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PATH-BREAKING INNOVATIONS  
FOR LUNG CANCER: A REVOLUTION  
IN CLINICAL PRACTICE

Coccia Mario

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# Path-breaking innovations for lung cancer: a revolution in clinical practice

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**ABSTRACT:** Lung cancer is one of main cause of death worldwide and traditional chemotherapy agents have reached the maturity phase in the treatment of advanced non-small cell lung cancer. The purpose of this paper is to analyse the evolutionary growth of knowledge patterns of vital radical innovations to treat lung cancer, driven by new technological paradigm of the targeted therapy, that have generating a revolution in clinical practice, increasing the overall survival of patients and quality of life. This new scientific pathway has evolving with an allometric process that involves a disproportionate growth of targeted therapy in relation to standard platinum-based chemotherapy alone.

**Keywords:** Radical Innovation, Technological Paradigm, Clinical Practice, Molecular Biology, Lung Cancer, Targeted Therapy.

**JEL Codes:** O33; I1; L65

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*La scienza di oggi è la vita di domani  
(Science of today is life of tomorrow)*

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## 1. INTRODUCTION

**R**esearch and experimental Development (R&D) processes consume considerable economic and human resources and contribute to the accumulation of intangible capital, which is fostering drug discoveries and medical innovations that lead to longer, better and healthier living. R&D intensity is higher in economic systems driven mainly by pharmaceuticals, chemicals industry, ICTs because it represents the main determinant of scientific and technological advances (Van Pottelsberghe de la Potterie, 2008, pp. 222-224). In fact, Mathieu and Van Pottelsberghe de la Potterie (2008) show that R&D intensity of Drug & Medicines industry (average across 10 countries in %) has high levels of about 20%. The R&D of this vital industry has supporting the convergence of genetics<sup>1</sup> and genomics<sup>2</sup> that has originating new pathways of anticancer drugs (Amir-Aslani and Mangematin, 2010). In particular, the interaction between medicinal chemistry and genomics has created the pharmacogenomics that examines the way drugs act on cells as revealed by their gene expression patterns. Lindpaintner (1999) argues that these breakthroughs are the basis for the development of personalized medicines (e.g. targeted therapy). The genomics has providing opportunities for new treatments in more than 100 multifactoral diseases, with 500-1000 disease-related genes and 3000-10,000 new drug targets (Jain, 2000, p. 318). Genetics, instead, has playing a key role because several tumors have a genetic component and

<sup>1</sup> Genetics studies the molecular structure and function of genes in the context of a cell or organism.

<sup>2</sup> Genomics is a discipline in genetics that studies the genomes of organisms. In particular, it determines the entire DNA sequence of organisms and fine-scale genetic mapping efforts.

scientific advances in this critical scientific field, associated to proteomics<sup>3</sup>, have helping to understand the disease biology in order to support effective new anticancer drugs for modern clinical practice (Jain, 2000, p. 319).

A main illness across several countries is the lung cancer that is a leading cause of cancer death worldwide (Laack *et al.*, 2010, p. 259). In particular, 85% of cases are represented by Non-Small Cell Lung Cancer (NSCLC), which is due to risk factors such as smoking, passive smoking and air pollution (cf. Molina *et al.*, 2008, *passim*). The treatments of advanced Non-Small Cell Lung Cancer (NSCLC), based on traditional chemotherapy agents, have reached the maturity phase and the current progress in genetics, genomics and proteomics represents the vast foundation underlying the recently development of new anticancer drugs for targeted therapy (Mitsudomi, 2010, p. 101). The purpose of this paper is to analyze the current scientific and technological pathway of vital radical innovations applied as targeted therapy to treat NSCLC that has generating a revolution in clinical practice. This important topic, based on evolutionary growth of knowledge of some new targeted therapies, can shed light on the common origin and evolution of several new drugs that has driving the modern medicine. Before analyzing the ongoing evolutionary pathways of radical innovations for lung cancer, next section describes the interesting history of these new anticancer drugs.

## 2. FROM ADVANCES IN MOLECULAR BIOLOGY TO TARGETED THERAPY: THE HISTORICAL ASPECTS OF VITAL RADICAL INNOVATIONS FOR LUNG CANCER

Cancer is an organism which lives off a host organ, growing by bio-genetic-molecular mechanism.

Lung cancer is a: “Cancer that forms in tissues of the lung, usually in the cells lining air passages.” (as defined by National Cancer Institute, 2011). Mitsudomi (2010, p. 101)

<sup>3</sup> The proteomics is the systematic analysis of protein profiles of tissues and parallels the related field of genomics.

claims that: “lung cancer is a major cause of cancer-related mortality worldwide”. In fact, Table 1 shows as lung cancer has the highest mortality rate (24.8) across developed regions (cf. also Parkin *et al.*, 2005). The Surveillance, Epidemiology and End Results (SEER) Program for cancer statistics in the United States estimates that 222,520 men and women (116,750 men and 105,770 women)

are diagnosed with and 157,300 men and women are died of cancer of the lung and bronchus in 2010 (SEER, 2011). The median age at diagnosis for cancer of the lung and bronchus is about 71 years. Based on rates from 2005-2007, 6.95% of men and women born today will be diagnosed with cancer of the lung and bronchus at some time during their lifetime (Howlader *et al.*, 2011).

Table 1. Most frequent cancers in developed regions (both sexes)

Cancer	Incidence ASR (W)*	Mortality ASR (W)*
Lung	31.3	24.8
Breast	66.4	15.3
Colorectum	30.1	12
Prostate	61.7	10.5
Stomach	11.4	7.2
Pancreas	6.8	6.4
Ovary	9.3	5.1
Liver	5.2	4.6
Leukaemia	7.3	3.7
Cervix uteri	9.1	3.2
Brain, nervous system	5.1	3.2
Oesophagus	3.6	2.9
Kidney	8.6	2.8
Non-Hodgkin lymphoma	8.6	2.8
Bladder	9.1	2.5
Corpus uteri	13	2.3
Gallbladder	2.2	1.5
Multiple myeloma	2.7	1.5
Lip, oral cavity	4.4	1.4
Melanoma of skin	9	1.4
Other pharynx	2.5	1.2
Larynx	2.8	1.2
Thyroid	6.1	0.4
Testis	4.6	0.3
Hodgkin lymphoma	2	0.3

Note: Incidence and Mortality: Population weighted average of the country rates applied to the 2008 area population. Age-Standardised Rate-ASR (W): A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardised rate is the rate that a population would have if it had a standard age structure.

Source International Agency for research on cancer. World Health Organization. GLOBOCAN 2008 (IARC) Section of Cancer Information (5/7/2011).<http://globocan.iarc.fr/>

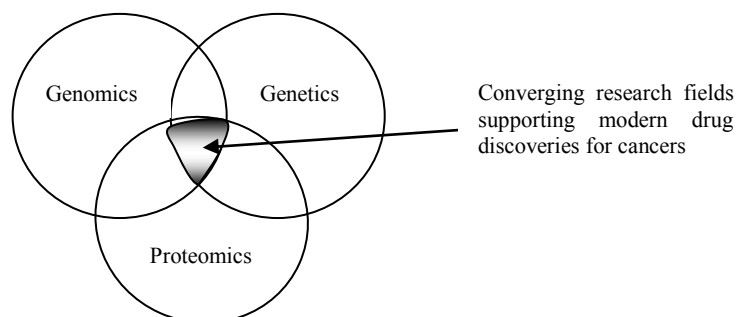


Figure 1: Convergence of scientific fields driving drug discovery pathway

The two main typologies of lung cancer are: small cell lung cancer and non-small cell lung cancer (NSCLC), which represents about 80% of cases. The stage of the illness is essential to treat the patients with lung cancer. Surgical resection is the most apt medical strategy of treatment when the disease is at the early stage.

However, about 70% of patients with lung cancer have micro (i.e. locally: in contiguous lobes) and macro metastases (spread in the next lung, brain and/or bones) when diagnosed (Laack *et al.*, 2010, p. 259; *cf.* also Molina *et al.*, 2008). The five-year survival rate of these patients is about 2-10% with current treatments based on chemotherapy agents (*see* Reck and Crinò, 2009, p. 1).

Up-to-date Cisplatin based therapy is the reference treatment for advanced NSCLC, but these traditional chemotherapy agents have reached a therapeutic maturity since the convergence of vital research fields, represented in figure 1 (grey area), has generated the insurgence of new technological paradigms that branch off technological trajectories of revolutionary anticancer drugs with higher effectiveness to treat cancers and lower adverse drug reactions. In particular, scientific advances in genomics, genetics and proteomics (fig. 1) have paved the pathway to potential technological paradigms that the “focusing devices” (Sahal, 1981) select on the basis of *ex-ante* and *ex-post* elements and give rise to some technological paradigms<sup>4</sup> (Dosi, 1982) represented by (Figure 2):

<sup>4</sup> “ ‘model’ and ‘pattern’ of solution of *selected* technological problems, based on *selected* principles derived from the natural science and

a) Gene therapy is an experimental treatment that involves introducing genetic material (DNA or RNA) into a person's cells to fight disease;

b) biological therapies use the body's immune system, either directly or indirectly, to fight cancer or to lessen the side effects that may be caused by some cancer treatments;

c) cancer vaccines boost the immune system's natural ability to protect the body against infectious agents, that may cause disease;

d) Targeted cancer therapies: “are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression” (as defined by National Cancer Institute, 2011). Gene and biological therapies as well as cancer vaccines are often considered to be targeted therapies.

The technological paradigm of targeted cancer therapies has spreading technological trajectories based on radical and incremental innovations and the main typologies are: signal transduction inhibitors, therapies that modify the function of proteins regulating gene expression and other cellular functions, targeted therapies inducing cancer cells to undergo apoptosis (cell death), other targeted therapies block the growth of blood vessels to tumors, some targeted therapies also act by supporting the immune system to destroy cancer cells and a class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically (*cf.* National Cancer Institute, 2011, *passim*).

on *selected* material technologies” (Dosi, 1982, p. 152, original emphasis).

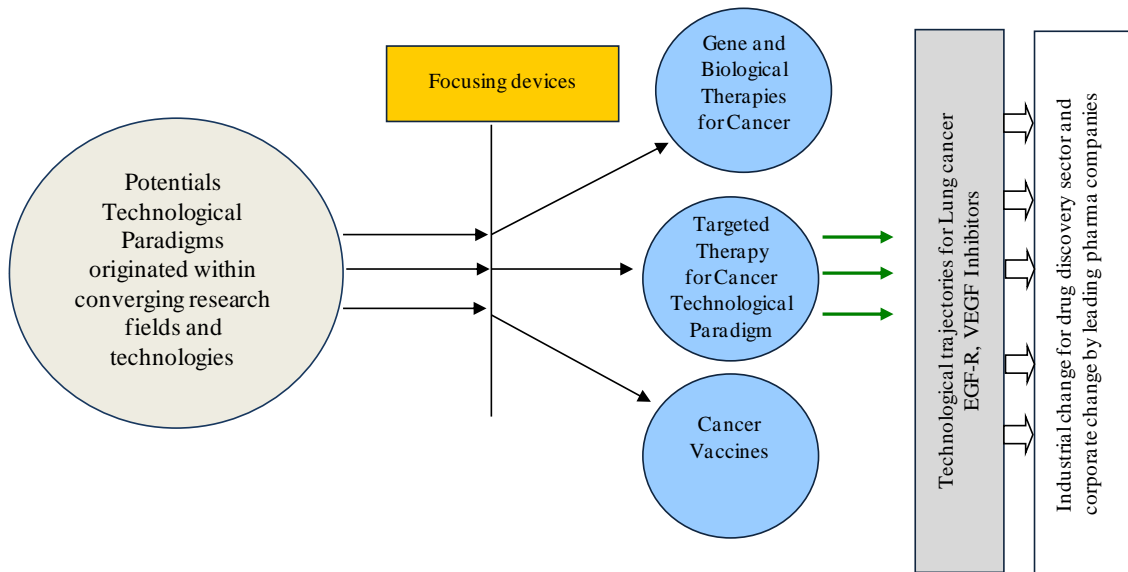


Figure 2: Scientific and Technological Patterns in Lung Cancer Treatments

This paper focuses on driving targeted therapies for lung cancer, as defined in point *d*) that have generating new anticancer drugs that target the tumor protein and its growth. In particular, the revolutionary progress in molecular biology has shown that cancer cells have self-sufficiency of growth signals through the accumulation of genetic and epigenetic changes. In 1986 Stanley Cohen of Vanderbilt University (Nobel Prize in Physiology and Medicine) discovers the Epidermal Growth Factor (EGF). It acts by binding with high affinity to Epidermal Growth Factor Receptor (EGF-R) on the cell surface and stimulating the intrinsic protein-tyrosine kinase activity of the receptor. The tyrosine kinase activity, in turn, initiates a signal transduction cascade that results in a variety of biochemical changes within the cells that ultimately lead to cell proliferation. In addition, these genetic roots of diseases and disease progression have induced the development of *biomarker*: “ ‘A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention’ (National Institute of Health)<sup>5</sup>”.

As genomic changes play a main role in cancer growth, mutations of EGF-R occurs in

some variety of lung cancer and it can be identified by a biomarker, which is important for understanding patient differences and applying specific treatments with effectiveness. In particular, the discovery of EGF-R blocking agents Gefitinib and Erlotinib has generated two main radical innovations that are Iressa® (based on Gefitinib) by Astra Zeneca Company(UK-Sweden) and Tarceva® (blocking agent Erlotinib) produced by Roche Group (Switzerland)<sup>6</sup>. These targeted therapies are generating a revolution in therapeutic treatments of NSCLC since block specific enzymes and growth factor receptors involved in cancer cell proliferation (Mitsudomi, 2010, pp. 101-102): this typology of targeted therapy is called signal transduction inhibitors(EGF-R tyrosine kinase inhibitors), which represent innovative anticancer drugs easily administered as one pill per day (also at home), whereas the standard platinum-based chemotherapy(such as Cisplatin, gemcitabine, etc.) is administered intravenously at the hospital for treatment of solid malignancies (*e.g.* NSCLC). The scientific advances in the grey area of figure 1 are the foundation of the modern medicine based on drug discoveries that have been moving from mass-oriented

<sup>5</sup> As quoted by Amir-Aslani and Mangematin, 2010, p. 204.

<sup>6</sup> The literature is vast and not fully cited here, but a good list of references is found in Dempke *et al.* (2010, pp. 262-263 and pp. 271-274).



products to target-oriented treatments driven by biomarkers that support the effective administration of new anticancer drugs to subsets of population. In fact, Paez *et al.* (2004) show that patients with mutated EGF-R appeared more likely to respond to Gefitinib than those without mutations of the EGF-R. Sequist *et al.* (2007) argue that these mutations are associated mainly to patients of Asian ethnicity, no-smoking habit and histology of adenocarcinoma (that is a typology of NSCLC). This group has the best response to this targeted therapy as showed by several studies (cf. Mitsudomi *et al.*, 2005). In particular, Miyagi Cancer Center in Japan conducted a phase III trial showing that patients with metastatic non-small cell lung cancer treated with gefitinib had significantly longer progression-free survival in comparison with patients who received combination of carboplatin plus paclitaxel (standard chemotherapy agents): 10.8 months vs. 5.4 months<sup>7</sup>. Gefitinib has also a non-inferiority vs. mono-chemotherapy agent, such as docetaxel. The main effects of Gefitinib in the group of patients with EGF-R mutations are a tumor regression and a longer progression-free survival than traditional chemotherapy drugs. In addition, Gefitinib, in comparison with traditional chemotherapy drugs, has lower toxicity and provides a higher quality of life.

Gefitinib was approved in Japan in the 2002 for the first time in the world (Mitsudomi, 2010, p. 102) and is now used in several countries for the treatment of adult patients with locally advanced or metastatic NSCLC with mutations EGF-R (Dempke *et al.*, 2010, p. 263).

Another radical innovation for NSCLC, similar to Gefitinib, is based on the blocking agent Erlotinib (produced by Roche Group). Erlotinib is also a pill that targets the protein epidermal growth factor receptor (EGF-R), which helps cells to divide. Erlotinib, interfering with EGF-R, can stop or regress NSCLC growing. In particular, Erlotinib inhibits EGF-R signalling by bidding to the intracellular tyrosine kinase domain, stopping tumor growth. The main effect of Erlotinib is

to reduce the mortality risk by 19% with an increase in median overall survival in the overall population from 11 to 12 months (cf. Brugger *et al.*, 2009). Clinical trial, over 2001-2003 period, led by Frances A. Shepherd (University of Toronto-Canada) showed that the median survival of patients who received erlotinib was 6.7 months compared to 4.7 months of placebo group. At one year, 31 percent of the patients treated with erlotinib were still alive vs. 22 percent of those taking the placebo<sup>8</sup>.

Continuous scientific advances show that cancer cells have to attract new blood vessels to bring nutrients and oxygen for them to grow over a certain size. New compounds block the growth of blood vessels to tumors (angiogenesis) and as consequence tumor growth. In particular, some new anticancer drugs target vascular endothelial cell growth factor (VEGF) playing a critical role for cancer angiogenesis. Inhibition of VEGF is the basis for new therapies and effective approaches to treat NSCLC and other variety of cancers (Reck and Crinò, 2009, p. 2).

The pathway of radical innovations for NSCLC, based on blocking agents Gefitinib and Erlotinib, has paving the pattern of incremental innovations focused on multi-targeted blocking agents that target EGF-R, human epidermal growth receptor 2 (HER-2) and VEGF-R signalling pathways. These incremental innovations are due to a learning process on the biology of diseases associated to the interaction between learning in scientific research<sup>9</sup> and “learning by doing” (Arrow, 1962) in clinical practice. According to Dosi (1982, p. 147): “the continuous changes are often related to progress along a technological trajectory defined by a technological paradigm [of the targeted therapy in our case study]”. In fact, as NSCLC has heterogeneity and complex growth patterns by signalling pathway, multi-inhibition offers fruitful effects to treat NSCLC and other variety of cancers. Minkovsky and Berezov (2008) show that the new blocking agent BIBW-2992 produced by

<sup>8</sup> The results are in The New England Journal of Medicine, July 14, 2005.

<sup>9</sup> Morlacchi and Nelson, 2011, p. 513 and p. 521, *passim*; cf. also Kim and Nelson, 2000.

<sup>7</sup> These results are in the New England Journal of Medicine (June 24, 2010).

Boehringer Ingelheim (Germany) is active against lung cancers that are resistant to the first-generation of EGF-R inhibitors (that is Gefitinib and Erlotinib). Other promising compounds for NSCLC by Boehringer Ingelheim, in the clinical phase III, are BIBF 1120 (triple angiokinase inhibitor) and Afatinib (Dual irreversible EGF-R and HER2 inhibitor). These new medical innovations, by a continuous learning process (Lenfant, 2003, Gershon, 1998), have providing encouraging results in NSCLC, increasing the overall survival of patients that can triple or quadruple in comparison with other treatments. It is granted fast-track status for some of these anticancer drugs and a first-line study vs. Gefitinib/Erlotinib (cf. Dempke *et al.* 2010, p. 264; Reck and Crinò, 2009, p. 7).

Next section describes a methodology to measure the rate of scientific and technological advances of new anticancer drugs, to analyse the evolutionary growth of knowledge and underlying factors driving the development of these targeted therapies for modern clinical practice.

### 3. STRATEGY OF RESEARCH

Grupp (2000, p. 143) argues that: “innovation literature centres more on technical advance and less on scientific change”. As a matter of fact, it is important to ascertain that scientific advances and changes can be considered as an ice-breaker for new scientific research fields, creating new pathways for future patterns of radical technological innovations.

In order to investigate the current scientific advances of drug discovery in NSCLC that will drive future “technological trajectories” (Nelson and Winter, 1982), this paper uses the database of Scopus (2011) and data mining is performed with a series of queries based on keywords of new anticancer drugs and Boolean operators.

Data mining is focused on:

- time horizon 1990 (first year) – 2010 for scientific research products (e.g. articles);
- time horizon 1996 (first year) – 2010 for patents;

Aim of the research is to explore the patterns of radical innovations for NSCLC, compared with standard platinum-based chemotherapy alone, such as Cisplatin agent. Data on scientific products, which indicate a proxy of scientific activities, are retrieved by the “Advanced search” window of Scopus website, using the “Article title, abstract, keyword” tag in the search window. Data on patents that indicate a proxy of technological activity are retrieved in the SciVerse Scopus instrument with a full text query<sup>10</sup>.

The vast sample, represented by 140,580 occurrences of articles and more than 97,000 occurrences of patents, is the basis to apply some models for analyzing the scientific and technological pathways of these new anticancer drugs.

As these radical innovations have been having an acceleration in their scientific activity, a first main aspect is to measure and analyse the *rate of scientific and technological advances* by the number of articles and patents growth over time.

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<sup>10</sup>Technology is based on inventions and innovations. Invention is a commercially promising product or service, based on new science and/or technology that meets the requirements for a patent application and/or the patent is already granted. On the other hand, innovation, which already has a valid and granted patent, is the successful entry of a new science or technology-based product into a particular market. In particular, innovations are protected by patents, which indicate the current innovation of industries and also commercially promising inventions.

An *exponential* model is a fruitful approach to measure the dynamics of new anticancer drugs based on the following *assumptions*:

1.  ${}_aP$  is the number of articles/patents at 2000 (1996 for patents)
2.  ${}_tP$  is the number of articles/patents at 2010
3.  $t$  is the period analyzed
4. articles are a proxy of the scientific activity, whereas patents are a proxy of the technological activity of these research fields.

The model is:

${}_tP = {}_0P \cdot e^{rt}$  where  $e$  is the base of natural logarithm (2.71828...).

Hence  $\frac{{}_tP}{{}_0P} = e^{rt}$ ;  $\text{Log} \frac{{}_tP}{{}_0P} = r \cdot t$ ;

$$r = \frac{\text{Log}\left(\frac{{}_tP}{{}_0P}\right)}{t} \quad [1]$$

$r$  = rate of scientific (or technological) advances

This method can offer an analytical framework for understanding the evolutionary growth of knowledge of these medical innovations for lung cancer that have generating a revolution in clinical practice. However for an in-depth analysis it is important to consider that the patterns of the scientific activity of specific innovations have friction effects over time that can be represented by *S-shaped* functions. An apt model to analyse the spatial aspects of technological substitution is provided by Sahal (1981, pp. 82-89). This spatial model is inspired by the analysis performed by zoologists concerning the developmental biology (cf. Huxley, 1932; Reeve and Huxley, 1945).

In particular, the second main aspect of this paper is to investigate the relative rate of growth of the technological output of some new radical innovations for lung cancer in comparison with innovative output of Cisplatin (applied as standard platinum-based chemotherapy).

A main condition of the model setting is the following assumption:

- *The innovative output (Patents) of medical innovations has an S-shaped pattern.*

Under this assumption, and the theoretical background described, the hypothesis is:

- *Hypothesis. The new targeted therapy for lung cancer has been developing, replacing current standard platinum-based chemotherapy.*

The purpose of the present study is to see whether statistical evidence supports this hypothesis. The analysis is carried out from 1996 to 2010 period.

In particular, let  $Y(t)$  be the total number of patents at time  $t$  of the drug  $Y'$  (radical innovation) and  $X(t)$  be the total patents at the same time of the drug  $X'$  (traditional chemotherapy drug).

Let  $b_1$  and  $b_2$  be the growth rates of total outputs  $Y$  and  $X$ , respectively, such that

$B_1 = \frac{b_2}{b_1}$ ; if  $Y$  and  $X$  increase according to an

*S-shaped* growth pattern, then  $B_1 = \frac{b_2}{b_1}$

measures the relative growth of medical innovation  $X'$  in relation to  $Y'$ .

If both  $Y$  and  $X$  increase according to an *S-shaped* growth pattern, one way to represent such a pattern formally is in terms of the differential equation of logistic function (cf. Phillips, 2007).

For  $Y(t)$ , the model is (figure 3):

$$Y = \frac{K_1}{1 + \exp(a_1 - b_1 t)} \quad [2]$$

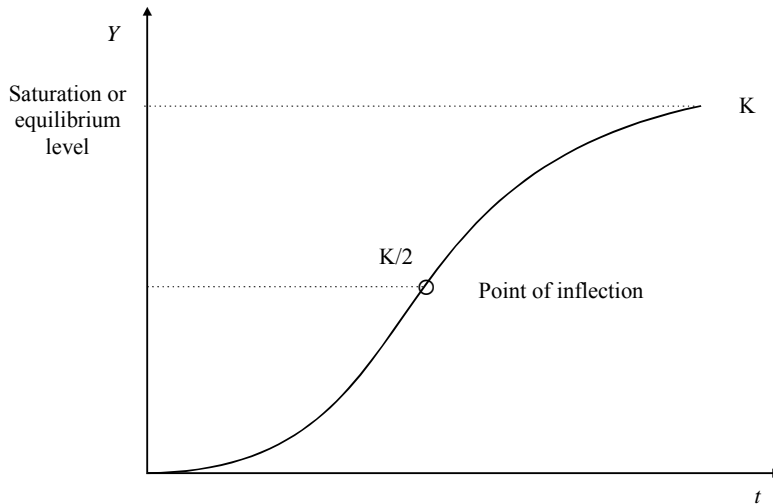


Figure 3: Diffusion of innovation according to a logistic curve (S-symmetrical)

The parameters of the logistic function indicate:  $K_1$ =growth equilibrium level,  $a_1$  =constant depending on the initial conditions and  $b_1$  = the rate-of-growth parameter,  $t$ =time Thus, the growth of  $Y$  and  $X$  is<sup>11</sup>:

$$\log \frac{K_1 - Y}{Y} = a_1 - b_1 t \quad [3]$$

in a similar way to  $Y(t)$ , for  $X(t)$  the model is:

$$\log \frac{K_2 - X}{X} = a_2 - b_2 t \quad [4]$$

It can be verified that the logistic curve is a symmetrical S-shaped curve with a point of inflection at  $0.5K$

Solving the equations [3] and [4] for  $t$ , the result is

$$\frac{Y}{K_1 - Y} = C_1 \left( \frac{K_2 - X}{K_2 - X} \right)^{\frac{b_1}{b_2}} \quad [5]$$

with

$$C_1 = \exp[b_1(t_2 - t_1)] \text{ since } a_1 = b_1 t_1$$

and

$$a_2 = b_2 t_2$$

Hence Eq. [5] can be reduced to a simple model of growth:

$$X = A_1(Y)^{B_1} \quad [6]$$

where  $A_1 = \frac{K_2}{(K_1)^{\frac{b_2}{b_1}}} C_1$

and  $B_1 = \frac{b_2}{b_1}$

The logarithmic transformation of the equation  $X = A_1(Y)^{B_1}$  is a simple linear relationship:

$$\log X = \log A_1 + B_1 \log Y$$

so that

$$Y = A + B_1 X \quad [7]$$

$B_1$  is the allometry exponent of  $X$  in relation to  $Y$ :

- If the relative growth of two dimensions were *isometric*, the allometry exponent  $B_1$  would have a unit value.

<sup>11</sup>This part is a re-elaboration of the spatial model by Sahal (1981, chap. 5, paragraph 3.2).

This hypothesis is expressed as:

$$B_1 = 1$$

- On the other hand, X increases at a greater relative rate than Y, the hypothesis of *positive disproportionate (allometric) growth*, could be expressed as:

$$B_1 > 1;$$

- The hypothesis that X has negative disproportionate (allometric) growth in relation to Y could be expressed as:

$$B_1 < 1$$

The model [7] measures the magnitude of relative growth in a simpler way than a wide variety of econometric approaches. Sahal (1981, Chp. 5) has applied this model to analyse the technological substitution of different innovations.

*Mutatis mutandis*, our model is given by:

$$y_t = a \cdot (x_t)^{B_1} \quad [8]$$

where:

$a$  is a constant

$y_t$  is the number of patents of the new anticancer drug, that is Gefitinib, at time  $t$ ;

$x_t$  is the number of patents of the Cisplatin-based therapy that is a reference treatment for advanced NSCLC.

The relevance of this spatial model of technological substitution is that it provides simple and fruitful results to analyse the patterns of this medical innovation. In particular, the scientific progress of innovations is generally analyzed by an allometric process of growth ("this term ... denote[s] disproportionate change in the size of an organ as a consequence of change in the overall size of a biological system" - Sahal, 1981, p. 97, footnote 6). That is, substitution of one innovative output for the other generally involves disproportionate growth of one in relation to the other.

The empirical evidence of technological substitution analyzed by the logarithmic transformation of the model [8] provides main

findings in simple way since contains only two parameters, estimated by ordinary least squares. This model is quite robust and its form remains invariant under a variety of different starting point.

#### 4. RESULTS

The main R&D process of NSCLC is focused on the last 15 years. This research uses data of the scientific production (articles and patents) of these vital innovations, because as it is well known, scientific pathways anticipate (drug) discoveries, opening technological trajectories that will be diffused in not-too-distant future for the wellbeing of societies.

The main findings of this paper are:

- *Rates of scientific and technological advances*

The rates of growth measured by articles and patents provide main information about the current scientific and technological advances. Table 2 shows that Gefitinib has higher rate of scientific growth based on articles of journals, whereas Erlotinib has high rates both of scientific and technological advances.

Table 2 shows, *ceteris paribus*, the rates of scientific and technological advances of new and traditional anticancer drugs for NSCLC, measured by model [1] applied on the overall period.

It is important to note that technological advances depend on the accumulation of knowledge and the dynamic pathway for lung cancer treatments has spurring new trajectories of anticancer drugs based on blocking agent BIBW-2992, Afatinib and BIBF 1120, which are incremental innovations in comparison with Gefitinib and Erlotinib: *e.g.* the rate of scientific production of the new anticancer drug "Afatinib" is 76.75%, whereas BIBW-2992 has a rate of technological advances equal to 77.42%, showing as these incremental innovations have an growing scientific and technological accumulation of knowledge.

Table 2: Rates of growth of drugs for lung cancer

Treatment for Lung Cancer	% Rate of scientific advances (measured by article) 2000-2010 period	% Rate of technological advances (measured by patents) 1996-2010 period
<i>New drugs based on targeted therapy</i>		
Gefitinib	46.76	18.77
Erlotinib	45.76	47.05
Afatinib (2009-2010)*	76.75	--
BIBW-2992( 2006-2010)*	48.67	77.42
BIBF 1120 (2004-2010)*	56.99	20.50
<i>Standard chemotherapy agents</i>		
Cisplatin	4.93	15.36
Gemcitabine (used in combination with the Cisplatin)	15.19	40.20
Docetaxel	32.00	30.09
Paclitaxel	21.44	25.34

NOTE: Gefitinib has a total number of occurrences equal to 9981 (articles) and 6875 (patents); Erlotinib has 8105 occurrences of articles and 5281 of patents. Afatinib has 33 occurrences of articles. BIBW-2992 has 147 occurrences of articles and 103 of patents. BIBF 1120 has 123 occurrences of articles and 156 of patents. *Standard chemotherapy agents have higher number of occurrences*: Cisplatin 55,390 (articles) and 44,971 (patents), Gemcitabine has 18,441 occurrences of articles and 17,092 of patents, Docetaxel 18,739 (articles) and 18,421 (patents), Paclitaxel 38,236 (articles) and 36,882 (patents). \* New compounds that are in the clinical phase III.

Specifically, these new compounds that are in the clinical phase III confirm that a great deal of scientific and technological progress is underpinned by gradual refinement of certain basic patterns. In other words, according to Sahal (1981, p. 112): “the evolution of technology . . . is governed by a process of cumulative change”.

In addition, as trends of these new anticancer drugs have S-patterns (Figure 1A and 2A in Appendix), in order to in-depth analyse their dynamics, it is important to divide the rate of growth in temporal phases. Table 3 displays the rate of scientific/technological advances per main phases of S-pattern.

Table 3 shows as the scientific advances of Gefitinib are started before of Erlotinib and now, Gefitinib is in a maturity phase of evolutionary growth of knowledge for articles and for patents. As far as Afatinib (*ibidem* BIBF 1120 and BIBW-2992) is concerned, this incremental innovation is at the early stage of growth and higher rates of scientific/technological advances indicate that future innovative pathways to treat NSCLC may be led by these new anticancer drugs, although some of them do not have and/or have low patenting activities.

*Table 3: Rates of growth of new drugs for lung cancer based on phases of the S-shaped pattern*

Period	Phases Articles	Radical innovations		Incremental innovation
		Gefitinib %	Erlotinib %	Afatinib % * (2009-2011)
1997-2002	Growth	93.02	67.17	76.75
2002-2006	Transition	29.39	43.67	--
2006-2010	Maturity	-1.03	10.16	--
Period	Phases Patents			
1997-2002	Growth	42.14	83.63	--
2002-2006	Transition	20.18	-1.73	--
2006-2010	Maturity	-11.68	--	--

Note: \* New compound that is in the clinical phase III.

*Table 4: Summary of log-linear model*

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.93	0.86	0.85	0.47

The independent variable is LN CISPLATIN (Patents). Data: 1996-2010.

*Table 5: ANOVA*

	Sum of Squares	df	Mean Square	F	Sig.
Regression	17.09	1	17.09	78.46	0.00
Residual	2.83	13	0.22		
Total	19.92	14			

The independent variable is LN CISPLATIN (Patents). Data: 1996-2010.

*Table 6: Coefficients of log-linear model*

	Unstandardized Coefficients		t	Sig.
	B	Std. Error		
LN CISPLATIN (Patents)	1.34	0.15	8.86	0.000
(Constant)	-4.83	1.18	-4.09	0.001

The dependent variable is LN Gefitinib (Patents). Data: 1996-2010.

It is also important to ascertain that firms in drug discovery sector could prefer to keep new compounds secret rather than patents them<sup>12</sup>, in order to avoid imitation processes in current competitive markets (cf. Ottoz and Cugno, 2009)<sup>13</sup>.

• *Technological substitution and rate of relative growth*

As the patterns of radical innovations and standard chemotherapy drugs for NSCLC are S-Shaped (Figs. 1A-2A-3A), it is possible to apply the model of technological substitution by Sahal (1981). The absolute production of patents of the new anticancer drugs relative to the production of patents of the traditional chemotherapy agent, plotted on double-logarithmic scale, show a linear trend (figure 4A).

Now it is essentially to measure the growth of the production of one (new) anticancer drug relative to the other (standard platinum-based chemotherapy alone). The coefficient of the independent variable in the model [7] of the spatial process of technological substitution provides this magnitude. The results for the new anticancer drug Gefitinib are presented in the tables (4-6), whereas for the anticancer drug Erlotinib, as the patenting activity begun later (*i. e.* since 2003), the estimates do not provide significant results because of the shorter period of data.

The first thing to be said about these results is that the model explains 85% variance in the data (Tab. 4). In addition the parametric

estimates of the model are unbiased and the significance of coefficients and the explanatory power of the equations are good (tab. 5 and 6).

The coefficient of the model [7] is equal to unity if the rates of production of the two anticancer drugs are equal. The result of table 6 indicates that the value of the relative growth rate is significantly differ from unity: that is, the rate of growth of the technological output of the radical innovation (Gefitinib) relative to standard platinum-based chemotherapy alone based on Cisplatin, is 1.34. This finding supports the hypothesis: radical innovation (Gefitinib) to treat NSCLC has generally an allometric process of growth; that is, substitution of the innovative output for the other generally involves disproportionate growth of one (new anticancer drug, Gefitinib) in relation to the other (standard platinum-based chemotherapy alone, *i.e.* Cisplatin).

## 5. DISCUSSION

Lung cancer is a main cause of death worldwide and some chemotherapy agents have reached the maturity phase in the treatment of advanced non-small cell lung cancer (NSCLC). This paper shows as new anticancer drugs are driven by the insurgence of the technological paradigm of targeted therapy originated by scientific convergence of genetics, genomics and proteomics (fig.1). Targeted cancer therapies, by focusing on molecular and cellular changes that are specific to cancer, are more effective than other types of treatments, including chemotherapy and radiotherapy, and less harmful to normal cells (cf. National Cancer Institute, 2011).

<sup>12</sup>I am grateful to Vittorio Valli for this observation.

<sup>13</sup>Friedman, Landes and Posner (1981) claim that: “ ‘ Inventors choose trade secret protection when they believe patent protection . . . will give them a reward substantially less than the benefit of their invention’ ” (as quoted by Ottoz and Cugno, 2009, p. 2).



Table 7: Different factors of technological substitution of new drugs for lung cancer

<i>Determinants of boost</i>	<i>Factors of friction</i>
<ul style="list-style-type: none"> <li>- Faster tumor regression</li> <li>- Lower adverse drug reaction</li> <li>- Longer overall survival of patients</li> <li>- Better living</li> <li>- Administer at home</li> <li>- Higher quality of life</li> </ul>	<ul style="list-style-type: none"> <li>- Time consuming <i>iter</i> to use new anticancer drugs (histological analysis, biomarker, etc.)</li> <li>- Lack of labs and/or technological knowledge and/or human capita, and/or equipment in hospitals for EGF-R mutation</li> <li>- High-cost drugs in comparison to traditional chemotherapy agents</li> <li>- Decision of oncologists affects by budgetary constraints of public health sector</li> </ul>

Converging research fields (grey area in figure 1) have improving the scientific understanding of diseases and underpinning these revolutionary innovations to treat NSCLC, which lead to longer and better living of patients. The targeted therapy for NSCLC is a vital case study since its scientific advances are similar to other new drugs that fight different cancers, such as lymphoma, leukaemia, as well as Alzheimer's and Parkinson diseases, human immunodeficiency and hepatitis C viruses.

Although these new medical innovations have lower toxicity, prolong survival and improve the quality of life of patients, their patterns of diffusion have friction effects due to high cost for healthcare. The main drivers and friction factors for the technological substitution of new anticancer drugs vs. standard chemotherapy agents are synthesized in the table 7.

The converging research fields in figure 1 are also driving a strategic change of corporate R&D Drug discovery process, which is based on translational medicine: "the interplay between basic laboratory science and exploratory clinical research. It encompasses preclinical investigations of the biological effects of therapeutics as well as clinical investigations aimed at enhanced understanding of disease biology" (as defined by Roche, 2011). as a matter of fact, the "technological guideposts" (Sahal, 1981, pp. 32-36), based on innovative drug design technology and experimental approaches, is

driving an industrial and corporate change, which is due to rational modes of drug discovery that develop integrative capabilities fundamental to support drug discovery process of firms (*cf.* Henderson, 1994, p. 607ff). Morlacchi and Nelson (2011, p. 513) claims that: "as the therapy evolves, the principal actors involved in advancing the therapy tend to change as well". In addition, R&D costs for drug discovery are increasing exponentially (at a pace of 10.8% per annum, whereas revenue from new drugs is growing at the rate of 7% -Jain, 2000, p. 320), with a development process of new drugs (over the past decade) of about 11-15 years (Biofocus, 2011) and less than 10% of drugs deliver acceptable commercial returns (Afshar, 2003, p. 392). In order to cope with these main tendencies in drug discovery industry, table 8 shows the current structure for R&D, research areas and corporate strategy of three leading companies that have driving innovation pathways to treat lung cancer and other typologies of cancers and diseases.

In general, leading companies, in order to improve the organizational behaviour for drug discovery (that have blockbusters status or potential) in fast-changing scenarios, have a current strategic change focused on:

a) high intensity of R&D focused on critical topics in order to reduce the cost of drug development;

b) reduction of the time to market to 4 years (Jain, 2000, p. 318);

c) strategic partnership with public and private labs as well as strategic alliances mainly with biotechnology and nanotechnology firms, in order to spur drug discovery process. In particular, the current scientific and technological advances of new drugs are also boosted by a vital learning process that is discussed in the next section.

- *Learning process underlying technological change in clinical practice*

The pace of innovation dynamics is based on continuous small scientific advances, rather than drastic breakthroughs, both in diagnosis and therapy settings. The scientific and technological advances of drug discovery take place in stages (assay development, lead optimization, pre-development, preclinical development, clinical research) and there are significant time lags between the acquisition of information in clinical research and the development/improvement of new anticancer drugs. The steps of R&D are interwoven and blockbusters are best pursued by a learning process in cooperation with end users (patients). In particular, this gradual R&D process that drives new therapies is affected by the progress of “Learning in practice” and “Advances in biomedical scientific understanding” (Morlacchi and Nelson, 2011, p. 512, *passim*). In fact, it is important to note that the radical innovations of modern medicine generally depend on learning processes driven by the acquisition of skills through the clinical research based on participation of patients and medical staff. This is the so-called “‘learning via diffusion’ .... The increased adoption of a technology paves the way for improvement in its characteristics” (Sahal, 1981, p. 114). Another essential aspect driving the targeted therapy is the collective and cumulative learning that supports the evolution of technological trajectories for new anticancer drugs (*cf.* also Morlacchi and Nelson, 2011, pp. 521-523). However, it is important to ascertain that in specific medical fields, the technological/

scientific learning is context dependent<sup>14</sup>. For instance, the role of learning in driving innovations for lung cancer is different from learning for failing hearts: a key role to treat failing hearts is played by developing effective medical technology (new implantable device for hearth) whereas for lung cancer, new anticancer drugs are driven mainly by a learning process based on scientific advances in genetics and genomics, associated to learning in clinical practice. Therefore innovations and learning process to treat several diseases tends to be of different nature: “the resulting know-how is often fragmentary and context dependent” (Sahal, 1981, p. 198). As a matter of fact, the advancements in scientific knowledge have a general diffusion in all clinical practice, whereas the development of new drugs is localized in specific diseases (*e.g.* new anticancer drugs are effective for NSCLC and not for small cell lung cancer)<sup>15</sup>. This learning process driving technological advancements in medicine is also systematically related to certain peculiarities present in managerial and organizational behaviour of firms: the three leading companies in lung cancer treatments have high level of cumulated investment in R&D as essential determinant of their innovation processes as well as corporate strategies focused on selected acquisitions and alliances both in pre-clinical discovery and in clinical development phases of research. In fact, one of the most critical variable in long-run technological development of drug discovery for lung cancer is learning by clinical research and externally strategic alliances and partnerships, which depend on total investment of company (not only R&D investments).

<sup>14</sup>The discussion of some parts of this sections has as conceptual background the theory of Sahal (1981, chaps 6 and 9).

<sup>15</sup>Allen *et al.* (1979, p. 695) argue: “Science may be said universal. . . . Technology, on the other hand, is not universal”.

Table 8: R&D Structure and corporate strategy of three leading company for medical innovative treatments

AstraZeneca In 1999 fusion between Swedish Astra AB and English Zeneca Group.	Roche (Switzerland)	Boehringer Ingelheim GmbH (Germany)
AstraZeneca currently employs 10,000 personnel in research and development, spends US\$3.5 billion on R&D annually.	In 2010, Roche had over 80,000 employees worldwide and invested over US\$10.6 billion in R&D. The Group posted sales of 56.9 billion US\$.	Boehringer Ingelheim has more than 7,000 highly qualified people working in R&D out of 42,224 Boehringer Ingelheim employees worldwide. In 2010, Boehringer Ingelheim posted net sales of 17.8 billion US\$ while investing almost 24 percent of net sales (about 3.5 billion euro) in the largest business segment Prescription Medicines on R&D.
R&D Areas of Interest		
<p>Oncology (apoptosis, cell cycle control, proliferation/angiogenesis, immune stimulation, motility /invasion, chemoprevention)</p> <ul style="list-style-type: none"> <li>• Cardiovascular/Metabolism</li> <li>• Central Nervous System</li> <li>• Gastrointestinal</li> <li>• Respiratory/Inflammation</li> <li>• Pain Control</li> <li>• Infection</li> </ul>	<ul style="list-style-type: none"> <li>• Oncology</li> <li>• Virology</li> <li>• Inflammation</li> <li>• Metabolism</li> <li>• Central Nervous System</li> </ul>	<ul style="list-style-type: none"> <li>• Respiratory diseases</li> <li>• Cardio metabolic diseases</li> <li>• Neurological diseases</li> <li>• Immunology</li> <li>• Infectious diseases</li> <li>• Oncology</li> </ul> <p>Boehringer Ingelheim's Research &amp; Development focus on angiogenesis inhibition, signal transduction and cell-cycle kinase inhibition. R&amp;D in oncology is committed to discover improved medicines against cancers as: lymphoma, solid tumors, and leukaemia.</p>
Corporate change for driving future drug discovery		
<p>Acquisition of biotechnology firms, partnership with public and private R&amp;D labs worldwide.</p> <p>It has seeking external alliances in both the pre-clinical discovery and the clinical development phases of research.</p>	<p>The disciplines of genetics and genomics have become central pillars of Roche's research. Roche is also the world leader in <i>in-vitro</i> diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Genentech, United States, is a wholly owned member of the Roche Group. Academy-industry partnership seeks to propel progress in translational medicine and personalized healthcare. Roche and university of Basel are entering a strategic alliance to establish and manage Translational Medicine Research Hub (<i>i.e.</i> to advance understanding of the cellular mechanisms that form the basis of disease and its treatment by bringing together medically oriented basic science and clinical research capabilities).</p>	<p>R&amp;D has been transformed thanks to ground breaking new technology, such as high-throughput and ultra-high-throughput screening. The acquisition of the injectables manufacturer has given the hospital segment a major boost. New marketing alliances have been formed with leading companies, such as Genentech, Abbott Laboratories, Glaxo Wellcome, Pfizer and Eli Lilly. Acquisition of the micro-technology company STEAG microParts GmbH from STEAG AG, Essen. Strategy for the next 10 years foresees Boehringer Ingelheim continuing to research and develop medicines supported by in licensing and selected acquisitions and alliances.</p>

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[http://www.rochecanada.com/portal/ca/research\\_development2](http://www.rochecanada.com/portal/ca/research_development2)  
[http://www.boehringer-ingelheim.com/research\\_development.html](http://www.boehringer-ingelheim.com/research_development.html) (accessed 29 June 2011)

## 6. CONCLUDING REMARKS

This study has shed light on current patterns of radical innovations for lung cancer, driven by converging genetics, genomics and proteomics that has generating a revolution in clinical practice, increasing the survival and quality of life of patients. In particular, this paper shows the allometric growth of scientific knowledge in new anticancer drugs. The interesting technological pattern of these new targeted therapies has a common origin to several new drugs and an evolution that can be generalized to understand the nature and barriers of the technological change that has driving the modern medicine.

The current adoption of these new anticancer drugs is determined by the superiority “relative advantage” (Rogers, 1995) over its predecessor (mainly chemotherapy agents), in terms of lower toxicity and higher survival of patients; however there are also some barriers over their process of adoption (table 7) based on budgetary constraints of hospitals and restrictive health policy by countries in current turbulent economic scenarios that seem inhibit the vast diffusion of these main radical innovations in clinical practice (the new anticancer drugs have roughly a double price in comparison with standard platinum-based chemotherapy).

As a matter of the fact, these new treatments for NSCLC seem that increase costs for health

sector at local level, but a global analysis may show reductions of cost in the long run, in comparison to tradition chemotherapy drugs (because of reduction in day-hospital costs, reduction of costs to cure adverse drug reactions of traditional chemotherapy agents, etc.). Chouaid *et al.* (2007, p. 1509), analyzing the economic impact of Gefitinib, show that: “the price of Gefitinib had little influence on the total cost . . . the cost of third-line Gefitinib therapy for NSCLC appears acceptable from healthcare payer’s perspective” (p. 1509). However, health policy of several countries is focused on short-term cost control behaviour and does not encourage long term disease management and cost saving strategies. In fact, socio-economic studies focused on new drugs for Alzheimer’s disease, with economic effects similar to new anticancer drugs for NSCLC, indicate a net saving of these new drugs in comparison with traditional medicine over a period of 2-5 years (Hauber *et al.*, 2000, p. 65).

Healthcare should have a non-myopic -or far-seeing- health policy (i.e. consider the long-run systemic costs of the overall health sector for cancer treatments rather than short-run comparisons based mainly on specific cost of new and old chemotherapy agents) in order to pave the pathway to spread of these targeted therapies that have generating a revolution to treat and we hope to cure the lung cancer in a not-too distant future.

## SUMMARY OF THE RESEARCH

**PURPOSE:** The purpose of this paper is to analyse the patterns of vital radical innovations to treat lung cancer that have generating a revolution in clinical practice.

**METHODS.** Exponential and spatial model of technological substitution are applied on 140,580 occurrences of articles and more than 97,000 occurrences of patents to determine the patterns of innovative targeted therapies.

**RESULTS.** The scientific pattern of growth of new anticancer drugs is an allometric process that involves a disproportionate growth in relation to standard platinum-based chemotherapy alone, driven by a high rate of scientific and technological advances as well as learning process in clinical practice.

**CONCLUSION:** Lung cancer is a main cause of death worldwide and traditional chemotherapy has reached the maturity phase in the treatment of advanced non-small cell lung cancer. This study has shed light on evolutionary growth of knowledge of radical innovations for lung cancer, driven by converging molecularly, genetically and clinically advances, that have been generating innovative treatments with therapeutic benefits in terms of overall survival of patients. A vital role is played by learning process underlying the technological and organizational change in clinical practice. These technological trajectories, spread from the technological paradigm of the targeted therapy, might drive future oncology to cure the variety of cancers in not-too-distant future.

APPENDIX A: S-SHAPED PATTERNS AND TREND OF ANTICANCER DRUGS

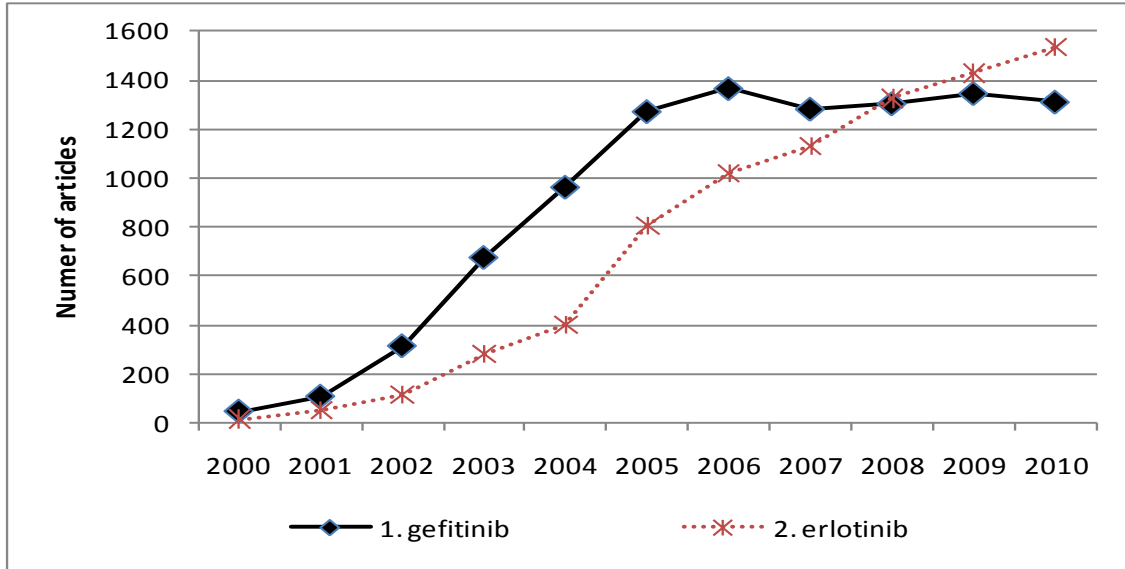
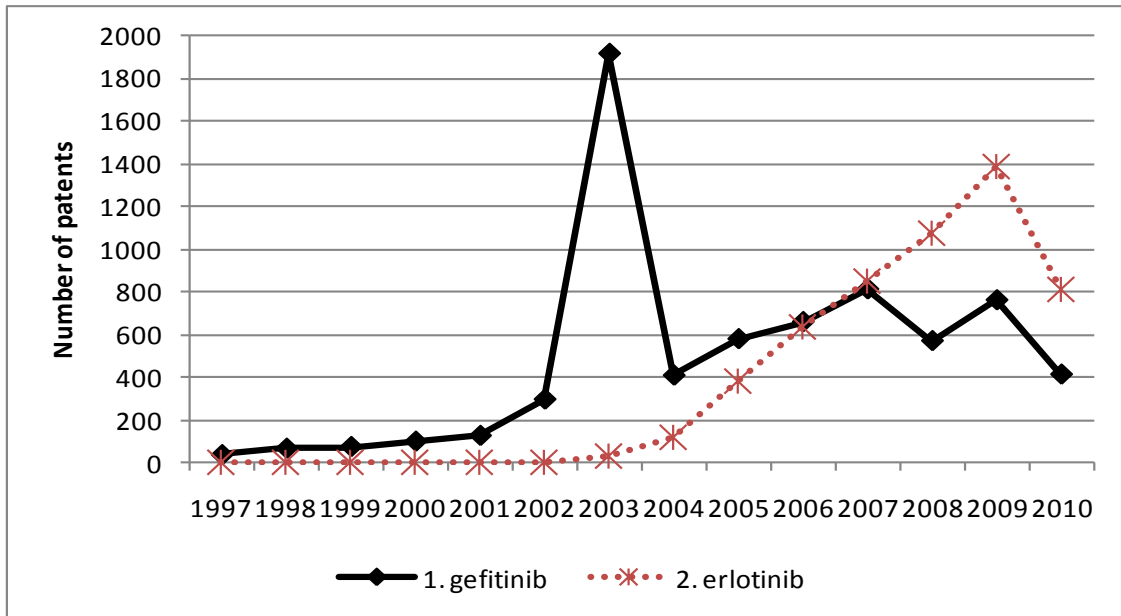
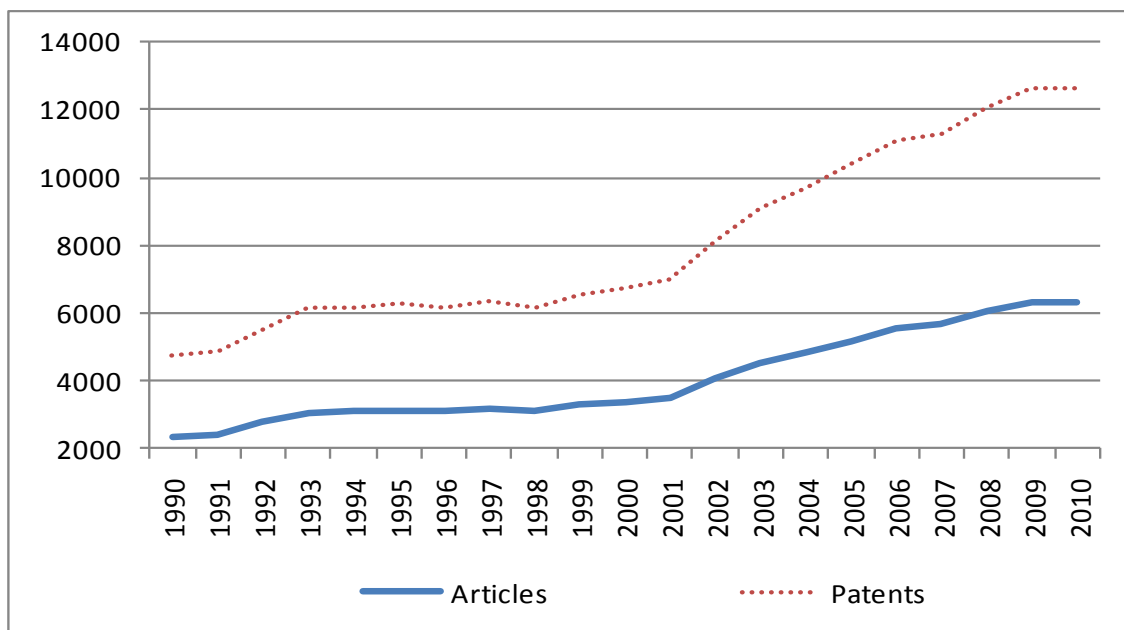


Figure 1A: Patterns of articles of two medical innovations for lung cancer over time (typical pattern S-shaped). Note: BIBF 1120 and BIBW 2992 have similar patterns



Note: BIBF 1120 and BIBW 2992 have similar patterns

Figure 2A: Patterns of patents of two medical innovations for lung cancer over time (typical pattern S-shaped)



Note: Gemcitabine has similar patterns

Figure 3A: Pattern of articles/patents of the standard platinum-based chemotherapy “Cisplatin” for lung cancer (typical pattern S-shaped over time).

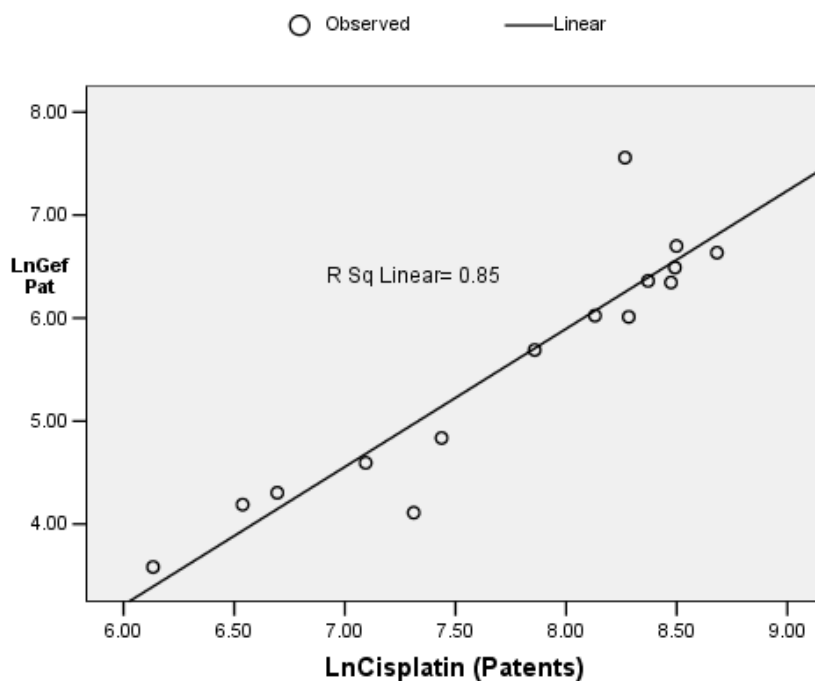


Figure 4A: Linear trend of data of new and standard anticancer agents for lung plotted on double-logarithmic scale over 1996-2010 period

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