000 person years in women. On the other hand, for never-smokers, the incidence rates are 20.3 in every 100,000 person years in men and 25.3 in every 100,000 person years in women (de Groot & Munden, 2012).

Recent evidence showed increased incidence of lung cancer in females compared with males. Oestrogen and progesterone play an important role in lung cancer. Lung cancer cells have been studied and found to have oestrogen receptors ER $\alpha$  and ER $\beta$ . New evidence suggests that the incidence and mortality of lung cancers in females with the use of hormone replacement therapy may increase. There is laboratory evidence which approved the carcinogenic effects of female sex hormones in lung cancer (Chakraborty, Ganti, Marr, & Batra, 2010).

## 2. Staging of lung cancer

According to the American Joint Committee on Cancer, staging cases related to lung cancer, the TNM (tumour, nodes and metastasis) staging system for various clinical stages of cancer, is subsequently the centre of this research. The tumour classifications include TX, Tis, T0 and T1-T4. In this case, Tx implies the tumour's inability for evaluation, while Tis refers to carcinoma *in situ*. Additionally, the classification T0 indicates that there are no signs of primary tumour, while T1-T4 shows the extension of the primary tumour. In this regard, T1 refers to tumours that are less than or equal to 3 cm, T1a refers to any tumour less than or equal to 2 cm in greatest dimension and T1b refers to tumours greater than 2 cm but less than or equal to 3 cm.

T2 explains tumours that are greater than 3 cm but less than or equal to 7 cm (this involves tumours that are greater than or equal to 2 cm distal to carina, even though they are involved in the main bronchus) when multiple cytopathology exams are carried out on pleural fluid (Toshihiko & Masato, 2015). Furthermore, the stage of cancer in a patient could be classified as M0 when the tumour is not associated with an exudate or bloody effusion.

For the occult stage, classification for the staging of cancer is Tx, N0 and M0, while for stage 0, it is Tis, N0 and M0. Stage IA is of two categories, namely T1a, N0 and M0; and T1b, N0 and M0. From stage IB, it is T2a, N0 and M0, while that of Stage IIA is of four categories. These include T2b, N0 and M0; T1a, N1 and M0; T1b, N1 and M0; and T2a, N1 and M0. That of stage IIB is also of two categories viz: T2b, N1 m0; and T3, N0 and M0. For stage IIIA, the staging is in eight different categories. These include T1a, N2 and M0; T1b, N2 M0; T2a, N2 M0; T2b, N2 and M0; T3, N1 and M0; T3, N2 and M0; T4, N0 and M0; and T4, N1 and M0. For stage IIIB, there are seven staging categories and they include T1a, N3 and M0; T1b, N3 and M0; T2a, N3 and M0; T2b, N3 and M0; T3, N3 and M0; T4, N2 and M0; and T4, N3 and M0. Finally, for stage IV, there are two staging categories and the first consists of any T, any N and M1a; and any T, any N and M1b.

## 3. Genetic susceptibility

There are genome studies that have made significant progress in the identification of the gene types that are involved in lung cancer (Brennan, Hainaut, & Boffetta, 2011). The identification features three separate loci that are strongly related to lung cancer. These are the genes that have the primary role of regulating telomerase production and also have a marked regulatory function on the acetylcholine nicotinic receptors. These genes are 5p15, 6p21 and 15q25. Rare variants of large effect in BRCA2 and CHEK2 affect the risks of lung cancer (Wang et al., 2014).

As a matter of fact, in mice, epidermal growth factor receptor T790 M mutation has a higher susceptibility of developing tumours than the epidermal growth factor receptors with both the T790 M and L858R mutations. This is due to the growth-promoting nature of the T790 M mutation (Steliga & Dresler, 2011). Apart from the environmental and lifestyle causes of lung cancer, familial issues can also be attributed as causative factors of lung cancer. The chromosome 6q in particular has been discovered to be highly contributory to the occurrence of familial cancer. To buttress this fact, a multipoint linkage analysis was conducted on families where some members have been diagnosed with lung, laryngeal or throat cancer at one point in time and it was discovered that the chromosome 6q (with marker D6s2436) saw a yield of maximum heterogeneity LOD score of 2.79 at 155 cM (Wang et al., 2013).

Another similar analysis was carried out on different sets of families and the results further revealed that the 6q23–25 showed a localization of a major susceptibility focus that influenced the risk of having lung cancer (Brennan et al., 2011). There is also a correlation between a sequence variant in the cluster of genes on the chromosome 15 that encodes the nicotinic acetylcholine receptors, and the smoking quantity as well as nicotine dependence of an individual (Steliga & Dresler, 2011). This implies that the cluster of nicotinic acetylcholine receptor genes on the chromosome 15q24 has an effect on the quantity of cigarettes that a smoker smokes and his or her nicotine dependency and these increase the risk of the smoker having lung cancer and other smoke-related diseases. Hence, nicotinic acetylcholine receptors serve as potential candidates for diseases and can be used as chemopreventive targets owing to the predisposition of the locus at 15q25 to cause lung cancer (Steliga & Dresler, 2011). An increased genetic susceptibility to lung cancer is associated with the status of the TP53 germline carrier, germline epidermal growth factor receptor (EGFR) T790 M sequence mutation, 6q23–25p, that of the mutation in region of chromosome 15 which contains three genes coding for subunits of nicotinic acetylcholine receptor and 15q24–25. Wang et al. (2013) observed that carriers of p53 germline mutations have a higher risk of having lung cancer. However, the risk is exacerbated when the person also happens to be a smoker. This observation was made in a comparative study of individuals that are carriers of the germline p53 mutation and those that are non-carriers.

The same case goes the other way round in the sense that a smoker is more likely to have cancer if he genetically belongs to a cancer-prone group. Some other environmental factors may also increase the risk of a p53 germline mutation carrier having cancer, especially in the case of cancer-prone groups like those that have Li-Fraumeni syndrome and hereditary retinoblastoma (Hwang et al., 2003). Germline mutations in the epidermal growth factor receptor gene also have the propensity to result in oncogenesis, though the incidences are quite rare.

#### 4. Classification of lung cancer

The two main categories of lung cancers include SCLC and NSCLC. Of these two, NSCLC is more frequent as it accounts approximately for 85% of overall lung cancers. Non-small cell lung cancer can be further classified into squamous cell cancer, adenocarcinoma, large cell carcinoma and other rare histological types.

Squamous cell carcinoma and adenocarcinoma are the common histological types of cancers affecting the lungs. They have notable differences in terms of growth and target-specific treatment features. Significantly, they are examples of non-small cell type of lung cancers. However, patients that have adenocarcinoma have a poor prognosis compared to those with squamous cell carcinoma (Weissferdt & Moran, 2013). Squamous cell carcinoma affects the flat cells lining the airways. Adenocarcinoma, on the other hand, affects the glandular tissues producing the mucus. The two types of cancers show distinct growth patterns that are unique. Adenocarcinoma can be papillary, solid, mucinous or micropapillary. Papillary adenocarcinoma takes place when the malignant tumour cells assume complex papillary structures (Sharma, Bell, Settleman, & Haber, 2007). These structures lead to the destructive growth that eventually replaces the normal tissue. Mucinous adenocarcinoma is notable for producing mucin, which is a major component of mucus. They grow rapidly in mucus-secreting cells that in turn become tumorous. In solid growth, the cell agglomerates assume a nest-like configuration that does not have acinar polarity. Cribiform areas, however, characterize the acinar growth patterns. In micropapillary growth, a genuine development of stroma-less micropapillae results in intra-alveolar tumorous cells (Sharma et al., 2007). The ring-shaped glandular structure may grow in the alveolar structures. Frankly, this is an invasive growth. In acinar growth, the differentiated tumours assume small glandular/ductal configurations that are irregularly angulated.

Distinctively, lung squamous cell carcinoma shows notable growth patterns that are differentiated. In addition to conventional growth patterns, lung squamous cell carcinoma may display distinct patterns. For instance, the growth pattern may extend to show prominent ameloblastic-like areas

that are similar to ameloblastomas in the jaw. In other unusual cases, squamous cell carcinoma displays prominent granular growth patterns that are unusual. Nevertheless, squamous cell carcinoma shows adenoid cystic-like growth patterns that resemble the cystic carcinomas (Weissferdt & Moran, 2013). Finally, squamous cell carcinomas exhibit interstitial growth pattern entrapped in the alveoli or respiratory epithelium. The growth pattern often mimics the glandular neoplasm or in some cases adenosquamous carcinoma.

Treatment that has been adapted lately involves guided EGFR-targeted therapy. Somatic mutations that occur in some tyrosine kinases have been pointed out as the major or central initiators and drivers of cancers (Kurzrock & Markman, 2008). These mutant proteins in the form of the kinase have become excellent substrates that are targeted by various therapies. This applies for the mutant EGFR-dependent lung adenocarcinomas. In such cases, EGFR mutation testing is conducted to help guide the available treatment options in achieving the desired results (Kurzrock & Markman, 2008). The major pathway that is targeted involves the epidermal growth factor receptor, to be specific EGFR, HER-1/ErbB1. This receptor consists of four closely related receptors all from the ErbB family. Following the binding of the ligand and the receptor homo- or heterodimerization and subsequent activation, the EGFR signals to the p13K/AKT and the RAS/RAF/MAPK pathways. These cellular pathways are targeted through target-specific therapy in cases of lung adenocarcinomas.

Lung squamous cell carcinoma is the second most common subtype of non-small cell lung cancer after lung adenocarcinoma. In the treatment of lung squamous cell carcinoma, FGFR kinase inhibitors have been pointed out to be effective. However, this study is not conclusive. The test was done on chromosome 8p12 following its amplification. The results obtained showed that these cell lines were sensitive to FGFR kinase inhibitors (Weissferdt & Moran, 2013). CLIA uses FISH to detect amplification of FGFR1 in patients (subjects). However, despite these advances, it remains unclear which of the patients with FGFR1 amplifications are most likely to respond positively to the available anti-FGFR1 therapy (Kurzrock & Markman, 2008). From the available pre-clinical data, additional biomarkers of the FGFR1 pathway are required to help identify the patients who will respond to the available therapy positively.

Although these have individual clinical and histological characteristics, they all share similar prognoses and treatment approaches. In the USA, adenocarcinoma represents approximately a range of 35–40% of the said lung cancer cases, making the country case the most frequent NSCLC as Gridelli et al. (2011) finds out. Most adenocarcinomas arise from peripheral lung tissue glands located in bronchioles or alveoli (Travis et al., 2015). Additionally, cancer could also manifest itself in the lungs as a “scar carcinoma” with its characteristic being the most prominent histological subtype. In the case of the mentioned scar carcinoma subtype, its manifestation is in the form of a bronchoalveolar that simulates multifocal tumours and is observable in smoking individuals. On chest radiographs, bronchoalveolar carcinoma appears in the form of a distinct subtype of adenocarcinoma that is characteristic of possessing a classic manifestation, which could also be an interstitial lung disease. Furthermore, this grows along the alveolar septa and goes ahead to develop from type II pneumocystis. Additionally, it may also manifest itself as a multifocal disease, solitary peripheral nodule. In some other cases, the disease may manifest itself in a rapidly progressing pneumonic form. The voluminous watery sputum serves as a characteristic finding in people that have advanced disease (Eleanor, Christos, & Mahbubl, 2015; Gridelli et al., 2011).

In fact, this condition accounts for approximately 25–30% of all lung cancer cases across the globe. While the adenocarcinoma tumors occur within the lung’s peripheral structure, SCC has its predominant place at the central parts of an individual’s lung. Significantly, the manifestation of SCC is characteristic of cavitory lesion manifested in the proximal bronchus. However, this subtype could not be defined without its histological feature characterized by the presence of keratin pearls as proposed by Cesare et al. (2012). It can also be informative to identify that this SCC could be

detected through cytologic studies due to its tendency to exfoliate. With SCC, this feature makes it most often associated with hyperkalemia.

Furthermore, research shows that almost 10–15% of studied and reported lung cancer cases have a close relationship with large cell carcinomas. Furthermore, lung cancer manifestation could be identifiable through chest radiographs since they usually are manifested as a large peripheral mass as a result of the improved technology for diagnosis and radiography for large cell carcinoma incidences (Sher, Dy, & Adjei, 2008). However, this lung cancer type does not have a significant evidence related to keratinization, which is typical of SCC. Similarly, the cancer type has no evidence that links it to gland formation, which is characteristic of adenocarcinomas. However, research indicates the prototype has sheets of cells that have focal necrosis that is highly atypical (Cesare et al. (2012)).

Over the years, scholars and professionals in the field of cancer have been striving to come up with various classifications of cancer, especially lung cancer. The importance of classifying lung cancer is hinged on the fact that there are various types of cancers and each of them behaves in a different manner. Most importantly, different types of cancers respond differently to treatment mechanisms and options at the disposal of the doctors. During the earlier years, classification of lung cancer hugely relied on the microscopic or histological look of the tumour cells.

Through the use of immunohistochemistry, professionals have been able to identify the different proteins exhibited by various tumours, thereby providing some refinery in the classification of lung cancer. However, the progress that has been made in the past 20 years has enabled professionals to employ the use of genetic and molecular marker expressions to further refine the classification process. It is important to note that such classifications play an important role. As a result of the classification, physicians are able to determine the best treatment plan for their patients. Personalized medicine and targeted medicine in the treatment of lung cancer are also based on the classifications.

## 5. 2015 Lung classifications

The 2015 lung classifications adopted the recommendations that were made by the 2011 report made by the International Association for the Study of Lung Cancer, the European Respiratory Society and the American Thoracic Society. Various specifications were made to be included in the classification of lung cancer. The 2015 classification emphasized and sought to improve various sections. First, the classification sought to expand on the usage of immunohistochemistry.

The classification recommends the use of immunohistochemistry not only for the large cell carcinomas, but also for the small cytology/biopsies as well as the resected specimens such as the neuroendocrine tumours, solid adenocarcinomas and the nonkeratinizing squamous cell carcinomas. The 2015 classifications have also further classified the non-small cell lung cancer (NSCLC) into finer pathological subtypes. For instance, adenocarcinoma and squamous cell carcinoma are further classifications of the NSCLC.

The 2015 classifications also set a new way of diagnosing lung cancer through the use of cytology specimens and small biopsies. The new method seeks to aid in the early diagnosis of the disease during screening. This is the first-ever classification to give a standardized terminology and criteria for diagnosing cytology and small biopsies. This has enabled the classification of the NSCLCs that had earlier been described as not otherwise specified (NOS). In this new diagnosis mechanism, tumours that depict clear patterns of adenocarcinoma such as papillary or micropapillary can be categorized as so without immunohistochemistry. Squamous cell carcinomas can also be diagnosed in the same manner.

Other specifications made in the 2015 lung classification include the need to diagnose adenocarcinoma through the use of histology. The classification points out that this is a clear predictor of improved income in case pemered therapy is used for treatment. It is also pointed out that lung

haemorrhage may take place in case individual's squamous cell carcinomas are treated through the use of Avastin, an angiogenesis inhibitor. Finally, adenocarcinoma should be looked out for epidermal growth factor mutations. The presence of such mutations is a clear predictive of response to tyrosine kinase inhibitors.

## **6. Important changes from 2004 WHO classifications**

The 2015 lung cancer classification made significant changes from the previous one which was passed in the year 2004. The key revisions that have been made on the classification are meant to improve the standards of diagnosing the disease. It is also believed that the changes will aid in improving patients' care, and will aid in the development of new treatment mechanisms as a result of new clinical trials.

The major changes include the use of immunohistochemistry in each and every classification. This also includes resected lung cancer. The new classification also puts an emphasis on genetic studies that are aimed at personalizing treatment mechanisms for cancer patients that are at an advanced stage of the disease. A new classification of cytology and small biopsies has also been developed in a bid to reduce the cases of not otherwise specified cancer cases. To further improve the diagnosis of lung cancer, the new specification has restricted the diagnosis of the large cell carcinomas to resected tumours only. However, it is only the large tumours that lack in a clear morphological differentiation that can be diagnosed as so. Otherwise, they should be further diagnosed. Neuroendocrine tumours have been grouped together.

Another differentiation that has been made from the 2004 classification is the moving of sclerosing haemangioma tumour to adenoma category and changing its name to sclerosing pneumocytoma. The name of hamartoma has also been changed to pulmonary hamartoma. Tumours of ectopic origin have also had another group created that have included meningioma, melanoma, germ cell tumours and intrapulmonary thymoma. Finally, the term mucinous bronchioloalveolar carcinoma has been changed to invasive micinuous adenocarcinoma.

According to Debevec, Jerič, Kovač, Bitenc, and Sok (2009), small cell lung cancer has several types combined into small cell, mixed small cell and pure small cell. This categorization presents a crucial and central lesion with the understanding of the mediastina invasion and hilar coupled with regional adenopathy. Nonetheless, its level of aggressiveness is more than that of NSCLC. According to Nicole et al. (2012), during the initial diagnosis of patients with SCLC, it is a common occurrence for them to already have metastatic disease. Metastasis of lung cancer is commonly found in the spinal cord, bones, adrenal glands, liver, brain and pericardium.

## **7. Management**

One of the most effective interventional means of treating NSCLC is complete surgical resection (IALT, 2004). However, IALT reports that other means are also in a position to increase the rate of surviving for patients with the condition. For instance, chemotherapy is a form of adjuvant treatment that can be used to manage the condition.

## **8. Treatment recommendations by the American College of Chest Physicians**

### **8.1. NSCLC stage I and II**

According to the American College of Chest Physicians (ACCP, 2007), there ought to be an evaluation of the patient before any surgery is carried out. In case there are no contraindications, then surgical resection can be conducted. Sub-lobar resection is more appropriate for patients at stage I of the condition. However, the use of sleeve lobectomy is recommended instead of pneumonectomy as an interventional strategy.

For the case of patients who are not in the position to be surgery candidates, the curative intent fractionated therapy is recommended. In this case, adjuvant chemotherapy is not necessary for

patients that are in the IB NSCLC stage. However, platinum-based chemotherapy is recommended for patients that portray good performance results from their initial management stages.

### **8.2. Stage IIIA1 or IIIA2 NSCLC**

Some of the surgical considerations to manage patients at this stage include the sampling of mediastinal lymph node or the complete dissection of the node. Lung resection may be completed if there is the discovery of the occult N2 at the resection. In this stage, adjuvant platinum chemotherapy may be recommended for patients with good progress results. However, adjuvant postoperative radiotherapy is recommended soon after chemotherapy. The work also warns against the use of concurrent radiotherapy and chemotherapy that is outside the projected clinical trials.

### **8.3. Stage IIIA3 NSCLC**

There ought to be a multidisciplinary evaluation by a thoracic surgeon when the treatment is at stage IIIA3. Also, chemoradiotherapy, a combination of platinum-based radiotherapy and chemotherapy, is recommended at this stage. It is not advisable to involve the use of adjuvant therapy outside the progress of the clinical trials. Instead, the use of platinum-based chemoradiotherapy is recommended.

### **8.4. Stage IIIA4 NSCLC**

In this stage, the use of platinum-based chemotherapy and radiotherapy is advised. However, there ought to be the use of concurrent chemoradiotherapy, as opposed to sequential chemoradiotherapy, in case there is an observed minimal weight loss in the patients. It is not recommendable to apply radiotherapy alone.

### **8.5. Stage IIIB NSCLC**

Patients in this stage ought to be subjected to thoracic radiotherapy once in a day, and not to be subjected to neo-adjuvant therapy. At the same time, concurrent chemoradiotherapy ought to be administered to patients who show a minimal weight loss. In case the patients lack malignant pleural, then a platinum chemotherapy should be their interventional strategy. In case they record a greater weight loss, usually around 10%, then there ought to be the use of chemotherapy, but only after there is proper and effective physician consideration. In other cases, palliative radiotherapy should be given to individuals who record poor performance status results.

### **8.6. Stage IV NSCLC**

It is the role of physicians and therapists to advise their patients regarding some of the risks and benefits associated with the interventional methods for them to make sound decisions regarding the treatments they feel suit them. For instance, a physician may advise a patient with low performance score to be subjected to chemotherapy. However, it is not recommendable to include a third agent in chemotherapy. Another example of a consideration that a physician ought to have in mind during the administration of the interventional methods is that single-agent chemotherapy ought to be administered to patients of age bracket <70 years. Also, it is worth noting that patients of age 80 years and above ought to consider some of the benefits associated with the therapies based on their personal circumstances.

In case a physician is using chemotherapy, then they should include bevacizumab, carboplatin and paclitaxel for patients that lack brain metastases, among other conditions. However, it is unclear on the effects of including the agents during chemotherapy, but there is the likelihood that the process would enhance the free survival of the patients. At the same time, cetuximab can be an essential additional agent to the platinum-based chemotherapy for patients that have advanced NSCLC.

## **9. Current therapies for non-small cell lung carcinoma**

There are different options for the treatment of NSCLC, such as radiation therapy, surgery and chemotherapy, depending on the stage of the tumour. The combination of cisplatin with agents of third generation such as paclitaxel has reached objective responses from 20 to 35%, with a median of 4–5

months (SLP) progression-free survival and overall survival (SG) of 8–11 months. Current chemotherapy regimens have limited effectiveness, with a modest benefit in terms of survival and entail significant toxicity, giving rise to limitation of this treatment, even in the context of first-line therapy. Accordingly, at present, there is a need to provide less toxic agents to the patients, as novel targeted therapies have the potential to improve efficiency and maintain a good quality of life with low toxicity. The inhibition of receptors with TK activity by administration of antibodies, monoclonal, interference RNAs or EGFR TKIs, prevent proliferation and survival of neoplastic cells, inducing cell arrest and apoptosis (Ma et al., 2005). Against the EGFR pathway, molecular treatments are one of the therapeutic strategies in NSCLC. The treatments with biological agents such as monoclonal antibodies and the EGFR TKIs are the choice to be used as first- and second-line treatments in patients with advanced NSCLC (Scaltriti & Baselga, 2006). Since then, they have an acceptable toxicity and have shown surprising results in a particular group of patients. Antibodies as cetuximab competitively bind to the extracellular domain of the EGFR which inhibits the association of its ligand and prevents their dimerization and phosphorylation and activation (Janku, Stewart, & Kurzrock, 2010). In addition, the inhibition of the receptor induces its down-regulation and eventually its internalization and degradation, a process that explains the antitumor activity of these antibodies (Kobayashi et al., 2005).

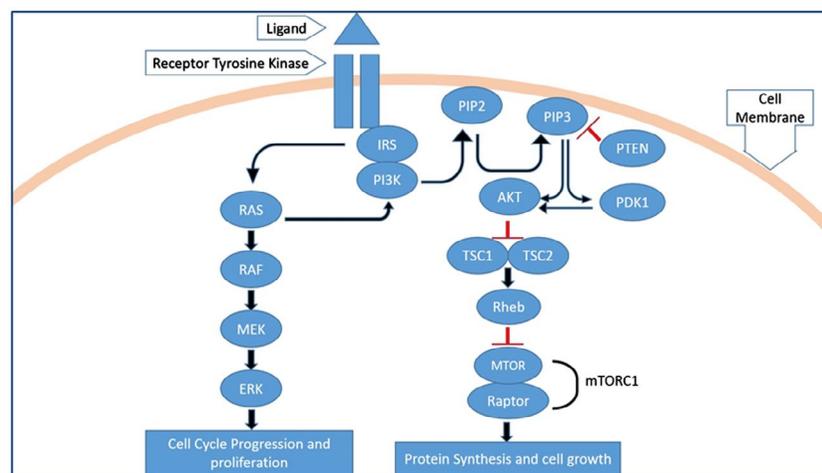
### 10. PI3K/MEK pathway

Non-small cell lung tumours posed a challenge for researchers because of its resistance to different therapies. Researchers have developed a possible treatment based on the combination of two inhibitors of kinases, which demonstrated a significant reduction of the tumour in cases linked to k-RAS gene mutations in animal model. The research concluded that cancers with mutations in this gene have been resistant to therapies designed to date (Kwak et al., 2010). A combination of inhibitors of PI3K and MEK, which are two families of drugs currently in development, was found to be effective in NSCLC (Kwak et al., 2010).

The study began with an approach to the signalling pathway of PI3K, key in cellular motility and adhesion, and whose mutations caused tumours in laboratory work (Figure 1). Its role has not yet been studied in mice, so the Group developed a GM model in which the administration of doxycycline induced the expression of PI3K mutations associated with cancer (Courtney, Corcoran, & Engelman, 2010).

Treatment of animals with an inhibitor of the gene allowed tumour regression. The researchers tested this inhibitor in mice with tumours stimulated with k-RAS and found that this therapy was not effective since k-RAS also activates MEK signalling pathway and treated the mice with an inhibitor of this gene in combination with the PI3K inhibitor (Pratilas et al., 2008).

**Figure 1. PI3K/AKT/mTOR signalling pathway.**



Alone, MEK inhibitor resulted in a minimum reduction of the size of the tumour; but, in combination, “the cancer disappeared virtually”. Kwon-Kin Wong, among the authors, believes that the results are enough to test in human therapy in phase I and II. As noted, the combination could also apply to other types of cancers mediated by k-RAS (Rinehart et al., 2004).

In response to the union of different ligands as the epidermal growth factor (EGF), the transforming growth factor alpha (TGF- $\alpha$ ), beta-celulina, epiregulina and amfiregulina, the EGFR is capable of joining another receiver of the same type (homodimerization) or with other receivers of the same family (heterodimerization) to induce the activation of its TK domain and carry out its auto phosphorylation in five residues of tyrosine (Tyr 1173 1148, 1086, 1068 and 992) (Engelman & Janne, 2008). The auto phosphorylation allows activation of multiple pathways of downstream signalling, as the RAS-RAF-MAPK and PI3K pathways via STAT induce the regulation of proliferation and cell invasion, angiogenesis, apoptosis and metastasis inhibition (Brugge, Hung, & Mills, 2007; Roberts & Der, 2007).

The constitutively activated EGFR, RAS-RAF-MAPK pathway influences the acquisition of a malignant phenotype through the synthesis of DNA and uncontrolled cell proliferation (Sos et al., 2009). On the other hand, reported mutations in KRAS appear in early events of NSCLC, mainly in adenocarcinomas. These mutations are mutually exclusive, EGFR mutations and are associated with the resistance of TK (EGFR TKIs).3 EGFR inhibitors (Montagut & Settleman, 2009).

The constitutive activity of the EGFR has been observed by more than 60% of patients with NSCLC, and is due to different mutations present on the receptor. These represent 50% in non-smokers compared to 10% of smokers and 40% in adenocarcinomas, 3% of other histological types, where 90% of these mutations are located in exons 19 and 21 of EGFR, where the binding site is located at the domain TK12 ATP. Exon 19 deletions, as the mutation L858R, are mutations of response to EGFR-TKIs such as the gefitinib and erlotinib. Due to the mutation L858R, gefitinib joins 20 times more to the L858R mutant, the wild EGFR (Engelman et al., 2005; Lynch et al., 2004; Zhou et al., 2011).

The PI3K signalling pathway plays an important role in the metabolism of cancer (Cully, You, Levine, & Mak, 2006), well contributes to the progression of the cell cycle, decreasing apoptosis and increasing the metastatic cancer cells' capabilities. Uncontrolled activation of PI3K route contributes to the cellular transformation and tumour progression in several types of tumours, including brain, breast, ovary and renal carcinomas (Cully et al., 2006). The activation of PI3K can occur through activated Ras or directly by some receptor tyrosine kinase, which responds to various growth factors and cytokines such as IL-1, IL-2, IL-3, IL-4, IL-6, factor of growth type insulin (IGF), epidermal growth factor (EGF), growth factor derived from platelets (PDGF), insulin (IGF-1 and IGF-2) growth factors and the Stimulator factor of colonies (CSF) (Janmaat, Kruyt, Rodriguez, & Giaccone, 2003). The activation of these receptor tyrosine kinases leads to the auto phosphorylation of the intracellular portion of them, which serves as a starting point to other intracellular proteins (Downward, 2003).

The PI3K/AKT activated route starts through the recruitment of PI3K to the plasma membrane through the union of its SH2 domain to the phosphorylated tyrosine. In particular, the receptor tyrosine kinase-phosphorylated tyrosine residues interact with the regulatory subunit of PI3K, p85 (Zhang, Yang, & Gray, 2009). Kinase activities are regulated by the phosphatases that act by eliminating the phosphates of the diana proteins. There is evidence that PTEN dephosphorylates PIP3, therefore acting as a regulator of the PI3K signalling path. PTEN is a domain protein tyrosine phosphatase, suggesting that PTEN suppresses tumour cell growth, exerting an antagonistic effect to the proteins tyrosine kinases regulating the invasion of tumour cells and metastasis through interactions with focal adhesions (Gadgeel & Wozniak, 2013).

PIP3 serves as a ligand to recruit the serine/threonine kinase Akt (c-Akt, also called protein kinase B, PKB) to the plasma membrane. Once on the inner side of the membrane, Akt is phosphorylated by a serine/threonine kinase, kinase 1, phosphatidyl inositol-3 (PKD1) dependent, resulting in the activation of Akt (Janmaat et al., 2003; Massion et al., 2002). The activation of Akt controls cell survival

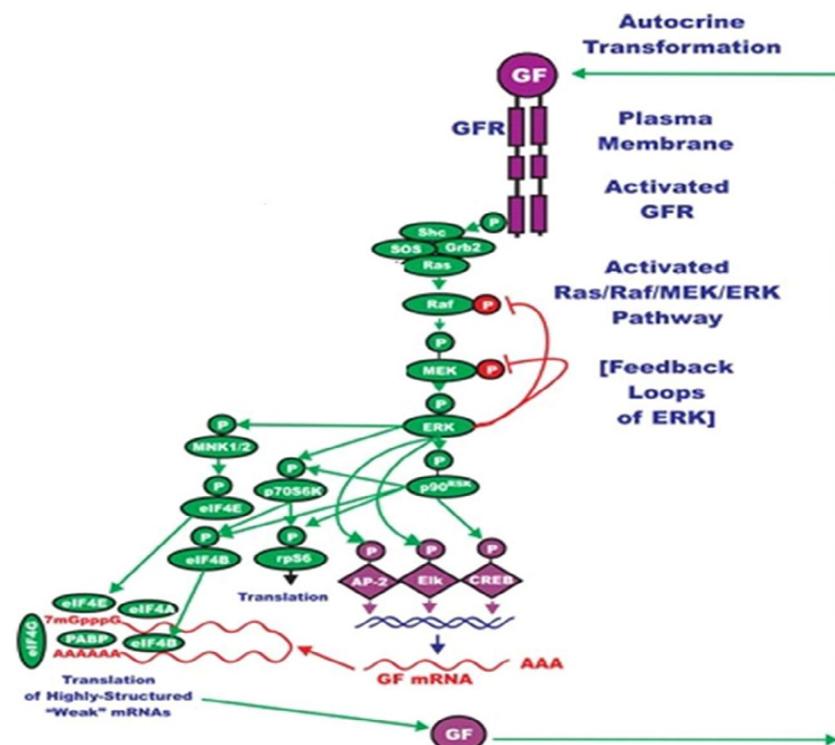
through the phosphorylation of the targets that depend on it, with the net result of an increase in cell survival, proliferation, growth and metabolism. The targets for the activation of Akt can be classified into three distinct groups: apoptotic proteins, factors of transcription and kinases (Hennessy, Smith, Ram, Lu, & Mills, 2005).

Akt phosphorylates directly two apoptotic proteins, BAD and caspase 9, inhibiting its activity, apoptotic, and thus promoting cell survival. Transcription factors may well be activated or inhibited after the phosphorylation of Akt. Akt activates HIF and CREB, NF- $\kappa$ B transcription factor which has resulted in an increase in transcription of anti-apoptotic genes. The NF- $\kappa$ B transcription factor is the central mediator of the immune response, inflammatory response and cell survival response. NF- $\kappa$ B is activated by Akt through the phosphorylation of the inhibitory kinase. After its activation, IKK phosphorylates I $\kappa$ B, marking for the ubiquitination and proteasome degradation. This exposes the locations of nuclear localization of NF- $\kappa$ B and allows the translocation to the nucleus where it induces the expression of genes, anti-apoptotic. EGF growth factors activate NF- $\kappa$ B and protect against apoptosis and, conversely, inhibit NF- $\kappa$ B-sensitized cells.

In addition, the EGF-induced and Akt-mediated HIF-1 activation leads to a greater expression of the endothelial growth factor (VEGF) that protects cells from apoptosis. Akt also phosphorylates CREB, directly activating its transcriptional activity and overexpressing antiapoptotic Mcl-1 genes. On the contrary, Akt inactivates FOXO transcription factors (Forkhead family) and p53, which directly express FOXO proteins or by phosphorylation and MDM2, negative regulator of p53 activation. In both cases, the expression of proapoptotic genes decreases causing an increase in cell survival (Morgillo et al., 2008).

GSK-3 is also a target of Akt phosphorylation, which determines its inactivity, blocking its transcriptional activity and the regulation of its metabolism. Inhibition of GSK-3 protects cells from apoptosis, but the exact mechanism is not known. Specifically, the phosphorylation of mTOR by Akt occurs through the inactivation of tuberous sclerosis (TSC) complex. The TSC is a heterodimer consisting of tuberin (TSC2), non-phosphorylated, and hamartin (TSC1), which acts as a protein GTPase

Figure 2. MEK signalling pathway (Steelman, Chappell, et al., 2011).



activating (GAP)/inhibiting the small protein G-Rheb. By phosphorylation of TSC2, Akt interrupts the complex, allowing Rheb to join ATP and pass from the GTP state from inactive to active. Rheb, together with GTP, activated mTOR (Serra et al., 2008). On a parallel route, the AMPK protein phosphorylated, although in this case enabled, TSC2, thereby inhibiting the activation of mTOR in response to changes in intracellular ATP/AMP ratio. This attaches the route that senses energy levels (via amino acids and ATP), with the path of mTOR. LKB1, a serine–threonine kinase (also known as STK11), is an activating kinase of AMPK, which serves as an important inhibitor of the route mTOR in response to energy shortages (Serra et al., 2008).

KRAS is a gene that is mutated in about 20% of all cases of NSCLC, especially adenocarcinomas and smokers. It is the most common oncogenic mutation and their prognostic value has not been clearly demonstrated (Wee et al., 2009). Currently, there is a need for investigating different drugs, highlighting especially those who act in lower levels of signalling pathway RAS, as inhibitors of MEK 1/2, whose effectiveness is also being evaluated, and inhibitors of PI3K/AKT/mTOR signalling pathway (Pratilas et al., 2008) (Figure 2).

### 11. Classes, structure and function of PI3K

Phosphatidylinositide 3-kinases belong to group of enzymes which are involved in functions of cells such as differentiation, proliferation, cell growth, survival, motility and intracellular traffic, which are in turn involved in cancer. These enzymes are capable of phosphorylating the hydroxyl group in position 3 of the ring of phosphatidyl inositol. They are also known as phosphatidylinositol-3-kinase. The route, with PIK3CA oncogene and tumour suppressor PTEN, is involved in the lack of sensitivity of the cancer tumours to insulin and IGF-1, in calorie restriction.

The class I PI3K is accountable for the production of phosphatidylinositol 3-phosphate, phosphatidylinositol bisphosphate and phosphatidylinositol-triphosphate. The regulatory subunit more highly expressed is p85a (Miled et al., 2007).

PI 3-kinases have joined a remarkably diverse group of cellular functions, including cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. Many of these functions refer to the capacity of the class I PI 3-kinases to activate protein kinase B, as in the PI3K/Akt/mTOR route. Isoforms regulate different aspects of the immune responses. There is a great interest in the role of PI 3-kinase signalling in non-small cell lung carcinoma.

### 12. Surrogate biomarkers

New therapies such as the PI3K inhibitor would be of greater benefit to the standard care therapy if they prove to improve morbidity and mortality, in clinical settings. Biomarkers however are an objective measure of biological and pathological responses to therapeutic intervention. Predictive biomarkers provide information on the response-dose effect of a given therapy, whereas prognostic biomarkers offer information on the course of disease and possible outcomes independent of therapy. The potential use of biomarkers as surrogate end points includes functional imaging techniques, blood-based assays for circulating tumours and direct molecular assessments.

Solid tumours such as NSCLC release metabolic by-products into bloodstream including proteins, RNA, DNA and circulating tumour cells. In NSCLC, the lack of CEA expression has precluded routine measurement of this marker in clinical evaluation. However, agents targeting direct tumour pathways hold great future promises. The major obstacles in detection of tumour by-products (cells, DNA and RNA) are the low cellular yield, specialized laboratory techniques for sample processing and isolation, undetectable levels of DNA/RNA, also some normal cells producing such by-products, hence compromising sensitivity, as well as specificity of detection.

Major improvements have been made on biomarkers that assess direct cellular processes using targeted agents such as EGFR (Felip et al., 2008), HER2 (Spector et al., 2005), MET (Yap et al., 2011),

**Table 1. Limitations on current assessment tools**

Assessment type	Measurement tool	Imaging	Limitations
Imaging-based assessment	Anatomical measurement of tumour size and location (Eisenhauer et al., 2009; Miller, Hoogstraten, Staquet, & Winkler, 1981)	CT-scan (Oxnard et al., 2011)	(1) Clinical variability between measurements (2) Difficulty in capturing complex lesions, e.g. asymmetrical growth patterns
		3D Volumetric measurements (Mozley et al., 2012)	Multicentred trials needed
Molecular imaging	Biological pathways and molecular targets (Kircher, Hricak, & Larson, 2012)	PET	(1) Imprecise anatomical localization (2) Cellular pathways not well identified (3) Physiological excretion or uptake may interfere, e.g. bladder/kidneys
		SPECT	
		MRI	
		Optical imaging	
Immunotherapy	Solid tumours including NSCLC expresses programmed cell death receptors/ligands	T-cell down regulation and tumour immune escape can be used as an advantage to immunotherapy targeted-imaging	Difficulty in identifying pseudo progression (probably due to immunecell infiltration) from true tumour growth (Wolchok et al., 2009)

BRAF (Flaherty et al., 2010), mTOR (Armstrong et al., 2010) and MEK (Weekes et al., 2013). Several barriers restrict the incorporation of biomarker measurements as end points of clinical trials. Major issues involve assay validation, assay standardization, regulatory measures, long-term trials and other technical laboratory and/or technological limitations (Table 1).

### 13. Mutations in PI3K pathway in lung cancer

The PI3K gene encodes an enzyme dimeric comprising a catalytic subunit and a regulatory subunit; the first of these may have four isoforms (p110 $\alpha$ , p110 $\beta$ , p110 $\gamma$  and p110 $\delta$ ) that are combined with subunits, regulatory (p85 and p101). Mutations in the p110 $\alpha$  isoform generate gain of function in the enzymatic activity of PI3K, with the consequent acceleration of molecular signalling which results in the activation of transcription factors and cell proliferation (Pao & Girard, 2011).

Despite the introduction of new treatments, the survival rate for patients with metastatic colorectal cancer remains less than 10% at five years. Currently, there are new treatment options such as the use of monoclonal antibodies directed against the receptors (EGFR) of epidermal growth factors, Cetuximab and Panitumumab. Both molecules bind to the extracellular domain of the EGFR by inducing an inhibition of the cascade of signal generated by the dimerization of the receptor normal conditions; this provides a significant clinical benefit. However, this benefit is limited to a segment of the treated patients.

It has been shown that mutations in the KRAS oncogene, affecting the “downstream” of the EGFR signalling pathway, may put at risk the effectiveness of the antineoplastic therapy in patients treated with Cetuximab or Panitumumab. The remnants of subjects group have mutations in genes BRAF, NRAS and PI3K; the last of these is mutated in approximately 20% of the tumour cells of patients with metastatic colorectal cancer. Alterations in this gene occur primarily (90%) in the (encoded by PIK3CA) p110 $\alpha$  catalytic subunit in two “hot spots”, specifically located in exon 9 (E542K, E545K) and exon 20 (H1047R) (Flaherty et al., 2012).

Mutations in the gene of PI3K oppose responsiveness of monoclonal antibodies directed against EGFR in patients with metastatic colorectal cancer through a mechanism similar to what happens when there are mutations in the KRAS gene.

### 14. Inhibitors of PI3K signalling in cancer treatment

The RAS oncogene encodes a protein that is located on the inner layer of the plasma membrane. To anchor RAS, it must join a farnesyl group and along with the presence of enzyme farnesyltransferase

which is an essential step for this process. The active form of RAS then interacts with effector molecules such as Raf and PI3K (Roberts & Der, 2007).

Given the requirement of FTasa activity for RAS function, compounds with capacity have been developed to inhibit the enzyme farnesyltransferase (FTIs). These agents are able to inhibit the proliferation of malignant cells *in vitro* and *in vivo* (with or without mutation of RAS). An observation that additionally supports the development of farnesyltransferase inhibitors in breast cancer is the fact that infiltrating breast tumours are significantly higher than the normal breast tissue farnesyltransferase activity (Sequist et al., 2011).

#### **14.1. PI3K inhibitor (targeted therapies)**

The treatment of these animals with an inhibitor of PI3K of experimentation led to rapid tumour regression (McCubrey et al., 2006). Previous studies have suggested that the inhibition of PI3K could also block the development of k-RAS-induced tumours; researchers also tested the PI3K inhibitor in mice with tumours stimulated with k-RAS. This treatment was effective, but since k-RAS also activated via signalling pathway MEK/ERK, researchers treated animals with an inhibitor of MEK of experimentation and a combination of both drugs. Just MEK inhibitor treatment caused only a modest reduction in the size of the tumour, but the combined treatment caused k-RAS-stimulated lung cancers to nearly disappear (McCubrey et al., 2006).

PI3K/Akt regulates the function of hexokinase and their association/displacement of VDAC, mitochondrial function, and how the hexokinase activity contributes to the FC-mediated cell survival requires further analysis. Thus, inhibition of glucose through inhibition of PI3K/Akt can determine events that target neuron cell death, and constitute a therapeutic target. In the endothelium, PI3K/Akt promotes survival by inhibiting apoptosis mediated via Fas to regulate the expression of FLIP (FLICE inhibitory protein); FLIP interacts with FADD (FAS-associated death domain), inhibiting the activation of Caspase 8.

#### **14.2. MEK inhibitors (targeted therapies)**

The results of clinical studies of dabrafenib and trametinib presented at the Congress are an important step towards the understanding of how these agents in research can help patients with advanced melanoma and metastasis. Above all, trametinib is the first inhibitor of MEK that has demonstrated clinical benefit in an advanced phase (phase III) clinical trial (Gossage & Eisen, 2010).

The discovery is of particular relevance because the combination therapies aimed at the network of kinases MEK/BRAF are considered standard treatments in patients with melanoma and mutations in BRAF, although it is known that many patients end up generating resistance. Inhibition of BRAF-resistant tumours tends to be more aggressive and invasive. According to the study, the cause of this aggression is the high activity of Epha2 protein, which also is strongly expressed in glioblastoma stem cells membrane. In cells resistant to BRAF inhibitors, the simple withdrawal of treatment with BRAF or MEK inhibitors reversed the aggressive behaviour of the cells. This has led scientists to propose a treatment in which BRAF or MEK inhibitors are administered intermittently, which also means that patients could continue this therapy for longer. The research also showed that inhibition of Epha2 decreases aggressive behaviour of the melanoma cells, indicating that therapies directed against this protein can prevent the development of new disease in patients receiving therapy with BRAF or MEK inhibitors.

#### **14.3. Synergy effect of PI3K and MEK inhibitors**

*In vitro* EGFR blockade follows an increase of apoptosis induced by RT, which causes a synergistic afford radio sensitization, which may be higher when using strategies simultaneously against EGFR and regulators such as PI3K and MEK signalling pathways. The *in vivo* data in animal models also show a positive interaction between PI3K and MEK inhibitors (Konstantinidou et al., 2009).

Improving the effectiveness of treatment of cancer patients by means of inhibitors with small molecule signal transduction is the goal of the current attention on development of inhibitors. Achieving this goal has not been easy as a result of a number of reasons. In first place, the success of a signal transduction in the suppression of growth happens to have a distinct susceptibility. Secondly, instead of being cytotoxic, many small molecule transduction inhibitors are cytostatic and will therefore need combination with a therapeutic modality that actually induces death. Finally, in cancer cell in general, more than one signal transduction pathway may be activated.

mTOR targeting has been examined in the treatment options for a number of diverse cancers as well as in melanoma therapy. In human melanoma cells, co-targeting Raf and Akt/mTOR inhibitors with Raf and PI3K/PTEN/Akt/mTOR pathways can arrive at lines; preclinical studies that have been performed have highlighted the synergistic inhibition.

This synergy has also been observed when using both monoclonal antibodies directed against the extracellular domain of the receptor, preventing its activation by the ligand, as with low molecular weight molecules that inhibit the auto phosphorylation in the intracellular domain. Of these agents, the most studied have been cetuximab chimeric monoclonal antibodies and the Ann inhibitors, gefitinib and erlotinib (Lynch et al., 2004). In neutrophils, two Fcγ receptors, i.e. FcγRIIA and FcγRIIIB, are expressed constitutively. The signalling pathways that regulate phagocytosis mediated by FcγRIIA have been described relatively well. However, different signalling pathways that lead to the activation of the NF after the commitment of each Fcγ receptor have only been partially described. To solve this problem, neutrophils were stimulated by cross-linking selectively each kind of Fcγ receptor with specific mAbs, and then activation of NF was analysed. FcγRIIIB, but not FcγRIIA, promoted a strong increase in ERK phosphorylation in the core and also efficient phosphorylation of NF Elk-1. However, mAb IV.3 (anti-FcγRIIA) only did not cause an increase in ERK phosphorylation within the nucleus. The FcγRIIIB-induced nuclear phosphorylation of ERK and Elk-1 was not affected by inhibitors Syk, PI3K and MEK. On the other hand, the FcγRIIA or the FcγRIIIB of ERK-mediated phosphorylation cytoplasmically depended on Syk, PI3K and MEK. Furthermore, ERK, but not MEK, was constitutively present in the nucleus and FcγRIIIB cross-linking did not increase levels of nuclear ERK and MEK (Meng et al., 2010). These data show clearly that different receptors of Fcγ neutrophils possess different capacities from signalling (Table 2). FcγRIIIB, but not FcγRIIA, activated a signalling pathway only which leads to phosphorylation of ERK and Elk-1 nuclear restriction, regardless of Syk, PI3K and MEK (Zou et al., 2012).

**Table 2. Recent clinical trials and phase of drug development in PI3K and MEK inhibitors**

Condition	Intervention	Phase	Sponsor
Lung adenocarcinoma	BKM120 drug used as inhibitor of PI3K	1	City of Hope Medical Centre
Unspecified solid tumour in adults	BKM120 drug used as inhibitor of PI3K	1	Cancer Institute Roswell Park
Glioblastoma	MK3475 drug is used	1	Council for Medical Research
	Biological suppressor of PI3K pathways	2	
NSCLC	SAR345409 used as PI3K inhibitor	1	EMD Serono
Haematologic malignancies	RP6530 drug	1	Rhizen Pharmaceuticals
Tumours activated by PI3K pathways	BKM120 drug is used	2	Novartis Pharmaceuticals
NSCLC	BKM120 drug is used	2	Novartis Pharmaceuticals
Lung cancer adenocarcinoma	MEK 162 drug used	2	Novartis Pharmaceuticals
NSCLC	MEK 162	1	H. Lee Moffitt Cancer Center
NSCLC	AZD6244	2	NCI (National Cancer Institute)
	Erlotinib and both in combination were used		

## 15. Conclusion

Although major developments have been made in the management of non-small cell lung carcinoma, the overall survival rates remain poor. The importance and appreciation of intracellular signalling pathways of MAP Kinase and its close relevant association with non-small cell lung carcinoma have provided the ground base for a new generation of pharmacological therapies known as targeted therapies. Downstream regulators of PI3K pathway have become targets for many cancer chemotherapy agents, and indeed many have already reached clinical stage. The coexistence of multiple PI3K pathway mutations within a single tumour suggests a superior effect with combinational synergistic therapy to shutdown the multiple mutated pathways to inhibit tumour growth.

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