

The Important Role of EGFR in Tumorigenesis and Treatment, Trials and Application of the Drugs Targeting EGFR

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Abstract: Non-small cell lung cancer (NSCLC) is a group of diseases that account for most lung cancer cases. Studies have shown that the cause of its mutation is the overexpression of epidermal growth factor receptor (EGFR) in human body. In this paper, the background, including the family of ErbB, of EGFR is given to show its importance in cancer therapy. The recent studies had developed inhibitors of EGFR that can slow or even prevent the reproduction of EGFR in human body. Some of the inhibitors are listed out in the paper, the brief summaries of their effect and usage have also been provided. Results for their trials on stage II and stage III patients are given to show their efficiency and safety.

1. Introduction

The accurate prediction of power load is of great significance for the electric power production and the safe operation of the power grid and the national economy [1]. Short term load forecasting is an important part of energy management system. The prediction error directly affects the analysis results of subsequent safety check of power grid, which is of great significance for dynamic state estimation, load scheduling and cost reduction [2-4]. Traditional prediction methods are based on linear regression, such as time series method, analysis method and pattern recognition method has defects of respectively [5].

2. Introduction

Non-small cell lung cancer (NSCLC) is a group of diseases that account for 80-90 % of lung cancer cases. Despite tremendous progress in recent decades, it remains a leading cause of death. Non-small cell lung cancer is caused primarily by smoking. A persistent cough and shortness of breath are symptoms of non-small cell lung cancer. Surgery, radiofrequency ablation, radiation therapy, and chemotherapy are commonly applied treatments for NSCLC. The introduction of inhibitors of the epidermal growth factor receptor (EGFR) has been one of the most significant developments in its treatment in recent years. In this paper, the background of EGFR will be provided, and the data of trials of EGFR inhibitors are given out.

3. Background

3.1 What is Epidermal Growth Factor Receptor

EGFR is a transmembrane protein that acts as a receptor for ligands from the epidermal growth factor family of extracellular proteins. Cell survival, proliferation, migration, adhesion, and differentiation are all controlled by the EGFR family of receptor tyrosine kinases. While growth factor-induced EGFR signalling is essential for many regular morphogenic processes and is involved in a range of other cellular responses, aberrant EGFR activation is related to tumour cell genesis and proliferation [1]. Activation of the EGFR proto-oncogene may lead to cellular phenotypic alteration and provide tumour cells with significant growth and survival advantages [2]. EGFR and its cognate ligands (which include EGF and transforming growth factor (TGF)- α) have been found as a common

component of several cancer forms over the last 40 years [3]. In many cases, abnormal EGFR activation, mediated mostly by changes in gene amplification and autocrine stimulation, appears to be a key element in carcinogenesis and a major driving force for cancer cells' aggressive growth [4]. Increased EGFR expression is thus expected to be a powerful prognostic factor in a variety of tumour forms and blocking its cellular functions is believed to bring significant therapeutic benefits. Therefore, drugs which specifically inhibit EGFR have been developed over the past years.

3.2 The ErbB receptors and their cognate ligand

The ErbB family of receptor tyrosine kinases (RTK) comprise four distinct receptors: the EGFR (also known as ErbB-1/HER1), ErbB-2 (neu, HER2), ErbB-3 (HER3) and ErbB-4 (HER4) [5]. The inclusion of an EGF-like domain composed of three disulfide-bonded intramolecular groups, which confers binding specificity, as well as additional structural motifs such as immunoglobulin-like domains, heparin-binding sites, and glycosylation sites, distinguishes proteins in this family. EGF-related growth factors can be split into three classes in terms of ErbB-receptor binding (Table 1) [1]. EGF, transforming growth factor (TGF- α), and amphiregulin (AR) are three proteins that bind to the EGFR specifically. Betacellulin (BTC), heparin-binding growth factor (HB-EGF), and epiregulin (EPR) are members of the second category, which bind both EGFR and ErbB-4. The neuregulins (NRGs) make up the third group and are divided into two subgroups according to their ability to bind ErbB-3 in addition to ErbB-4 (NRG-1 and NRG-2, NRG-3 and NRG-4) [6-9]. ErbB-2 would not favour any of the EGF peptides.

Table 1. The ErbB receptors and their cognate ligands

ErbB Receptors	EGFR	ErbB-2	ErbB-3	ErbB-4
Cognate ligands	EGF	None	NRG 1	NRG 1
	TGF- α		NRG 2	NRG 2
	AR			NRG 3
	BTC			NRG 4
	EP			Tomoregulin
	HB-EGF			HB-EGF
				BTC
				EP

3.3 Role of EGF-like peptides in development

In animals lacking EGF and TGF expression, the prostate gland does not mature normally [10]. TGF-knockout mice had increased proliferation of anterior, dorsal, and lateral prostatic buds compared to wild-type mice. The development of buds in EGF deficient mice did not increase. The formation of the prostate bud was not observed in animals with null mutations in both EGF and TGF- α . As a result, both EGF and TGF- α appear to be required for prostate development, with TGF- α possibly being required to prevent EGF-dependent overstimulation. EGF, HB-EGF, and TGF- α are all members of the EGF family of growth factors that govern cellular functions such as proliferation, migration, and differentiation in the central and peripheral nervous systems [11]. Although knockout mice for the TGF- α gene have defects in their skin, hair, and eyes [12], the lack of the TGF- α gene does not affect the development or function of the neurological system in these animals, despite lower numbers of neurons in the midbrain and forebrain [13,14]. Furthermore, TGF- α knockout mice showed no differences in peripheral nerve regeneration [15]. Other ErbB ligands may compensate for deficiencies in TGF- function in the neurological system, according to these findings. There is no substantial change in the shape of the gastrointestinal mucosa in mice having specific null mutations for TGF- α , EGF, or AR [16-18]. In contrast, mice with triple null mutations lacking AR, EGF, and TGF- α showed growth retardation, which was attributed to gastrointestinal changes such as decreased duodenal mucin production, the formation of short, fragile villi in the ileum, and reduced DNA synthesis in the cryptic cells of the intestinal mucosa [15]. Triple knockouts lacking AR, EGF, and TGF- α , on the other hand, survive to adulthood with modest growth retardation, implying that other EGF-family members may

activate ErbB receptors, resulting in normal gastrointestinal development and physiology. Null mutations for EGF, AR, and TGF- α had no effect on proliferation or apoptosis inside the mammary gland terminal end bud, and pubescent mice lacking AR had defective ductal development but were still able to nurse their young [18]. Triple knockout animals lacking expression of AR, EGF, and TGF- α exhibited abnormal mammary alveolar growth and decreased milk production, indicating that these growth factors play a key role in alveolar formation and lactogenesis. These findings show that ErbB ligands may play a crucial role in the development and function of specific organs when taken jointly.

4. EGFR inhibitors

NSCLC is one of the epithelial malignancies with high levels of expression of the EGFR family of ligands and receptors [19]. Overexpression of EGFR has also been found in bronchial premalignant lesions, implying that the EGFR-mediated pathway may play a role in lung cancer development [20]. Monoclonal antibodies (mAbs) aimed at the EGFR extracellular domain and low molecular weight tyrosine kinase inhibitors (TKIs) reduce EGFR's tyrosine kinase activity by competing with ATP for the ATP-binding site. Small-molecule EGFR TKIs can be classified as reversible or irreversible TKIs, as well as selective for the EGFR or actions against other members of the EGFR family, based on their mechanism of action. The biologic effects and modes of action of mAbs and small-molecule TKIs may differ (way of administration, biodistribution, induction of EGFR downregulation, possible activation of immune functions), which could be clinically significant. The inhibition of cancer cell proliferation with G0/G1 cell cycle arrest and, in some cases, induction of apoptosis; antiangiogenesis through inhibition of angiogenic growth factor production; inhibition of invasion and metastasis; and potentiation of antitumor activity of cytotoxic drugs and radiotherapy are all antitumor effects of EGFR inhibition in human cancer models [19].

4.1 Erlotinib (Tarceva)

The FDA approved erlotinib for the treatment of chemotherapy-resistant advanced NSCLC patients in November 2004, and the European Medicinal Evaluation Agency (EMA) approved it in October 2005. The pharmacokinetics of erlotinib are dose-dependent. Drug build-up is not a problem with daily doses. The maximum-tolerated dose of erlotinib for achieving physiologically relevant plasma levels was determined to be 150 mg/day, and this dose was recommended for phase II trials [21]. Erlotinib was tested in a phase II trial in advanced refractory NSCLC [22]. Complete responses (CRs) were seen in two patients (4%) in the phase II trial, partial responses (PRs) in five patients (9%), and prolonged stable disease (SD) in 22 patients (39%). The MST (median survival time) was 8.4 months in this study. Erlotinib treatment alleviated symptoms of lung cancer (fatigue, dyspnea, and cough). Erlotinib has also been studied as a single agent as a first-line treatment in patients with advanced NSCLC [23]. Oral erlotinib (150 mg/day) was given to 53 chemotherapy-naive patients with stage IIIB/IV NSCLC. After 6 weeks, the total rate of nonprogression was 52.8 % (28 of 53 patients). The objective response rate (OR) was 22.7 %, and the median time to respond (MST) was 391 days.

Chemotherapy provides symptomatic alleviation and a slight increase in survival in advanced NSCLC. After platinum-based therapy, second-line chemotherapy with docetaxel can help patients live longer [24,25]. Pemetrexed has also been approved as a second-line treatment when it was shown that it is not inferior to docetaxel in terms of clinical efficacy but has much fewer adverse effects [26].

In a similar phase II research, 80 chemotherapy-naive elderly (>70 years old) patients with stage III/IV illness were treated with erlotinib as first-line monotherapy [27]. Eight PRs (ten %) were found, and 33 patients (41%) had SD for two months or longer. 9 to 10 months was the mean survival time. The survival rates after one and two years were 46 % and 19 %, respectively. The toxicity of erlotinib in this population is equivalent to that seen in other studies of NSCLC patients over 70 years old.

4.2 Afatinib (Gilotrif)

Afatinib is a drug that is used to treat non-small cell lung cancer. It is available under the trade names Gilotrif and others (NSCLC). It belongs to the class of drugs known as tyrosine kinase

inhibitors. It is taken orally. It has been approved by the FDA for use as a therapy for NSCLC, and there is growing evidence to support its use in other malignancies, including breast cancer.

Phase II Trial Here presented a phase II trial taken in 2014 (28). In stage I of the trial, patients were randomly assigned to afatinib or cetuximab in a 1:1 ratio, stratified by the number of prior chemotherapies for R/M HNSCC (0 versus 1). Patients in stage I was treated with afatinib (50 mg once a day) or cetuximab (400 mg/m² loading dose followed by weekly dosages of 250 mg/m²) until progression or severe side effects (AEs). Patients who failed or had unacceptable AEs on afatinib or cetuximab could switch to the opposite medication, cetuximab or afatinib, in stage II.

Patients who had grade \geq 3 drug-related adverse events (DRAEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 or grade \geq 2 diarrhoea, nausea, or vomiting for \geq 7 days in a row despite receiving optimal supportive care had their treatment paused (maximum 14 days). Afatinib was reintroduced with a 10 mg dose reduction after this and recovery to a grade \leq 1 AE; this reduction could be repeated twice. Afatinib was stopped after the third occurrence of the above-mentioned AEs. Patients who did not improve after 14 days were moved to afatinib or cetuximab in stage I, while those who did not improve after 14 days were stopped in stage II. During the first cycle, safety was reviewed every two weeks, then every four weeks. Tumour shrinkage (mm) before crossover was the primary endpoint, defined as the change in the least post-randomization sum of the longest diameters (SLDs) of the target lesions from baseline. The best response evaluation criteria in solid tumors (RECIST) evaluation, overall respond (OR) duration, progression-free survival (PFS), overall survival (OS), safety, pharmacokinetic assessments (PK), and patient-reported outcomes were all secondary end objectives (PRO).

During stage I, 124 patients were randomized to either afatinib (62 patients) or cetuximab (62 patients) between October 2007 and June 2011. Although there were more patients with ECOG PS 0 in the afatinib group [23 (37.1%)] than in the cetuximab group [11 (17.7%)], baseline characteristics were similar.

Result of Stage I Both afatinib and cetuximab groups showed comparable tumour decrease (P= 0.57 per Institute of Cancer Research (ICR) and 0.76 per institutional research (IR)). According to ICR, 16 of 47 (34%) afatinib-treated patients had tumour sizes reduced by more than 30%, compared to 9 of 48 (18.7%) cetuximab-treated patients.

Result of Stage II Overall, ICR reduced SLD in 12/30 (40%) of afatinib-treated assessable patients and 8/26 (30.8%) of cetuximab-treated assessable patients. One patient in each group had a tumour size reduction of more than 30%, according to waterfall plots.

RECIST-defined response Institutional researches (IR) reported 16.1% verified ORR with afatinib and 6.5 % with cetuximab (P= 0.09), while Intensive Cardiac Rehabilitation (ICR) reported 8.1 % with afatinib and 9.7 % with cetuximab (P= 0.78) during stage I. There was a disconnect between IR and ICR, particularly between reviewers inside the ICR, with 49 of 106 cases (46%) requiring third-reader arbitration due to disagreements between the first two readers. By IR (P= 0.48), disease control was achieved in 31 (50%) afatinib-treated and 35 (56.5%) cetuximab-treated patients, with similar results utilising ICR in stage I. ORRs in both groups were similar per ICR, regardless of prior chemotherapy in the R/M setting; per IR, afatinib showed higher ORR in patients with prior chemotherapy in the R/M setting. During stage II, the disease control rate (IR/ICR) for patients who switched from cetuximab to afatinib was 38.9%/33.3% compared with 18.8%/18.8% for those who switched from afatinib to cetuximab. Interestingly, several patients on both treatments appeared to maintain disease control after crossover.

Phase III Trial This Phase III trial was taken in 2013 [29]. Eligible individuals with stage IIIB/IV lung cancer were examined for EGFR mutations in this phase III investigation. Patients with mutations were divided into two groups based on their mutation type (exon 19 deletion, L858R, or other) and race (Asian or non-Asian) before being randomly assigned to 40 mg afatinib per day or up to six cycles of cisplatin + pemetrexed chemotherapy at normal doses every 21 days. PFS was the major end point, as determined by an independent evaluation. Tumour response, overall survival, adverse events, and patient-reported outcomes were all secondary end goals (PROs).

A total of 1,269 patients were screened, with 345 receiving therapies at random. Afatinib had a median PFS of 11.1 months and chemotherapy had a median PFS of 6.9 months (hazard ratio [HR], 0.58; 95 % confidence interval [CI], 0.43 to 0.78; $P = .001$). PFS was 13.6 months for afatinib and 6.9 months for chemotherapy in individuals with exon 19 deletions and L858R EGFR mutations ($n = 308$) (HR, 0.47; 95 % CI, 0.34 to 0.65; $P = .001$). For afatinib, diarrhoea, rash/acne, and stomatitis, and nausea, exhaustion, and decreased appetite for chemotherapy, the most prevalent treatment-related side effects were diarrhoea, rash/acne, and stomatitis. PROs preferred afatinib because it improved cough, dyspnea, and pain control.

4.3 Gefitinib (Iressa)

Gefitinib, also known as Iressa, is a cancer treatment that is used to treat some types of breasts, lung, and other cancers. Gefitinib, like erlotinib, is an EGFR inhibitor that prevents target cells from signalling through the EGFR. As a result, it is only beneficial in tumours with mutant and hyperactive EGFR, although other mutations can lead to resistance to gefitinib. AstraZeneca and Teva are the companies that market it.

Phase II Trial The IRESSA Dose Evaluation in Advanced Non-small Cell Lung Cancer (IDEAL)-1 study, which was conducted mostly in Japan, Europe, Australia, and South Africa, and the IDEAL-2 trial, which was conducted primarily in the United States, have both been published in 2003 [30,31]. Patients with locally advanced or metastatic NSCLC, who are less responsive to chemotherapy (including platinum-based treatments), were studied to see if orally administered gefitinib had an anticancer impact. The RRs in IDEAL-1 were 18.4 % in the 250 mg/day group and 19 % the 500 mg/day group; in IDEAL-2, the RRs were 11.8 % and 8.8 %, respectively. Treatment was stopped in 14.5 %–15.5 % of patients in the 250 mg/day group. Although less than 1% of patients in the 250 mg/day group required a reduction in their daily gefitinib dose due to adverse events, the dose was reduced in 22.8–28.3 % of patients, and 8.8–10.4 % of patients in the 500 mg/day group could not continue gefitinib therapy. Japanese, female, non-smokers, and AC were identified to be factors predicting responsiveness to gefitinib in the IDEAL investigations. The frequency of grade 3/4 adverse events was 8.7% and 6.9% in the 250 mg/day groups, respectively, in these two investigations. They occurred in 30.2 % and 17.5 % of individuals in the 500 mg/day groups, respectively. Although the clinical efficacy of gefitinib was nearly identical in both groups, the side effects were clearly less in the 250 mg/day groups; consequently, 250 mg/day was determined to be the recommended dose.

Phase III Trial Two large-scale randomised clinical trials, IRESSA NSCLC Trial Assessing Combination Treatment (INTACT) -1 and -2 [32,33], were conducted on 2,130 patients with advanced NSCLC to determine the additional benefit of gefitinib as a first-line treatment (in combination with gemcitabine plus cisplatin or paclitaxel plus carboplatin) (Table 1). Unfortunately, no further effect of gefitinib in combination with normal chemotherapy was reported at the European Society for Medical Oncology (ESMO) congress in 2002 revealed from the INTACT investigations. These unfavourable results have been attributed to the following factors: (1) They did not assess the status of EGFR overexpression or genetic mutations because studies indicating that EGFR mutations could be used as a marker for cancer have not been published; (2) they did not investigate the state of EGFR overexpression or genetic mutations since research demonstrating that EGFR mutations could be utilised as biomarkers to predict gefitinib clinical outcome were published after the INTACT investigations were completed. The population of patients used in these studies might make it difficult to perform a precise analysis of the effects of gefitinib; and (3) gefitinib exerts an antiproliferative effect and may not have an additive effect when all proliferating cells have already been killed by other forms of chemotherapy [34]. In 2004, 1692 patients with advanced NSCLC were included in the IRESSA Survival Evaluation in Lung Cancer (ISEL) Phase III placebo-controlled research. The populace was pre-programmed to be resistant to or intolerant of their most recent treatment. As a result, while gefitinib did not significantly prolong median overall survival (OS) in all patients or patients with AC in INTACT, it did so in a subset analysis of 342 Asian patients (9.5 versus 5.5 months, respectively; hazard ratio [HR] 0.66, 95 % CI 0.48–0.91, $P = 0.01$) and 374 non-smokers (8.9 versus 6.1 months, respectively, HR 0.67, 95% CI 0.49–0.92, $P = 0.012$)

4.4 Osimertinib (Tagrisso)

Osimertinib, sold under the brand name Tagrisso, is an oral, third-generation, irreversible tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitising and EGFR T790M resistance mutations.

Phase II trial A phase II study was reported in 2017 [35]. Patients with EGFR-TKI-pre-treated EGFRm- and T790M-positive advanced non-small-cell lung cancer (NSCLC) received once-daily osimertinib 80 mg. The T790M status of a tumour sample taken after the most recent disease progression was confirmed by central testing. Patients who had asymptomatic, stable CNS metastases and didn't need corticosteroids were eligible to participate. The major outcome measure was the objective response rate (ORR) as determined by independent radiological evaluation. Disease control rate, duration of response, progression-free survival (PFS), and safety were secondary end goals. An exploratory goal was to look at patient-reported outcomes. At the time of data cutoff (November 1, 2015), 201 patients had received treatment, with a median treatment duration of 13.2 months. The ORR was 62 % (95 % CI, 54 % to 68 %) in evaluable patients (n = 198), while the disease control rate was 90 % (95 % CI, 85 to 94). In 122 responding patients, the median duration of response was 15.2 months (95 % CI, 11.3 to not calculable). PFS was 12.3 months on average (95 % CI, 9.5 to 13.8). The most common potentially causally associated adverse effects (as determined by the investigator) were diarrhoea (43 %; grade 3, 1%) and rash (grouped terms; 40 %; grade 3, 1%). Eight patients (4 %; grade 1, n = 2; grade 3, n = 3; grade 5, n = 3) had interstitial lung disease (grouped words). The conclusion was osimertinib gives a high ORR, promising PFS, and sustained response in patients with EGFRm T790M advanced NSCLC who progress following EGFR-TKI treatment.

Phase III trial A phase III study was reported in 2018 [36]. Participants in AURA3 had to be at least 18 years old, have a WHO performance status of 0 or 1, and have histological or cytological confirmation of NSCLC. Patients were randomly assigned 2:1 to osimertinib or platinum-pemetrexed after central confirmation of EGFR T790M-positive status. 116 patients with measurable and/or non-measurable CNS lesions, including 46 patients with quantifiable CNS lesions, were randomly assigned to treatment out of 419 patients. CNS ORR in patients with one or more measurable CNS lesions was 70% (21 of 30; 95 % CI, 51 % to 85 %) with osimertinib and 31% (5 of 16; 95 % CI, 11 % to 59 %) with platinum-pemetrexed (odds ratio, 5.13; 95 % CI, 1.44 to 20.64; P =.015) with platinum-pemetrexed at data cutoff (April 15, 2016). In patients with quantifiable and/or non-measurable CNS lesions, the ORR was 40 % (30 of 75; 95 % CI, 29 % to 52 %) and 17 % (7 of 41; 95 % CI, 7 % to 32 %), respectively (odds ratio, 3.24; 95 % CI, 1.33 to 8.81; P =.014). Patients with measurable and/or non-measurable CNS lesions had a median CNS duration of response of 8.9 months (95 % CI, 4.3 months to not calculable) for osimertinib and 5.7 months (95 % CI, 4.4 to 5.7 months) for platinum-pemetrexed; median CNS progression-free survival was 11.7 months and 5.6 months, respectively (hazard ratio, 0.32; 95 % CI, 0.15 to 0.69; P = 0.004). In conclusion, in patients with T790M-positive NSCLC who had disease progression after a first-line EGFR-TKI, osimertinib was superior to platinum-pemetrexed in the treatment of CNS metastases, with a higher CNS ORR and longer CNS PFS than platinum-pemetrexed.

5. Conclusion

Those medications are all EGFR inhibitors, which were discovered to induce cancer cells to divide at a considerably faster rate when a large amount of EGFR was present. Further study could focus on developing new options for suppressing EGFR or developing other medicines for non-small cell lung cancer in the future. Because using the inhibitor might lead to resistance over time, it is critical for researchers to develop new types of inhibitors to prevent cancer cells from spontaneously mutating.

References

[1] Yarden, Y. 'The EGFR Family and Its Ligands in Human Cancer: Signalling Mechanisms and Therapeutic Opportunities'. European Journal of Cancer, 2001, 6.

- [2] Huang, Shyh-Min, and Paul M. Harari. "Epidermal growth factor receptor inhibition in cancer therapy: biology, rationale and preliminary clinical results." *Investigational new drugs* 17.3 (1999): 259-269.
- [3] Nicholson, R.I, J.M.W Gee, and M.E Harper. 'EGFR and Cancer Prognosis'. *European Journal of Cancer* 37 (September 2001): 9–15. [https://doi.org/10.1016/S0959-8049\(01\)00231-3](https://doi.org/10.1016/S0959-8049(01)00231-3).
- [4] Salomon DS, Bradt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Critical Rev Oncol/Hematol* 1995, 19, 183–232.
- [5] Burgess, Antony W., et al. "An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors." *Molecular cell* 12.3 (2003): 541-552.
- [6] Carraway III, Kermit L., et al. "Neuregulin-2, a new ligand of ErbB3/ErbB4-receptor tyrosine kinases." *Nature* 387.6632 (1997): 512-516.
- [7] Yokomizo, Takehiko, et al. "A G-protein-coupled receptor for leukotriene B 4 that mediates chemotaxis." *Nature* 387.6633 (1997): 620-624.
- [8] Huang, Shyh-Min, Jonathan M. Bock, and Paul M. Harari. "Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck." *Cancer research* 59.8 (1999): 1935-1940.
- [9] Carroll, Rona S., et al. "Expression and activation of epidermal growth factor receptors in meningiomas." *Journal of neurosurgery* 87.2 (1997): 315-323.
- [10] Abbott, Barbara D., et al. "EGF and TGF- α expression influence the developmental toxicity of TCDD: dose response and AhR phenotype in EGF, TGF- α , and EGF+ TGF- α knockout mice." *Toxicological Sciences* 71.1 (2003): 84-95.
- [11] Xian, Cory J., and Xin-Fu Zhou. "EGF family of growth factors: essential roles and functional redundancy in the nerve system." (2004).
- [12] Mann, G. Bruce, et al. "Mice with a null mutation of the TGF α gene have abnormal skin architecture, wavy hair, and curly whiskers and often develop corneal inflammation." *Cell* 73.2 (1993): 249-261.
- [13] Blum, Mariann. "A null mutation in TGF- α leads to a reduction in midbrain dopaminergic neurons in the substantia nigra." *Nature neuroscience* 1.5 (1998): 374-377.
- [14] Tropepe, Vincent, et al. "Transforming growth factor- α null and senescent mice show decreased neural progenitor cell proliferation in the forebrain subependyma." *Journal of Neuroscience* 17.20 (1997): 7850-7859.
- [15] Troyer, Kelly L., et al. "Growth retardation, duodenal lesions, and aberrant ileum architecture in triple null mice lacking EGF, amphiregulin, and TGF- α ." *Gastroenterology* 121.1 (2001): 68-78.
- [16] Luetkeke, Noreen C., et al. "TGF α deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice." *Cell* 73.2 (1993): 263-278.
- [17] Mann, G. Bruce, et al. "Mice with a null mutation of the TGF α gene have abnormal skin architecture, wavy hair, and curly whiskers and often develop corneal inflammation." *Cell* 73.2 (1993): 249-261.
- [18] Luetkeke, Noreen C., et al. "Targeted inactivation of the EGF and amphiregulin genes reveals distinct roles for EGF receptor ligands in mouse mammary gland development." *Development* 126.12 (1999): 2739-2750.
- [19] Normanno N, Bianco C, De Luca A et al. Target-based agents against ErbB receptors and their ligands: A novel approach to cancer treatment. *Endocr Relat Cancer* 2003;10:1–21

- [20] Kurie JM, Shin HJ, Lee JS et al. Increased expression in metaplastic bronchial epithelium. *Clin Cancer Res* 1996;2: 1787–1793
- [21] Hidalgo M, Siu LL, Nemunaitis J et al. Phase I and pharmacologic study of OSI-774, an tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001;19:3267–3279.
- [22] Perez-Soler R, Chachoua A, Hammond LA et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol* 2004;22:3238–3247
- [23] Giaccone G, Gallegos Ruiz M, Le Chevalier T et al. Erlotinib for frontline treatment of advanced non-small cell lung cancer: A phase II study. *Clin Cancer Res* 2006;12:6049–6055.
- [24] Shepherd FA, Dancey J, Ramlau R et al. A prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
- [25] Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced nonsmall-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
- [26] Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
- [27] Jackman DM, Yeap BY, Lindeman NI et al. Phase II clinical trial of chemotherapy-naïve patients > 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol* 2007;25:760–766
- [28] Keating, Gillian M. "Afatinib: a review of its use in the treatment of advanced non-small cell lung cancer." *Drugs* 74.2 (2014): 207-221.
- [29] Sequist, L. V., Yang, J. C. H., Yamamoto, N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *Journal of Clinical Oncology*, 31(27), 3327-3334.
- [30] Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced nonsmall-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol*. 2003; 21(12):2237–46.
- [31] Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA*. 2003; 290(16):2149–58
- [32] Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol*. 2004;22(5):777–84.
- [33] Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol*. 2004;22(5):785–94.
- [34] Araki, Takuya, et al. "Review of the treatment of non-small cell lung cancer with gefitinib." *Clinical Medicine Insights: Oncology* 6 (2012): CMO-S7340.
- [35] Yang, J. C., et al. "Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component." (2017): 1288-1296.
- [36] Wu, Yi-Long, et al. "CNS efficacy of osimertinib in patients with T790M-positive advanced non-small-cell lung cancer: data from a randomized phase III trial (AURA3)." *Journal of Clinical Oncology* 36.26 (2018): 2702-2709.