Universitat Internacional de Catalunya
Faculty of Economics and Social Sciences

TRABAJO FINAL DE GRADO

Administración y Dirección de Empresas

Could we improve efficiency on healthcare systems reorganizing investments on cancer treatments?

Curso académico 2018/2019

Autor: Paula García Rodríguez

Tutor: Marta Trapero Bertran

Date: 13th May, 2019

Table of contents

Abstract

This project research analyses the setting of the price of innovative oncologic treatments and its impact on the Spanish Health System. It pursues a global perspective including the pharmaceutical industry and the Spanish Public health authorities. The work follows-up the drug development in terms of costs, efficiency and benefits, from the R&D project selection until the establishment of the reimbursement price. The objective of the research is analysing all influencing factors and key agents, looking for opportunities to improve the efficiency of health public allocation resources, in particular in the oncologic field. Finally, summarizing some alternatives that have been proposed already in the literature.

Acknowledgements

I would like to thank in first place to Dr. Marta Trapero Beltrán, my research paper supervisor, for guiding me in this learning period. I appreciate that when I asked for help, I did not get answers, but tools to reach my own conclusions. That has made me able to reason and test myself, stimulating my interest in economic policies beyond this work.

I also appreciate the advice from some of the Research Institute for Evaluation and Public Policies[1] research team members: the director, Dr. Marta Trapero Beltrán, and Laia Orteu, Dr. David Roche Vallés, Dr. Manuel Flores and Dr. Irene Sánchez Collado. Their constructive criticism helped to steer this project when it was still very premature. In addition, their advice helped me to open my mind and take into consideration aspects that I did not know until now.

Furthermore, I would like to express my sincere gratitude to my aunt M. Angeles. She has put all her efforts into making me understand perfectly the connections between the world of the pharmaceutical industry and the health authorities. Thanks for sharing with me your experience and your learning.

Last but not least, I would like to thank my family and my closest friends for their support. They have believed in me, they smiled at me when I was in a bad mood and I felt lost and they were interested in my progress, even though they were not the domain of their interest.

[1] Institut de Recerca en Avaluació i Polítiques Públiques belonging to the Universitat Internacional de Catalunya (IRAPP)

Acronyms – List of Abbreviations

WHO: World Health Organization

YPLL: Years of Potential Life Lost

OCDE: Organisation for Economic Co-operation and Development

MSCBS: Ministerio de Sanidad, Consumo y Bienestar Social

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios

MA: Marketing Authorization

EMA: European Medicines Agency

DGCBSF: Cartera Básica del Servicio Nacional de Salud y Farmacia

CCAA: Autonomous Communities

GCPT: Grupo de Coordinación de Posicionamiento Terapéutico

IPT: Informe de Posicionamiento Terapéutico

SNS: Sistema Nacional de Salud

QALY: Quality-Adjusted Life-Year

CIMP: Comisión Interministerial De Precios De Medicamentos Y Productos Sanitarios

PVL: Precio de Venta de Laboratorio

RSS: Risk-Sharing Scheme

HTA: Health Technology Assessment

ICER: Incremental Cost-Effectiveness Ratio

CEA: Cost-Effectiveness Analysis

Personal Motivation

I've been always keen on pharmaceuticals; I think is a powerful industry able to save people's life or take them a turn for the better. Moreover, I judge pharmaceutical companies as successful businesses due they capability to get high margins and profits. Actually, many pharmaceutical companies are listed as the most powerful companies worldwide (1). As a BA student, I would like to understand how investments are planned, while bearing in mind all risks laboratories take until they find the optimal solution to palliate diseases. Also, I been fascinated how they do to make those substantial profits from a basic necessity, and able to commercialize around the world, where each country has a different health public system and economic situation.

Likewise, I'm very interested in study how health public authorities are interested in providing health to our society, sometimes implying to buy many treatments at reasonable prices for guaranteeing the recovery of all patients who require it. Also, I would like to know a little more about the process of introducing innovative anticancer resources are introduced in hospitals' portfolios; even though the high cost they have. Usually, innovative solutions and technology, use to present a high-price when launched, in particular in the oncologic framework. I would like to understand which facts raise drugs' price. Personally, I have heard different arguments, such the high expense on R+D, legal issues, conflict of interests, etc.

From a macroeconomic point of view, I would like to know how the government manages the budget in order to be sustainable and provide quality and innovative services for all patients previously commented. Moreover, taking in account that there are limited resources to share between all autonomous communities, hospitals and patients with different diseases and needs. Unfortunately, since the economic crisis in 2008, austerity policies entailed noticeable cutbacks in public health, so institutions and hospitals not always can afford offering some anticancer treatments or offering to all people who need it.

Taking in consideration my studies in Business Administration and Industrial Production Engineering, I thought I was able to contribute to find out a solution for a real problem for our society, in a field that is an essential part of everyone's life.

Furthermore, I rely on the IRAPP (Institut de Recerca en Avaluació i Polítiques Públiques), a research institution that has recognized experience evaluating health policies specially analysing the efficiency of programs and interventions.

Whereas, I would like that this research project help me to understand a little bit more the limits between business profits and social needs. In other words, how priorities are set considering this context raises conflict of interests. People do need urgent and affordable drugs, which cannot be free-of-charge because pharmaceuticals are a business, so their principal objective is maximizing benefits. On the other hand, due to real necessities of these medicines, unaffordable prices or lack solutions could endanger population's health.

I would like to work on one of both sides of this buying process, either offering solutions for fighting against diseases in pharmaceutical company or like a public institution create policies and deals to provide drugs to people who cannot afford treatments by themselves. I hope this project will bring me knowledge and a different vision of successful business and public policies, my two major interests since I was on high school.

1. Introduction

1.1. Background of cancer disease

Last year, 2018, around 9.6 million people around the world died because of cancer. This disease, by definition is "*a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs, the latter process is referred to as metastasizing. Metastases are a major cause of death from cancer*."[2] It is the second principal cause of death worldwide. (2) It is also in Spain (25,4% out of the totals deaths in 2015 (3) and the 26% in 2017)(4). (Figure 1)

The cancer that is more extended worldwide is the cancer lung, followed by the colorectal. In Spain 2017, the cancers which were diagnosed mostly in 2017 were colorectal and prostate cancer (5). In despite of the lung cancer is the most common in Spanish men, for women it is the breast cancer. Fortunately, these two last cases have decreased along the last decades, especially since a great part of the population has let the habit of smoking up. (3)

Figure 1- Estimated incidence of the most frequent tumours in Spain in 2017 (both sexes). Data from GLOBOCAN 2012, disaggregated by age and sex, and extrapolated to the data of the Spanish population for the year 2017 provided by the INE.(5)

[2] Cancer's definition by the World Health Organization (WHO)

Furthermore, tobacco is the principal cause of the vast majority cancer types (2, 6). In fact, is in charge of the 22% of cancer deaths. The reason is the presence of carcinogenic substances. Exposure to other toxic substances like radon, ultraviolet light or pollution increases the risk of suffering cancer too. Finally, diet is fundamental to avoid this disease: the presence of fruits and vegetables prevents it as long as obesity can contribute to develop malign cells. (2, 7)

Unfortunately, cancer diseases apart from producing deaths and pain for patients and their families, this disease has an important economic impact in the country taking into account not only the resources needed to palliate cancer but the mortality and morbidity it produces, damaging the overall society (8). This impact has a healthcare and non-healthcare costs, and productivity losses for any country. Direct healthcare costs are principally related to outpatient care, primary care, drug treatment and hospital care. (9)

In fact, in 2015 cancer cost about 7.168 million € to the Spanish National Health System (that means the 10, 93% of the public health expense). From all this cost, 1.171 million € where used to buy antineoplastic medicines (10). Moreover, this outlay grew an 8.6% from 2008 to 2015 and it is continuous growing up with the introduction of new therapies to fight against this disease, turning the supply of anticancer drugs into one of the biggest expenses for the national pharmaceutical expense (11).

We consider also the productivity losses associated to mortality and morbidity, previously commented. This means the years of potential life lost (YPLL) which have a negative impact on Spanish productivity in a long term basis – taking in terms of mortality- as well as the loss of productivity due partial or permanent disability-in terms of morbidity. (9, 12)

On top of that, cancer generates huge additional costs for who suffers it and their families. In despite of the Spanish public health system finances drugs and surgeries, patients deal with other expenses. Different medicines to face up side effects, specific cosmetics and self-care products, special diet food, transport to hospital and some cases, move to other cities where they can be treated. Moreover, we might take in account the salaries they are losing while not working and some extra outlay for help like contracting a babysitter or a person who helps in the household tasks. In case of the transport to go and come back to the hospital daily, weekly or monthly; was financed by the state years ago, the Minister of Health, Ana Mato, reformed the law; as it was expressed in the BOE published in April 2012.(13)

1.2. Oncologic treatments

To begin, there are many ways to treat cancer disease. The doctor, the oncologist, decides using one treatment or another mainly based on the type of tumour, where and how it is. The treatment depends, additionally, on the age, gender and general state of health of the patient, as well as if the tumour has affected some lymph nodes.

There is not a single solution for a patient; what's more, in many cases different treatments are combined, such as surgery and chemotherapy. The principal forms of treatment are surgery, radiotherapy and chemotherapy. In despite of that, new forms have been discovered and used during the last years like hormone therapy, immunotherapy and others.

Surgery

Surgery is the main treatment for solid tumours that are located in one part of the body, this means, the cancer has not spread. This technique is commonly followed by other treatments (chemotherapy, radiotherapy etc.). Surgery is normally perceived as cutting a zone and removing the tumour (14). Actually, this happens, but there are many other cancer surgery forms: using freezing trough nitrogen or argon gas (cryosurgery), lasers, high temperatures (hyperthermia), and drugs that react to some kind of lights (phototherapy). (15) As previously said, the way surgery is done would depend on the type, size and location of the cancer (if it is on an internal organ, on the surface, the blood, etc.).

Operations can present different purposes: to prevent, to diagnose, extirpate the tumour or to palliate it, among others. (16). The surgery has some risks that can provoke pain during and after the operation, like haemorrhages, infections or deep vein thrombosis.

Chemotherapy

The chemotherapy consists in administer a drug that kills cancer cells, preventing their growth or stopping it. It can be used before another cancer treatment in order to reduce the tumour size (neoadjuvant chemotherapy) or used directly to treat the cancer (adjuvant chemotherapy) (17, 18). This kind of drugs is called antineoplastic or chemotherapeutic drugs; and can be used individually or in combination.

Nevertheless, killing cancer cells and avoiding its spread to other parts of the body, the drug kills healthy cells too, in particular those located in the mouth and intestines and those in charge of hair growth. Thus, common side effects are hair loss, mouth sores, nausea as well as extreme tiredness.

In addition, the drug can be taken via oral or injected. In the first case, most patients are treated at their own homes. On the other hand, if the drug is injected, people have to go to a Day Hospital or be admitted for a couple days in the hospital; due they require specific safety and sterility measures (19).

Since the drug has an aggressive effect on malign and healthy cells, the treatment should be rationed out and include periods of rest with the purpose of giving the body the opportunity of developing new healthy cells again. This combination of treatment and rest is called cycle. The duration of the treatment and its cycles is determined by the oncologist, who will decide based on the state of progress of the cancer and its location. The drug can be administrated weekly, every two weeks or three or monthly. It can also vary the time of transfusion: 15 minutes, 30 minutes or for a couple of hours (20).

The principal indicator to evaluate the effectiveness of neoplastic drugs is the survival of the patient, obviously free of relapsing on the cancer disease again.

Radiotherapy

Radiotherapy consists in exposing a part of the body or tissue to high doses of X-Ray with the purpose of killing cancer cells. As a consequence, as happens in chemotherapy, it also kills nearby healthy cells so the patient can experiment some side-effects (21). Furthermore, it is an individualized therapy: every single patient would receive a different treatment.

Although the duration of the treatment can vary depending on the health state of the patient, kind of tumour etc. The standard duration is between two and seven weeks; and the sessions, which last just a few minutes, are done five days per week.

This kind of cancer treatment can be done in two ways. The first is externally, in which the patient receives radiation produced by a machine, but it has not direct contact with the tumour. It is used when the tumour is not spread, so it is a local treatment. On the other hand, the internal radiotherapy consists in inserting a radioactive source inside the body, in solid (brachytherapy) or liquid form (systemic radiation therapy).(22)

Immunotherapy

Immunotherapy is a cancer treatment which objective is to stimulate the patient's immunological system in order to make it capable to kill the cancerous cells by itself, through the lymphatic system. This kind of drugs turns the immunological system able to distinguish and select the harmful cells (therapeutic target) from the healthy ones, avoiding toxicities on these last (23). In addition, immunotherapy is a biological therapy, owing to is made up by substances of living beings.(24)

In addition, there are three types of immunotherapies: specific, non-specific and passive (25, 26). The specific immunotherapies provoke a response against a concrete cell. Examples are vaccines and adoptive cell therapies. On the contrary, non-specific immunotherapies stimulate the whole immunological system of the patient to fight against the tumour, such as the cytokines and immune control proteins. These solutions are pretty new. Actually, immunotherapy presents some uncertain results yet(27). The first drug of this type that arrived in Spain was *Ipilimumab*, in 2015. It treats advanced melanomas.(28)

As we have seen on chemotherapy, immunotherapy is administered through cycles, and the duration can vary from weeks to months, depending on each patient's situation.

Others

Apart from the cancer therapies commented, some different therapies are also used, such as hormone therapy, stem cell transplant or targeted therapy. The last one has already been developed, because it's a product of the last year's pharmacological innovation. It is also important to know that more biological treatments are being developed nowadays, but they have not been definitely drawn up yet.

1.3. Aim and Scope

The aim of the project is finding a proposal to increase the efficiency and sustainability of the Spanish Healthcare System being able to attend the higher number of cancer patients and giving them the highest number of quality adjusted life years. In other words, how to establish prices to drugs in a more efficient way, analyzing all the steps and parties who intervene in the process. Firstly, I will focus on the research and operational costs for the pharmaceutical company owing to develop a new drug, in which price will be based. Secondly, I will describe the Spanish Ministry of Health's role. The centralization/decentralization level of decision, timing frame, the political and

legal framework, evaluation criteria for setting prices and at the same time reaching an agreement with the seller company. Seeing the wideness of the objective, four specific sub-objectives have been set in order to achieve the principal aim: Sub objectives: (a) how pharmaceutical companies set the cancer drugs prices; (b) budgets of health authorities in our country; (c) meeting point or price negotiations between pharmaceutical companies and health authorities; and, (d) alternative methods for setting cancer drug prices.

To begin, it's important to have a clear idea about what efficiency and sustainability mean. Efficiency is about achieving the highest health related results and benefits with the minimum number of resources. Reaching efficiency could imply to disinvest in some health technologies or drugs to reinvest the money/resources in other technologies/drugs that achieve higher quality of life or life expectancy. In the current setting, this goal can be achieved through strategic planning. Nowadays we are able to forecast what is coming, and being capable to anticipate future situations and evaluate all possibilities consistently in a clinical and economical way (29). Both pharmaceutical companies and health public institutions count on sufficient technology to record patients' evolution testing new drugs (through clinical trials as well as application in real situations) and then develop models to predict treatment functioning in the future in different scenarios. Stakeholders also have considerable number of articles and studies on hand, composed by researches from all over the world and skilled in different oncologic, innovative and economical fields that can result useful at the time of designing new ways to plan health necessities, bearing in mind the finite budget, the business environment and the urgency of the demand. Having systems to predict efficiently the development of cancer diseases and the most probable ways to take the illness out would help to save time and money resources, and above all, allow patients to a faster access to innovative drugs able to cure them as a guarantee of better health results as well as stopping the tumor's evolution before than treatments used in the past. Thus, standardizing a new planning and evaluation method can help to provide more efficiency to our public healthcare system and consequently increase the quality and quantity of cancer treatments for the Spanish citizens.

On the other side, sustainability - in this context-has to do with making grow the financing capability of the State for the standard of care in the long term. This also can be improved through structural changes in public health policies.

In order to reach a convincing conclusion, many aspects should had been consulted and analyzed.

First of all, it is essential to understand the cancer framework: what is this disease, what effects can provoke not only to patients but in the whole society; and how can be treated in order to cure them or palliate its effects. Moreover, translate the theory into data reflected in the national healthcare system. This means, setting the number of people affected by cancer in Spain and which cost has for the public healthcare system.

In second place, it has been necessary to find reasonable arguments for the high prices of oncology drugs, focused on pharmaceutical companies, as well as how they set prices with their payers (that are part of the health system), and which methods are used nowadays to try to keep a sustainable public healthcare system while buying innovative drugs, which present a higher price year after year.

In order to find disruptive innovative solutions, more research has been done, which includes many topics from different domains. However, the fundamental topics to review were: (a) Multi-criteria decisions method; (b) Cost-effectiveness valuation and value based pricing; (c) Evaluation method for investment and disinvestment in public health; (d) Criteria that should be taken in account at the time of approving the commercialization of a new oncologic treatment; (e) Flow of information between innovation stakeholders: pharmaceutical companies, governmental health authorities, cancer institutions, research centers and patients; (f) Innovation's drivers and incentives.

These points represent different solutions and information that must be considered and reviewed in order to be implemented someway in the process of setting prices. All of them take as participants the pharmaceutical companies and laboratories (buyers or producers) and the Spanish health public institutions (payers). Reviewing this knowledge about economy of health would provide multiple pathways which present the possibility of an agreement between all stakeholders maximizing their own benefits and interests. The materialization of this goal is dealing for lowering the price of innovative anticancer treatments.

2. Method

2.1. Literature Review

This project research has been principally based on a literature review. The vast majority of the information has come from academic articles published by other researchers in the past, and afterwards contrasted with the actual situation. To find out this kind of literature, I initiated searching in the net through Google Scholar. Keywords used for the search according to the different scopes and topics covered were prod*[3], pharma*, efficiency/ effic*, drug, medicine, onco*, innova* and price. Two more screening criteria were included. At first, set only a time criterion for filtering information, delimiting results from 2005 until 2019, with the purpose of reading studies made in similar circumstances as today. Nevertheless, some exceptions were made, due to few articles were published previously – mainly about economic models and decision-making criteria – and contributed interesting arguments to my project research.

After establishing this searching criterion, I've found myself forced to filter according to the geographic results on literature, focusing the research in European and Spanish studies. The reason was that the most popular and abundant articles were done in the US, which has a very different health system, because it is a private system, and this project talks about the public health system in Spain. In the US, the pharmaceutical companies are the only ones setting the drugs' prices, and the buyers are directly the final users (patients) or their private insurance. The high and unaffordable prices for US citizens are extremely polemic in the country and a great number of studies about the issue have been published there. Even if American papers did not serve to base my project on, they were handy for contrasting information, owing to the magnitude of studies about the topic.

To reach the major accuracy as possible, actual numbers and data has been looked up in official documents, reports and audits published by consultancy firms, Governmental Institutions and from different Public Health Institutions and levels, like *World Health Organization (WHO), National Cancer Institute (NCI), International Medical Services (IMS), The Professional Society for Health Economics and Outcomes Research (ISPOR)* and others. In the European framework, since it is the initial stage for drug launching in our country, reports from the *Organization for Economic*

[3] The asterisk sets the written lexeme to be search with any of its morphemes, so more results are allowed. For example, in this case, using the lexeme "prod" we are looking fundamentally for product, production and productivity keywords.

Cooperation and Development (OCDE) and the Health department from the European Union site. For national data the *Ministerio de Sanidad, Consumo y Bienestar Social* (MSCBS) and *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS) have been the main resource, as well as Instituto *Nacional de Estadística* (INE). On the other hand, for autonomic information *CatSalut* has been established has my reference point.

Moreover, in order to get a wider vision of this subject, I've read much news published in newspapers and economic and health magazines worldwide. I've done the same with blogs of independent or private organizations which are involved with the cancer topic like *Asociación de Economía de la Salud* (*AES*), *Asociación Española Contra el Cáncer (AECC), Sociedad Española de Oncología Médica (SEOM),* among others. This kind of method has been useful not only to discover more points of view but to meet new resources that have provided me reliable data. In addition, I did interview a person who works in a pharmaceutical Company, specifically in the oncologic commercial department, as part of a research in the field. This fact also helped me to vision this research project from the industry perspective, because the major publications, in despite of being theoretically objective, are written from the opposite position.

Regarding external help from others, I have received advice from the IRAPP's research team (*Institut de Recerca en Avaluació i Polítiques Públiques*). They have proposed me new questions to answer along this project with intrinsic visions and ideas to become more creative, accurate and complete at time of proposing solutions.

To conclude, I've complemented the research watching some documentaries, reading some chapters from the book *Innovation Management And New Product Development (Paul Trott)* and consulting some other books about innovation, decision-making methods and other business areas.

3. Results

3.1. Cost of developing new oncologic drugs: point of view of pharmaceutical companies

Pharmaceutical companies are known for setting excessive prices to their products, which are almost considered commodities. As the WHO affirms: "*The literature describes four broad determinants of medicine prices from the industry perspective: costs of research and development; costs of production and commercialization; the "value" of medicine; and sufficient returns on research and development"*.(30). Hence, establishing launch prices is not an easy decision for pharmaceuticals. Once the product is launched onto the market, it is difficult to push up prices of our present treatments in the long run. Owing to that, initial prices tend to double or treble the price of drugs with the same purposes currently available in the marketplace.(31)

The main argument the industry provides is that high prices are the path for recovering the huge inversion required to develop a new and innovative drug. Pharmaceutical offer solutions for increasing somehow life expectancy as well as improving quality of life for patients through diminishing side effects, which could result so hard and expensive to alleviate. In addition, results of these improvements must prove producing additional benefits with respect to existing treatments in the market. However, carry through these drugs entails high research costs in order to find out the higher effectiveness as possible. This implies discriminating target population (32) for being more specific and resolute. Actually, all the process brings a large path of costs: buyers should not consider only the cost of developing new molecules and drugs, but many other ancillary expenses as drugs that did not work during the study, salaries, equipment or clinical trials, which are so expensive due they imply also insurance programs.

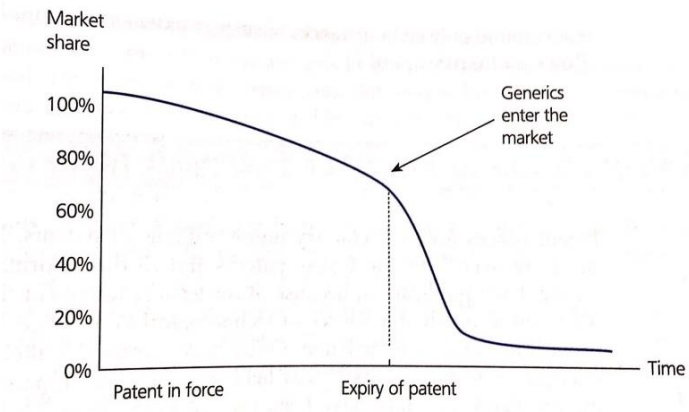
Contrary to this argument, Andrew Witty the GlaxoSmithKline's CEO affirmed *the $1 billion price of developing a drug tag was "one of the great myths of the industry"*.(33) (London, 2013). Anyway, there are other reasons for the pharmaceutical industry for establishing high prices. Medicines are basic necessity products, which price must be fair and worth. But the low offer because the lack of substitutes or complementary solutions, lead to a less-elastic demand curves (34). Nevertheless, even if two drugs look alike in terms of benefits and secondary effects as toxicity, prices are also similar. Then, the price sensitivity decreases, and buyers cannot make

decisions based on cost savings (35). Some specialists say that the industry uses some tactic strategies as in the "game theory" with the purpose of creating a collective monopoly and maintain high prices during a period (36).

These monopolies are reinforced by patents, which protect pharmaceutical companies from direct competition. The company can develop a new anticancer drug with exclusive rights to launch onto the market the new medicine (37). In contrast, this right of exclusivity last for 20 years, including the time of developing the antineoplastic, that usually takes around 10 years to be finished. Therefore, pharmaceutical companies rise prices with the purpose of recovering research costs during the remaining years, just as obtaining a substantial benefit during its monopoly (38). It has been shown that patents lead to a lack of competitiveness among pharmaceutical companies, so the incentives to compete in terms of price disappear (39).

In relation to this 10-remaining years for "enjoying" the patent rights for a new drug, marketing costs use to be considerably higher than R&D costs (40). Given that once the patent expires the generics will reach the market with a much lower price and the pharmaceutical companies run the risk of losing market share. For this reason, they invest on aggressive marketing campaigns with the aim of creating brand loyalty, and guarantee that once the drug is off-patent, asking for the branded it. If the company is unable to reach this goal, benefits plummet immediately (The effect on its market share of a drug coming off-patent). (Figure 2). In parallel investment in research is also established to improve the existing product in order to acquire new patents. Let's say that companies focus on monopolizing the market of a specific oncological treatment as long as possible (39). In addition, the industry refers increasing research and operational costs increase as more drugs are launched to market; due to the fact there are less unexploited targets in the market and more specialized therapies, which most of the time require higher investments. (34, 41)

Figure 2 The effect on its market share of a drug coming off-patent



Pharmaceutical companies' financial accounts are a well-kept secret. It takes chances of being the faster in-time-to-market, and this implies millions of dollars (42). The industry affirms that bringing information to the public can compromise their interests or strategies. It is also common to use ambiguous language, include contradictory descriptions or inconsistent policies (43). Whereas most companies publish their annual reports, actually they do not ensure disclosure on results. For example, it is challenging knowing if a company has received some kind of subsidy from the government for incentivising innovation. They present an evident lack of transparency, making harder to set a price based on costs. Therefore, pricing drugs turns very speculative, indeed. (38)

Experts affirm worldwide prices are settled using the reference pricing model, called the "*market spiral pricing strategy"(35)*". It consists in the taking a similar and old drug and incrementing its price by a 10%-20%. Likewise, other companies try to avoid this model by taking a fix price equally to current drugs that provide same therapeutic results and contain the same active agent. This method, called "*Reference pricing*", fosters (43) the cost-effectiveness analysis (CEA)+regarding oncological treatments. Even though *Reference pricing* helps not to raise prices, also does not decrease them. Companies competing cluster maintaining prices up, according to their commercialization goals, independent of drugs' intrinsic value, just as willingness-to-pay of buyers. The only way to cut a little the price is through negotiations with the national's health institution from each country, but hospitals often do not find incentives to avert cancer drug costs.

As a result of these actions, is known that during the last years brand name companies are getting elevated profits, 20% or more. Such as Hoffmann-La Roche Pfizer, GlaxoSmithKline or AbbVie did in 2013(40).

It's important to consider that providing new and stronger benefits to people who suffer cancer disease signifies adding substantial value to the product. That fact should be also considered by stakeholders while setting prices, meaning that innovation should be awarded too, apart from all operational costs. Unfortunately, added value is not always supported by objective because of the difficulties to present consistent evidence on clinical trials. On top of that, it must be taken into account that apart from the active agent and its doses, a drug would affect different therapeutically and regarding adverse-effects to each patient; depending on their race, weight, age, gender, previous diseases, etc. (44). If improvements on survival rate cannot be proven, other relevant aspects from the treatments must be presented to stakeholders at least. Oncological researchers are mainly focused on the late phase of the disease (45), when cancerous cells have spread along many organs.

At this stage, risk of non-survival becomes greater and it is hard to measure results at an endpoint. But some objective data can be shown such as reduction of tumor's size or better quality of life, estimable through decreasing side-effects.

In despite of numbers, the "*Reference pricing Method*" does not guarantee a reasonable proportion between price and patient's outcomes. Many studies have demonstrated number of added-months a person under these new anticancer treatments can life is around 3 months (30), very far from the increasing profit of the companies which commercialize them. In conclusion, prices grow faster than health improvements, so new drugs' cost per unit of benefit is every year even higher[4]. (34)

3.2. Health authorities setting prices

The government has the obligation of ensuring health and health equity for all citizens. This long-term purpose is managed by the Public Health Sector. – Constitution WHO (46)

Ensuring health is not only about ethics, it is also about the duty Governments have with patients. They should guarantee solutions (medicines and treatments) to minimize diseases and maximize quality of life of their citizens.

Bringing a drug into the Spanish market is a long process which needs the cooperation of a wide net of agents from different fields and geographic levels. Technology/drug needs to be tested empirically and theoretically, considering its health benefits and social and economic impact.

In brief, before setting a price for initiating sales, the medicine should prove its benefits on clinical trials. Then, a specialized commission evaluates those results, preparing a report that will base the decision-making process about price. (Figure 3)

Before setting a price for a medication

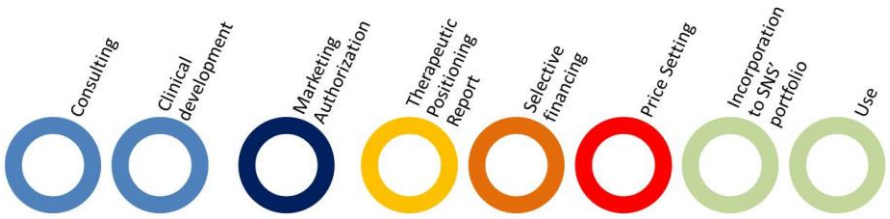
Clinical study

First and foremost, a new molecule able to fight against cancer must be discovered -is hard to make this event happen- and develop it until creating a chemical solution. The compound may be tested on animals with the aim of being accurately improved. The mean time of this process goes from 8 to 10 years and it is named *preclinical phase* (42). Once the drug is almost developed, the laboratory as the obligation to accomplish a clinical study to prove the quality, safety and efficiency

[4] Prices have been inflation-adjusted.

of the new drug on human beings (Appendix 1). This study consists of three mandatory investigation phases, which, in the case of oncologic drugs, usually take more time than the majority of drugs (47, 48).

Figure 3- Drug development and sales' overview.



a) Phase I. The main objective is to determine which are the minimum and maximum[5] doses of such drug in the human body can tolerate and how the organism reacts to it. Hence, the test shows if the drug is effective and if it is, in which measure. This first trial works with a little group of healthy volunteers (between 20 and 50 people) and lasts between 1 and 2 years.

b) Phase II. This phase is carried out on hundreds of patients, in order to measure the effectiveness. With "efficacy" we refer to physical benefits, dose and duration of treatment needed to obtain results and observation of possible side effects. For this reason, security and toxicity levels can be inspected too. Just as the phase I, this stage takes from 1 to 2 years.

c) Phase III. The study is applied to thousands of users, who are divided into two main groups. On the one hand, the new drug is administered; while the other half is offered a placebo (although users do not know it). Within these groups, subgroups of patients with similar characteristics are usually established. The objective of this third and final clinical phase is to have definitive evidence about the efficacy and safety of the new treatment. Due to its complexity, phase III lasts around 4 years and has a very high cost in comparison to the previous phases.

However, the AEMPS should approve all clinical studies before its realization.

[5] Minimum dose makes reference to the minimum quantity of drug needed to work on illness people. Maximum means the maximum quantity of such drug the body can absorb without being damaged.

Evaluation

Once the preclinical and investigation phases have been finished with positive results, the pharmaceutical company should apply for an authorization in order to place the product on market. Selling or distributing without the permission and setting of official public price is forbidden. The enterprise and/or the responsible laboratory have to send to the evaluating agency the new drug's expedient. This document might reflect (a) all results obtained along all the study phases, (b) manufacturing data, (c) a risk-management plan, (d) economical information about the cost of the drug. Economic data provided to health governmental institutions is confidential.

All in all, the evaluating agency must receive unequivocal and convincing evidence for giving to the pharmaceutical company the go-ahead for accessing to market. This authorization is called Marketing Authorization (MA). The product is suitable to obtain MA only if shows more benefits than risks (47, 49).

The evaluating agency is different depending on the authorization procure selected by the business, according to the location limits of its sales plan.

a) National procedure: the applicant business sends all documentation to the AEMPS (*Agencia Española de Medicamentos y Productos Sanitarios*), with the purpose of obtaining the permission for selling the drug in the Spanish territory.
b) Decentralised procedure. the applicant asks for authorization to many EU countries at the same time. All the national agencies work in cooperation, so one of them takes the manager role. The final decision report is identical for all the requested countries.
c) Mutual recognition procedure. This process takes place when the drug its authorization is applied for, has been given by another EU country in the past. Both EMA (*European Medicines Agency*) and the country which accepted the drug commercialization and should be notified. The last, must submit the report to the new country involved. Then, the approving decision devolves to the new country evaluating agency.
d) Centralised procedure. The applicant aims for all the EU States' authorization simultaneously. Owing to that, the examination and following decision are EMA's responsibility. It is compulsory for some medical products, such as anticancer products. For this reason both European and Spanish medical evaluating agencies are involved on the supervision of new oncologic treatments' access into the market.

EMA authorization

Within the EMA, economical and scientific experts made up the Committee Human Capital (CHC) in order to evaluate (a) the drug marketing, commercialization and its future application to the European target population; (b) managing the adverse effects' risk for its real application on population (phase IV); (c) provide scientific advice to the developer laboratories (d) arbitration processes (50).

As previously commented, anticancer treatments are a mandatory kind of drug that must be approved by the EMA before reach an agreement on price with the host-country. However, it is important to distinguish the EMA main duty: evaluate and approve drugs. The institution does not price treatments, because it is a national competition for each EU country member.

AEMPS Authorization: process for setting a price for a medication

After the EMA decision, the European final report and all the documentation available would be sent to the AEMPS. Both entities use the same evaluation criteria and framework. This cooperation stimulates the efficiency of procedures, owing to that; they meet once a month using teleconference.

The AEMPS works on behalf of the MSCBS, in conjunction with the *Dirección General de Cartera Básica del Servicio Nacional de Salud y Farmacia* (DGCBSF) and the Autonomous Communities (CC.AA.). They work together as *Grupo de Coordinación del Posicionamiento Terapéutico* (GCPT) of medicinal products for human use, since 2013, because in the past three different evaluations were made for the same drug, providing redundant and similar conclusions, so they were missing resources. However, each entity is independent and has its own competences on health's administration. Thus, all points of view collaborating loyally are required to make an efficient single evaluation (51).

As previously said, the MA takes only in consideration the cost-benefit analysis. Benefit is defined as "*quality, safety and efficacy of the drug for patient's health or public health, understood as risk-benefit*" (52). In contrast, other criteria are applied for going through the next stage, which is the writing of the *Informe de Posicionamiento Terapéutico* (IPT) (Appendix 2). The IPT evaluation sets up the basis for the selective financing decision and the subsequent official public price determination. Producer and financing parties would come up to a number using judgement criteria over the IPT provided by the AEMPS. Moreover, IPT, apart from being an authorisation (or not) for

commercialization, must include additional information based on the empirical supplied[6], for positioning the drug on the market, in comparison to other drugs which are already available in the market.

As the MSCBS declares; "*The IPT reports will contain, in a first phase, the evaluation of the effectiveness and comparative safety, as well as the criteria of use and follow-up. Optionally, it may include an economic evaluation at the discretion of the GCPT. In a second phase, after the pricing and financing procedure, it will always incorporate the economic and budgetary impact assessment*"[7]. It is important to bear in mind that economic criteria are not mandatory.

All in all, IPT shows an exhaustive analysis of drug's benefits, consumption guides - to which target and how should be applied, information about doses, duration and so forth technical aspects. At the end, the report has the conclusion about if adding the treatment in the *Sistema Nacional de Salud* (SNS) portfolio. In other words, the GCPT decides if financing the product or not. Note the final resolution applies binary logic (financing/not financing) (53).

Furthermore, the evaluation procedure renewal report in 2013, the MSCBS informs that the GCPT *will establish a new methodology* for evaluating and confectioning IPT.

The selective financing decision must be indiscriminate and objective. Some "general[8]" criteria is considered: (a) Gravity, duration and physical damages of the different pathologies for which they are indicated, (b) Specific needs of certain groups, (c) Therapeutic and social value of the drug and its incremental clinical benefit, taking into account its cost-effectiveness ratio, (d) Rationalization of public spending for pharmaceutical benefit and budgetary impact in the National Health System, (e) Existence of medications or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost, (f) Degree of innovation of the medicine.

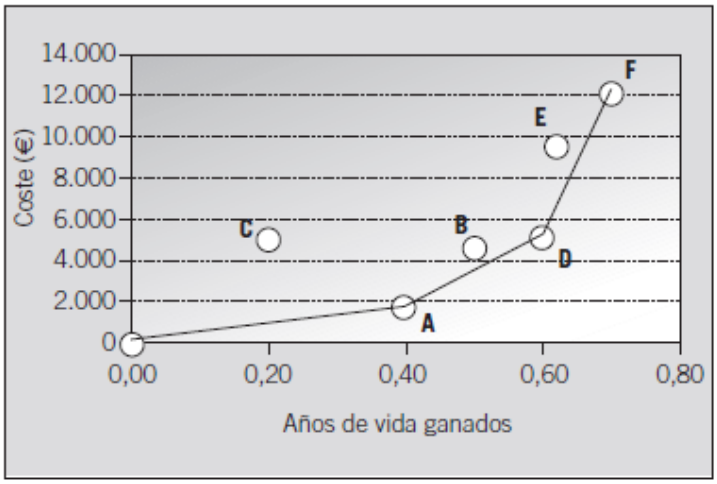
It is desirable to further clarify that cost-effectiveness analysis *estimates the cost and health gains of alternative* treatments. The assessment seeks to ensure the most effective and least costly alternative supplying health (54, 55). CEA ratio expresses the unitary cost per unit of health gained using the analysed treatment. QALY are commonly used as the health benefit measure. Hence, a cost-effective ratio in the SNS would be euros per quality-life[9] year gained with the new drug. By

[6] Clinical and economic data provided by the applicant.
[7] Translation from the *Propuesta de colaboración para la elaboración de los informes de posicionamiento terapéutico de los medicamentos* report
[8] The law RD1/2015 uses this word.
[9] Quality-life makes reference to a year within good health for the patient.

comparing two alternatives calculating the difference between the QALY they provide, you can obtain the ICER. It signifies how much costs an additional unit of benefit vs. a more expensive alternative. To conclude, it may result helpful to construct the Markowitz's efficient frontier graph to get a clearer idea about which option is the most cost-effective (Figure 4). Another useful tool for comparing the cost of added-value between different technologies is the so-called *League Table*. It consists in writing in descending order all alternatives according to their CEA ratio, positioning the lowest value at the top and the alternative with the higher CEA ratio at the bottom. (56, 57).

There is absence of official publications clarifying how much weight each criteria have and how it is measured. The only exception is a the law published before, in 2006 and later modification in 2012, says: "*For the decision to finance new medicines, in addition to the corresponding cost-effectiveness analysis and budgetary impact, the innovation component will be taken into account, for undisputed therapeutic advances by modifying the course of the disease or improving the course of the disease; prognosis and the therapeutic result of the intervention and its contribution to the sustainability of the National Health System if, for the same result in health, it contributes positively to the Gross Domestic Product"(RD 16/2012, bis 89,2)*. In conclusion, we just know that the budgetary impact is measured by means of GDP.

Figure 4 - Example of the Markowitz's efficient frontier (57)



Merits special attention that later on the same article, is written that the CIMP "*will consider the cost-effectiveness analysis and budget impact (RD 16/2012 bis 89, 4)*". First of all, omitting the innovation fact creates confusion. On second place, vocabulary on laws is important. "Considering" cost-effectiveness doesn't warrant the use as the CEA analysis as a criterion for decision-making and nowadays it has not been yet applied in practice.

The CIMP (*Comisión Interministerial de precios de los medicamentos)* is the national institution in charge of fixing a price and setting the maximum wholesale price (PVL) the government would pay for supplying the new treatment along the SNS (58). Prices tend being inflexible along time. However, they can be modified once two years have passed. In case of having similar drugs on the market, the CIMP uses the Reference Pricing model. This consists of selecting a price based on drugs with the same active agent. However, there is a current medicine shortage in Europe that leads to a speculative market because of the lack of some kind of medicines and/or alternative solutions (59-61). The problem of scarcity in some type of oncological medicine implies a high price for two reasons: (a) with few references you cannot analyse the value added vs. other treatments (b) the lack of supply in the face of a growing and urgent demand leads prices upward (62). For these reasons we say that the shortage of certain anticancer drugs is an incentive to increase the price using human-based criteria, or speculation. Moreover, it is not only about drugs, but also other factors necessary to treat the disease. For example, nowadays in Spain the lack of radiologists dedicated to oncology prevents certain treatments from being carried out (63).

Spain has a decentralized system, so once the CIMP has set the PVL, each CC.AA, will negotiate individually the final reimbursement price with the pharmaceutical. Besides that, each CC.AA. can decide if establishing the same price for the oncologic drug in all the hospitals of the region; or allowing each hospital to negotiate with pharmaceutical companies individually. This is the case of Catalunya, for example. CatSalut[10] designed a new entity, the XHUP[11], a net of hospitals that enables relations with the medical industry and all the public Catalan sanitary centres. Another entity was added recently, the ICS[12], which works concurrently in the same way (64). This means, all this public centres get different deals with providers.

As a general rule, prices proposed by the enterprise might be a 10% lower than the PVL to be taken into consideration in the SNS' regional portfolio.

Even if the dealers have become more cost-conscious in the last years, there is a lack of concrete official guidelines for economical evaluations or CEA requirements coming from the national government since each CC.AA. present coverage restrictions (65). The CC.AA. regulators neither received an explicit threshold of efficiency, measured in ranges of ICER (Cost-effective ratio) (66). Some studies affirm that leaders should be both "bench scientists" and "business scientist" to reach

[10] CatSalut: Catalan Health competence
[11] XHUP: Xarxa hospitalària d'utilització pública
[12] ICS: Insitut Català de Salut

a good deal. Moreover, this type of deals is strictly confidential, so it's no worth considering knowing how much is paid for a medical product (67, 68).

In contrast, some news have been published during the last years, affirming that drug prices have been increased after the crisis in 2008. It is not true at all, since the prices are similarly but the financial system is weaker than fifteen years ago. That's why the high cost of drugs aggravated the financial inconvenient on the issue. In fact, the hospital expense (which includes anticancer treatments) has been increased by an 84% from 2006 to 2017. In particular, the anticancer treatments represented the 11, 6% of the whole hospital expense in 2016 (69). The changing budget has to do also with the political party leading the CC.AA. government the unstable political situation in Spain. Due to the different ideologies about health topics between parties make unable to write strong health politics since counsellors do not reach an agreement during the time they compound the government. Even tough, CC.AA. with progressive governments use to assume a high health cost per inhabitant (70, 71) (Appendix 3).

3.3. Meeting interests between Health authorities and pharmaceutical companies

Both pharmaceutical companies and health authorities try to meet a win-win scenario when setting up prices. However, they share the challenge of providing efficient benefits for citizens as well as leading to a sustainable path for medical innovation. This purpose becomes difficult since oncological treatments notably costly and their effectiveness is, in most of the cases, uncertain at the purchase time. For that reason, innovation might not come only from the industry side. It must be sought and offered by the pharmaceutical companies, but also by the buyer, this means the Spanish Public Health Authorities. While the industry searches innovative processes on laboratories, Public health entities can look for innovation by staring smart purchase schemes and maintaining an active listening to the pharmaceutical proposals and patients' real necessities (72).

Commercial nature agreements between pharmaceutical companies and a third party (in this case, Spanish Public Hospitals) have been used so far. These were commonly applied as discounts or reimbursements when a determinate volume or budget is purchased and had a wider use due to its simplicity in comparison to other types of contracts (73).

This objective led to Risk Sharing Schemes (RSS), which can be defined as "*the agreement between third party payer and manufacturers which links the final remuneration or reimbursement of a pharmaceutical to a previously agreed objective, mainly focusing on effectiveness or budget*

impact" (74). By means of RSS, payers set limits to pharmaceutical expenditure's growth. In other words, with RSS payers set a health results on patients as collateral for high prices on treatments (75).

RSS present many advantages.

- Maximize results in real situations, since the gap between a study design and real practice is suppressed. Like this, strong data and conclusions are provided, reducing uncertainty regarding effectiveness.
- Accelerate the access to innovative drugs and get shorter waiting times. Since target patients with urgent necessities are able to test drugs on medical trials, they do not have to wait for the medicine to be approved by the different institutions, since it is a process that, in general, tends to be prolonged.

In fact, a study about this situation in Italy has shown surprising results." *Oncology product authorized under a risk-sharing agreement benefits from earlier patient access by a mean shortening of 256 days in Italy in comparison to products with no agreement (83.7 days v. 342.7 days)(76)".* (Figure 5)

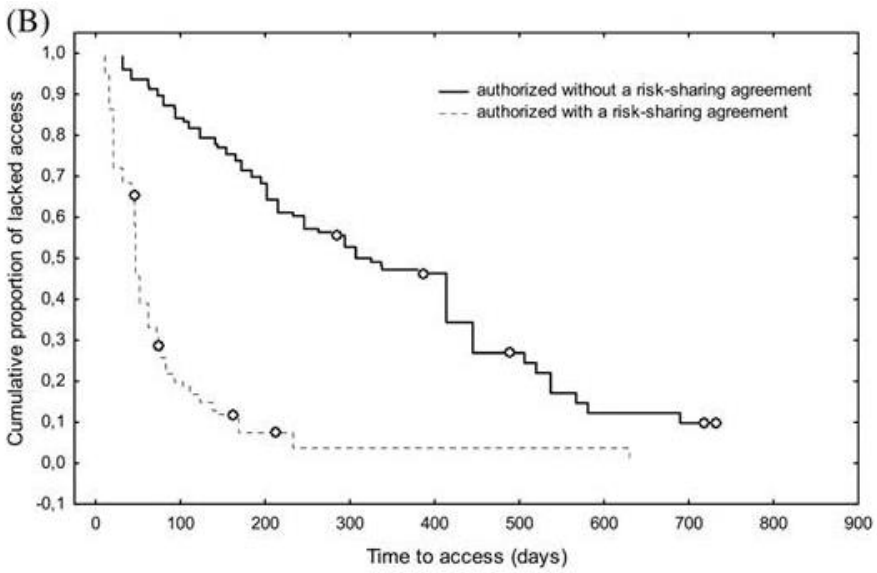


Figure 5 Kaplan–Meier analyses of time to regional patient access according to the authorization with or without a risk-sharing agreement (B).(76)

- Dispense with unnecessary expenses for both authorities and patients. Thus, it is easier to keep budget controlled and ensure a more sustainable system. Moreover, incentive to detect ineffective drugs (77) applied in the first stages or contact with users. Because they would not be paid or not in their totality, saving money to buyers and encouraging sellers to present meaningful results.
- Improve the health system's sustainability without denying access to medicines for needed treatment. Pharmaceutical companies take this opportunity to present new and challenging treatments to future buyers, faster than competitors and promising successful results. Therefore, RSS are a platform for promoting innovation.
- Contribute to improve efficiency both innovation technologies/drugs and decision-making processes.

These kind of agreements might present either financial or outcome basis (Figure 6).

There are many ways to practise innovative purchase systems but I will go deeper on those which can be better applied on oncological treatments and drugs.

Financial Basis

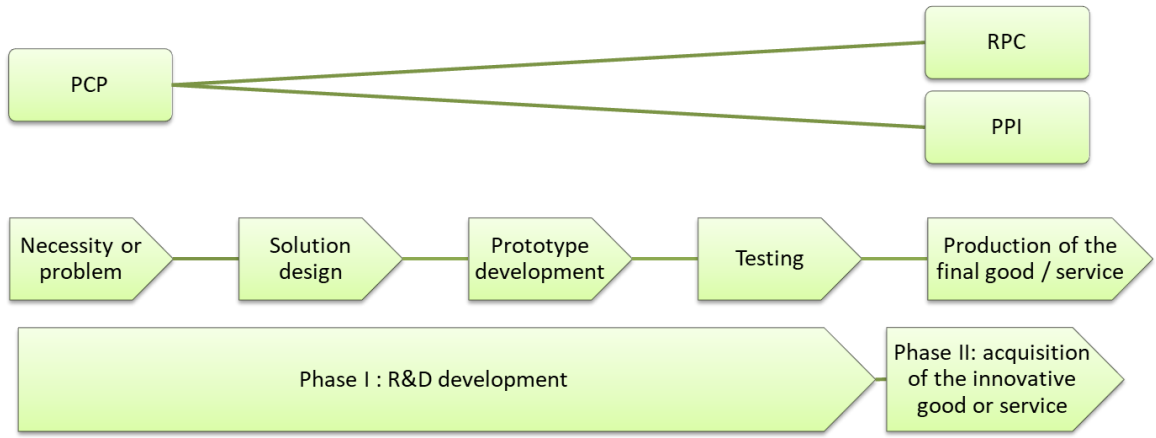
Financial basis deals take only on board financial aspects. The pharmaceutical company applies discounts or reimbursements (money or free-or-change technology/drugs) avoiding disruptions in the official price. So, they reduce uncertainty about the budgetary impact of introducing innovative treatments in health public services (78). They can be applied on population level (total cost) or patient level (cost per patient).

- Price-volume agreements. Price is set based on the number of prescriptions purchased by the payer. In other cases the price is settled before and an ex-post discount is applied or, the pharmaceutical pays the difference (conditioned refund).
- Cross-selling. The pharmaceutical brings the single-product sell to a multi-product to enhance the portfolio's customer (79) (in this context, the payer). The company offers the main treatment and some complements for it, free of charge or within a discount. Those complements should add value to the principal.
- Price ceiling. Price is fixed between parties' ex-ante for a determined quantity of a medicine for a therapeutic target during a specific period of time. If said figure is exceeding, the laboratory might afford the difference and the public entity can prescript the treatment for free – always in the determined target of patients. This particular financial option

encourages public authorities to give a chance to novel drugs, which means, innovation too (80).

- Public procurement. Firstly, the public authorities and one or more companies seal a Pre-commercial Public Procurement (PCP) agreement. As a result, the government contracts R+D services of a non-existent drug in the market yet. From that point, *pilot-projects* can be born (81), after that a Public Procurement for Innovative Solutions (PPI) may be considered. In the PPI the authorities, after detecting a public demand or necessity. The product is not still in the market, nevertheless is possible to develop it in a reasonable period of time. The European Commission has created *Horizon 2020*, a set of measures that stimulates innovation drivers from the demand side (82). (Figure 7)

Figure 7- Phases of innovative public procurement through the PCP. (81)



- Cost-capping/Dose-capping. The company gives free-of-charge drugs (83) to those patients who are in need of more than X-amount of cycles or doses of that treatment. This method can be used as a cost-effectiveness driver, related with how much consumption the patient need to undergo meaningful benefits.

Financial-based agreements can come out useful in treatments which have been used in the past or effectiveness has been already proven and no further research is needed.

Outcome Basis

In contrast, contracts based on outcome or health results set the price/total cost based on empirical evidences from clinical trials or real-data, in which patients subject themselves to trials to prove the expected effectiveness' degree to a certain extent. That turning point must be determined at the beginning, by means of a CEA measure or a biomarker and eventually the review period. Cost per

QALY is generally used. The effectiveness may be tested at the end of the treatment or in a middle-period point.

That's why outcome basis RSS limits the risk sanitary decision-makers assume. Health authorities receive a guarantee of results for a novel treatment (84, 85).

From a financial perspective, agreements based on results can be driven in two ways.

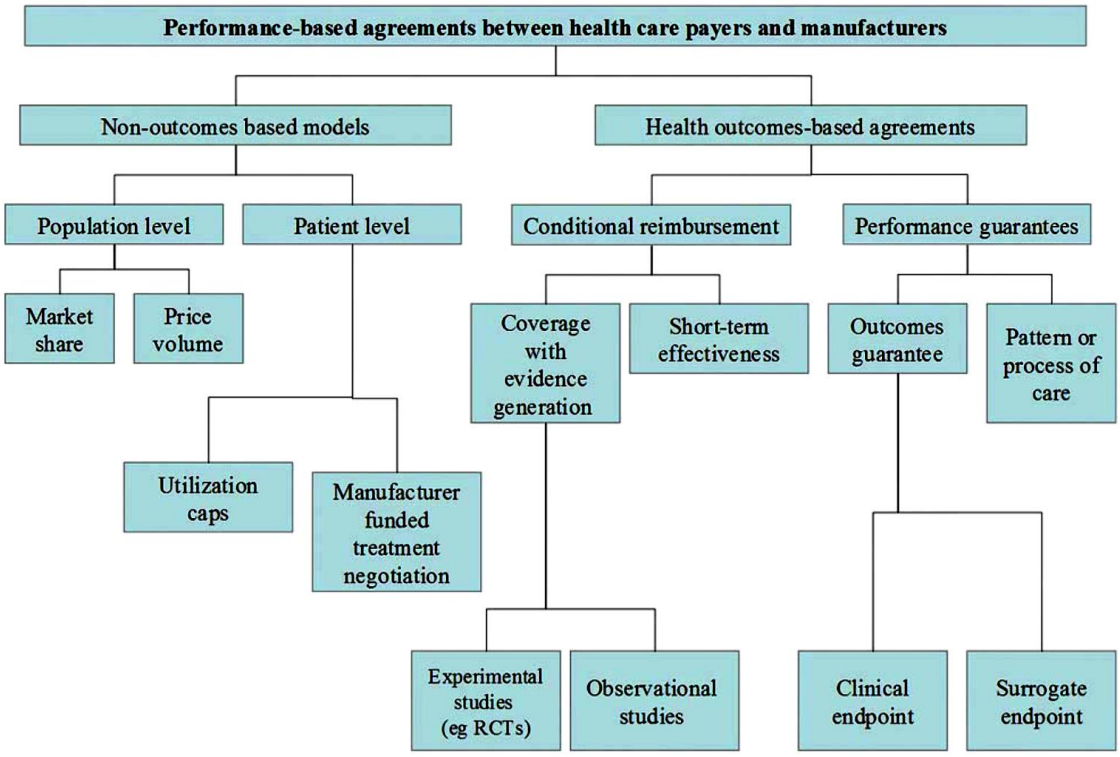
- Conditional reimbursement. Financing is conditioned by a study or clinical trial of a target population for data gathering. This modality leads to purchase systems:
    - Coverage with evidence generation. The financier commits itself to pay the medicine if the producer accomplishes a clinical study showing the expected results at least. If there is a success, the laboratory only pays the treatment those participating in the trial. For that reason, some laboratories include results and pharmaeconomic research in the last phases of treatment's development (III & IV) (84).
    - Short-term effectiveness. The payer covers the medicine for a determined group of patients during a short-term lapse of time, such a clinical study. After that, the reimbursement for the rest of the treatment is continued only for those patients who present reliable results in the short term. This purchase method avoids financing drugs which do not benefit sufficiently the living expectancy or quality of life of the patient.
- Performance guarantee. The unit price paid for an innovative technology/drug is linked to real data results in health terms – applied in real situations, instead of a clinical trial. That means, the pharmaceutical company takes the risk of assuming a lower reimbursement if real use of its product do not reach the expected objectives (78), since the financing is conditioned by the medical effectiveness shown. It is useful when multiple treatments compete offering the same solution level.
    - Outcomes guarantee. The seller will discount or reimburse x-amount if the product does not achieve the results mentioned in the initial agreement. The turning point of results must be determined at the beginning, by means of a CEA or a biomarker and eventually the review period. Cost per QALY[13] is generally used as measure, as well as percentage of reduction of the tumour size or patient behaviour. Experts recommend using the most accurate measuring method as possible in real situations

[13] *quality-adjusted life year* or *quality-adjusted life-year* (*QALY*)

and not only for a selected sample. The effectiveness may be tested at the end of the treatment (long-term) or in a middle-period point (short-term).

- Pattern or process of care. The financing part would set the price according to the medical impact of the innovative treatment in real circumstances in a finite time frame.

Figure 6- Taxonomy of risk sharing agreements (75)



As a consequence of implementing RSS schemes, some unusual infrastructures, financial and information flows are required to keep tracking all information, measuring and monitorization about patient's evolution. Therefore, the provision of these resources creates some controversy, essentially because RSS supposes sharing patient's data, threating confidentiality (85).

Owing to the novelty and little experience holding RSS, an additional evaluation (74) is needed to avoid hindering the effectiveness of these new purchase methods. The utility of the measures used, as well as times, patients involved and the conclusion of results should be reviewed in order to prove the price-setting process' upgrade .

RSS are not suitable for all kind of medicines. Drugs which normalized consumption by a large part of the population and with already standardized costs, for example. Using RSS to launch an

improved version would imply bureaucratic, training and operational costs that overtake the cost of the treatment itself, misusing the RSS processes. However, cancer disease presents an increasingly urgent and costly treatments and demands evidences for proper functioning of medicines in a finite time frame so RSS schemes are highly recommended being implemented. The opportunity cost is worthwhile because drug price is higher than the RSS execution.

Nevertheless, Risk Sharing Schemes are rarely used in Spain.

3.4. Alternative methods for establishing more efficient prices on oncological drugs

Economical evaluation of drugs was born as a tool for ensuring rational use of medicines and getting the SNS closer to an equitable health system. Providing this equality and access to medical solutions has been always fundamental, and nowadays in Spain it is even more. This is because there is an increasing demand for sanitary resources, especially the incidence of cancer (5). This event occurs at the same time as budgetary limits come very marked by austerity.

The system for finding the financially optimal medicine currently used in Spain does not demand anything beyond the budgetary impact as mandatory criteria to be considered (86). Whereas this method can add some value to decisions, this modus operandi does not supply the expected effectiveness reflected on results. In fact, a review made in Spain of 40 oncological therapies resulted that the increase in overall survival compared to the alternative with which it was compared was less than three months between 65% - 76.5% . However, in 22 of the 40 therapies studied there was an added cost of more than 15.000€. What is more, six of them increased their cost between 30.000€ and 60.000€, with an overall survival increased between 2 and 3,7 months.

For this reason, multitude researchers suggest including the CEA as an indispensable criterion for fixing prices. Assessing cost-effectiveness against more alternatives (similar treatments already on the market or different but providing the same results) is a measure to boost the efficiency of the SNS. Once the cost-effectiveness analysis is used in a standardized manner and as an universal criterion for all final decision makers, it could be complemented by other criteria. Multi-criteria analysis will be commented later on this paper.

In addition, CEA has become an innovation driver for the pharmaceutical industry. Once developers notice which aspects are considered as providing more therapeutic value on new technologies, it becomes an incentive to refocus further investigations Cost-effectiveness encourages not only the industry, but the direction of government activities. CEA is a tool that helps to be aware about the

socially interesting innovation, and which health policies might be priced in the first place(87).. In conclusion, CEA is a channel able to prioritize which aspects have a higher impact on population and must be improved as soon as possible. Finding out a cure with such high impact would mean disruptive innovation.

For this reason, some modifications and alternative methodologies have been proposed during the last years by researchers worldwide.

Cost-effective valuation and value based pricing

Within the cost-effective valuation method, there is not a pre-defined optimal range of reference. This means there is no measure about how cost-effective the medicine should be for considering it a worth investment for the SNS. In contrast, the WHO has suggested a measure that helps to clarify this issue. It consists on determining three categories, according to each country economic circumstances: (a) high-effective strategies those with ICER lower PCI; (b) cost-effective strategies those with ICER value higher than PCI but three time lower than PCI; (c) non-cost-effective strategies those with ICER over three times the per capita income (66). Moreover, having an objective measure for classifying results prevents decision-making from being distorted by human judgement.

Some other specialists suggest using the value based pricing method, basing its criterion on previous economic data analysis such as cost-benefit or cost-effectiveness. This pretends changing the paying per cost tendency for paying based on its real impact, settled as its value. In other terms, questioning if the new drug's worth what it costs. Economical evaluation might include the adequate budgetary impact, the opportunity cost of buying this drug instead of another in monetary and well-being and health terms for the SNS and all individuals. Or rather, "*How many QALY have we stopped winning in some people at spend X-amount to earn 1 QALY in others*"(88).

For instance, when comparing two drugs with similar therapeutic value indirect costs may be added to the total ones. Indirect costs are those not included in the treatment itself. If cancer patients are in working age, they should ask for a medical leave. People who suffer cancer represent a decrease in Spanish labour, directly affecting to the national GDP and the overall productivity too. They cannot work while being treated, or if –unfortunately- die (mortality) or endure some illness' consequences making them unable to work anymore after the cancer (morbidity)(9). Another indirect cost is the post-treatment cost: if the patient survives, which cost would represent to the SNS? How much cost

treatment for risk-adverse effects and future check-ups? More hospitalization would be needed? It is an oncologic treatment for those kinds of cancer are considered as chronic diseases? Marginal costs or savings are often ignored by evaluators (32).

Moreover, the therapeutic value has to be defined together with some measurement requirements to make data objective and subject to evaluation. Measures could be endpoints like the overall survival rate; but also some middle points such as the improved quality of life, degree of tumour shrinkage or hair loss degree (36).

Finally, decision-makers may judge correctly of alternatives. The presence of similar oncologic drugs has become almost more important than the manufacturing cost of them, as we previously discussed. But what would happen if substitutes become complements? Considering creating a combination of similar drugs or using one of them as an adjuvant, ("*multidrug*") able to provide significant improvements respect their individual benefits can impact positively on prices, and thus, increase the cost-efficiency of the treatment (34, 89).

Bearing in mind these criteria helps to positioning therapies and asses better their value. In conclusion, paying for value, since it represents a social and economic contribution, instead of costs brings the chance of capturing more benefits per QALY for oncology drugs and incentives the industry to align social necessities with their R&D portfolios (41).

Multi-criteria decisions method

We already know that price per unit of benefit on innovative oncologic drugs has been raised during last years. Hence, we are unable to compare them to solutions which were already in the market in terms of cost-effectiveness. Therefore, CEA may be complemented by other approaches to increase the efficiency of the health technology assessments (HTA) and add more value to the final decision (34).

Because of that, a new method for decision-making has been proposed, aiming to improving resource allocation. Multiple challenges and agents involved in SNS decisions can provoke some struggle when allocating resources. Multi-criteria decision analysis *values the consequences of the option even to the extent of treating risks as criteria rather than as probabilities (90).* This is possible since the three different perspectives are handled (financial, operational and decision analysis), and from each of them we calculate costs and risks. Trade-off judgements are essential in cost-effective investments. Further than setting lots of criteria to deal with until reaching a proper

decision, multi-criteria analysis suggests an agreement about some criteria which is important for different key agents. Once different priorities are shared, each criterion should be weighted jointly enabling the risk-adjusted value-for-money calculation. For example, the common practice is using QALY as unit of benefit. In contrast, society values more the fair access to health and the urgency for treating severe illnesses (91). This is called prioritization, the key point in multi-criteria analysis. Another example could be weighting higher the support to long-term strategy than QALY or cost-per-QALY. Decision-makers must prioritize on best value obtained for the available resource, is risk-adjusted benefit divided by cost. This methodology has already been used for deciding oncologic treatments in Portugal (92).

Moreover, this breakthrough way of deciding fruit of sharing perspectives, has translated the holistic vision to the product which is subject to evaluation. Discrete but sustained growth of RSS deals have shift from a single product to a portfolio of products offered by pharmaceutical companies to payers (68). The objective is to present more reimbursement options and thus, ensure consistent contracts. Decision makers (in CCAA or hospitals) can weigh the intrinsic values of the public health authority according to the predominant local needs. Then, calculate the different future options presented in terms of value-for-money. The overall projects should be projected through the efficient-frontier. That way, eases the valuation of future events as parts of the same investment, taking the portfolio as a whole; rather than evaluating the impact of medicines individually.

An interesting example is the Allergan's case, a pharmaceutical company which used multi-criteria analysis for planning its R&D projects. The company introduced the Future Value criteria in order to add-value to its long-term vision and making better decisions for the business' strategic plan. If decision-makers attach future value criteria when setting prices, some important issues would be considered too, apart from the drug development's cost. For instance, analysing the drug innovation value along time and the chance of converging different types of oncologic treatment on future healthcare. Furthermore, considering future criteria can turn into an advantage for the health Spanish authorities by means of establishing long term policies, which macroeconomics understand as more effective than the short term ones. The future vision can include, for example: (a) the analysis of the Spanish population pyramid; (b) aging of the population; (c) the impact of the introduction of new technologies in the medical field; and (d) future rationing the resources allocated to health (29). Taking in account the future target population for an oncology drug could be useful for multiplying the unitary price per the number of prescriptions forecasted and number of

doses needed to complete a treatment. Bear in mind there is a meaningful difference between buying a 100€ hypothetical drug for a thousand people target than for a one hundred people target (93).

Standardization

Nowadays, the drugs' final price decisions just involve the offer and demand (the pharmaceutical company and the health public institution) that negotiate based in their own interests and criteria in closed-door meetings. This "secret flow of information" and exclusive responsibility does not benefit the transparency and fairness that oncologic drugs' prices both parties affirm that are meant to be.

Standardizing evaluation method and price-setting convert them into a competitive advantage. Firstly, because it can fix the challenging differences between regional decisions taken in Spanish CCAA, as a result of a decentralised system. Designing a common procedure would support equality in access to health, engage just key players in the decision-making process and prevent for overspending resources and involving more people than necessary.

Another benefit from setting standard procedures would be guarantee transparency, one of the most controversial issues on the field. Ensuring transparent flows of information, apart from respecting ethics, help to take smarter decisions. The lack of transparency can mask conflict of interests and bad practices. But it also makes the evaluation task harder: when companies present the clinical studies reports, tend to use ambiguous language and general words as "all" and contradictions. For this reason, the validity of results might be questionable.

As a consequence, the person who would judge the new drug's benefits has not clear, objective and complete information, and asymmetric information happens. In fact, the 43% of the studies make arbitrary decision about what studies to use to inform effectiveness data (65). On the other hand, it should be pointed out that regulations and guidelines asking for results to the pharmaceutical industry are often poorly specified (43). Finally, providing guidelines for maximizing results and transparency would help to draw together other stakeholder's vision. Research centres and cancer institutions can contribute to research providing regional and local data. Moreover, the patient's role is emerging and experts say it should be considered when evaluating treatment benefits and setting prices. Their principal variables often are not the same as the ones clinical studies look for, even if theoretically laboratories want to maximise patient's well-being (53, 94).

In a certain way, some progresses have been done in the standardization challenge. The EMA designed in 2016 some guidelines, called *Adaptive Pathways*, for easing countries to authorize MA some kind of diseases.(32)

Innovation's drivers and incentives

Apart from establishing proper measures to include this criterion while setting prices, like CEA, governments might provide some policies to encourage innovation. Increasing the innovation degree will be a competitive advantage at national and global level. A new entity can be composed in charge of coordinating the presence of innovation in Spain (29).

First of all, forming a stable economic environment at macroeconomic level is a basic solution for reducing projects' uncertainty and impulse further research and innovation. Tax policies supporting R&D projects, low interests rates and low inflation expectations would encourage private investors and develop new technologies in Spanish territory, contributing to the national GDP's growth (39).

Another policy could be offering some complementary assets needed by laboratories to find out solutions. For example, provisioning them electricity and water or cession of industrial territories through items of the Ministry of Industry.

Furthermore, if governments want to attract innovative technologies, they should reward them. The current system recognizes medical innovation by patenting new drugs and treatments. In fact, the pharmaceutical companies where the ones with a higher number of new patents, a 42% more than the previous year (95). However, we have seen this method blocks price elasticity in the meantime one company has the monopoly of a treatment and limits the government bargain power with suppliers. Moreover, the patent system limits competition, because other companies are usually not interested on investing for a medicine that has exclusive rights owned by another company. Experts refuse patents even more, but companies which produce innovation and discoveries must benefit from health revenues to continuing with their business purpose (36). Joseph E. Stiglitz, the economic Nobel Prize Winner in 2001, suggested to governments giving prizes instead of patents to innovative companies. He said that patents restrict the use of knowledge, and that is totally inefficient. Applying this system means the presence of free market on drugs. As a consequence, free competition would stimulate the drug price reduction; as the same time as companies would receive monetary benefits or licenses, because we cannot expect innovation without paying for it. Then, incentive patterns can be a feasible way to promote innovation (96, 97).

Finally, another solution could be establishing collaborative models of research between private pharmaceutical companies and public agents coming from the health and education fields. The government can create policies which develop knowledge networks and promote new technology diffusion, for example, between public universities and pharmaceutical companies. Since students can participate in pharmaceutical's research projects as a way of learning, the high –qualified workforce in Spain will increase. What is more, the presence of innovative projects in Spain it one of the largest employment generators in the country and could help mitigate the present "*Brain Drain*" (98, 99).

Promoting collaborative research projects can help the pharmaceutical industry to clarify R&D priorities, focusing innovation on the present and future health demand in the country. Setting together the expected goals at the very beginning can be useful to reverse the declining tendency of return-on-investment in R&D the pharmaceutical industry is suffering nowadays. (68, 100) Actions such modifying the design of trials can be taken, which can provide accuracy to results and mitigate uncertainty risks for public investors. These could improve meeting the Spanish health necessities as well as increasing the willingness-to-pay of the government if a greater efficiency and long term meaningful benefits are demonstrated. On top of that, research may be boosted also in science parks, encouraging public research originating from public universities, cancer public organisations, cancer patients societies and so on. Joining forces encourages speed dating between pharmaceutical companies, academic institutions and public agents would create a "*precompetition*" situation. This framework of knowledge sharing allows better resource allocations for all parties and ensures a consistent growth of economic, technologic and social benefits (44). In the States, George Bush's government founded the Project Data Sphere, a global data pooling initiative were pharmaceuticals could base their future projects according to data from the public sector. The project was precisely created for companies which investigated solutions for treating cancer (101).

3.5. The Spanish National Health System's actions: public health policies

According to the basic principles of the Spanish General Health Law (1986)[14], health authorities' actions must be oriented to provide health and prevent illnesses. This service is described as universal for all the Spanish population.(102, 103) This means every person in the Spanish territory has the same right to receive public health assistance. In other words, Spanish people and those who have applied for the residence permit have the same access to public health as someone living undocumented, because the Government considers that health is a basic right that cannot be denied to anyone. Spaniards living in a country not belonging to the European Union and unable to get access to public health in that country, has the right to be attended by the Spanish public health authorities too; and said cost will be assumed by public funds. In addition, the service supplied has to be equally effective in every point of the Spanish territory. The "universality" and "equality" facts are controversial points. Firstly place, the condition of Spanish population should be well-defined: it is not fair to deny the right of health; as the same extent that using public resources without paying taxes is unfair too, from the community perspective. Setting some constraints can help to equilibrate the inputs and the outputs and therefore, contribute to efficiency. Secondly, the equality between individuals around the national territory is currently studied, given that some theories talk about considering people in groups which are not equal among them due to dissimilar frameworks and necessities. Grouping them might be considered as a measure for effectiveness as well (104).

The Spanish Government condition in matters of health is a decentralized system. In other words, there is division of competences between the Central Administration and the autonomous communities (CC.AA.). In brief, the National government has the duty of proposing, evaluating and setting health policies. It also must proceed to the health technology evaluation (HTS) in order to determine either a new drug or treatment against cancer is effective or not and must be included in the public health services' portfolio. However, this last activity has been proposed to be common for all the EU members. In other words, Mandatory assumption of joint evaluations of clinical evidence and technological innovation - the economic and social aspects would remain an exclusively national competence. The objective is to reach more transparency and provide the same evaluation system for pharmaceutical companies so they should not change it for each country. Hence, there would be acceleration in the patients' access to new treatments and consequently each

[14] The General Health Law was established in 1986, but the commented points, in the newest version of (30th April, 2019), remain as the original ones.

public health system would increase effectiveness some matter. The proposal's resolution will be after the European elections, the 26th May 2019 (105, 106).

On the other hand, each CA is responsible of the execution, administration and management related to health. This suggest that each autonomic health department has the obligation of setting the price of new treatments, and means each CA will judge according to different criteria or assigning them diverse weights in terms of importance. To illustrate it, the same anticancer drug is susceptible to have up to 17 different prices in Spain[15].

Fruit of the authority decisions, the patient has the right to be informed about *the health services he/she can access and about the necessary requirements for its use (107).* Conversely, if the patient wants to respond by making a proposal or getting involved in health management issues, the only way is when going on behalf of a trade union or private business (108).

3.6. Alternative methods for establishing more efficient health policies

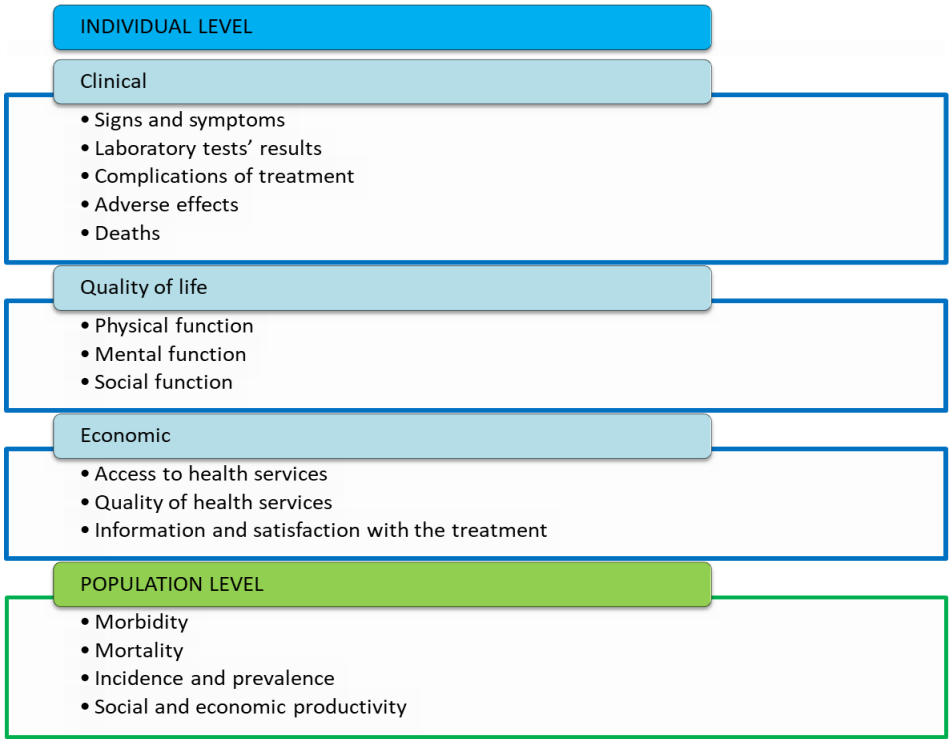
As previously commented, efficiency in the health public system means providing the maximum quality of life to citizens at the lowest cost as possible. Apart from dealing with economic aspects redirecting evaluation to cost-effectiveness analysis, other factors are equally important for sustaining the health factor on the welfare state. Quality of life can be raised by means of diminishing social costs[16] (Figure 8). An effective way to reach a higher level of welfare is editing the list of preferences the Government should focus their efforts on, in terms of time, budget and policies (87). Including citizens for laying down the social preferences for government actions is basic for raising the welfare status and redirecting innovation research. Authorities ought to bear in mind some patients would be disposed to pay for their treatments with the purpose of eliminating its cancer or at least, stop it. Even so, is unfeasible to base health policies on personal treatments. For this reason a strategic vision, focused on the long term, must be settled on in a democratic manner. One option might be that each party candidate to the presidency must publish its list of health priorities and inform properly to the Spanish community. Then, citizens, who are also patients, can support those lists by using their vote (111). The result, will be a guide for prioritize resource allocation additionally to encourage both government and pharmaceutical industry to focus

[15] Leaving aside the autonomous cities of Ceuta and Melilla

[16] Social costs are considered the total cost of something for the society. It is the sum between the private cost (monetary) and the externalities. *Externalities are a loss or gain in the welfare of one party resulting from an activity of another party, without there being any compensation for the losing party (109, 110).*

innovation on the biggest social concerns, in order to yield higher impact while supplying oncologic solutions.

Figure 8 - Example of types of results in health research. Possible factors decisions about the economic and social productivity in oncology (112, 113)



Furthermore, the fact of involving patients on policy –decisions implies the unavoidable necessity of real practice of transparency, beyond the theory mentioned on laws. Transparency is needed for avoiding misunderstandings and absence of some information that could lead to inefficient procedures. Recent literature suggests unifying the evaluation methodologies in all CCAA will contribute to guarantee transparency in prices. The proposal is a centralised price-fixing procedure, or setting some basic standardization for first stages of price-agreement. An option is to provide a series of standard values that researchers can use to calculate their costs or calculate standard costs for some oncologic key points, taking use of medical records from all the CCAA (112).

Apart from being more socially-engaged method, it is more efficient. Reducing the degree of outsourcing decisions entails a lower transaction cost and simplifies the alignment of priorities along the territory. Hence, a higher degree of equal access to public health would be offered in Spain. Another proposal would be creating an *independent agency to make good decisions with legally binding power (87)* , away from possible conflict of interests and ensuring total

accountability to citizenship. One real example is the British National Institute for Health and Care Excellence (NICE).

> Moreover, the lack of transparency stimulates climate of distrust, which becomes an obstacle to innovation. The doubts feed the uncertainty, hindering disruptive solutions' investment, as well as to attract companies to offer their innovation in our country. The Spanish country has technical capacity for promoting innovation but doesn't take the most of it. Redirecting the pharmaceutical market in an innovative way can be a solution. Instead of conceiving and demand and supply, understand innovation as "capacities demanded" and "incentives supplied" for attracting quality talent and investment for innovation. This organization requires redirecting public policies onto the concept of "maximizing the shareholder value" , since the public Spanish agencies would be able to offer disruptive solutions for fighting against cancer, more attractive our country will be in the financial market. This goal can be promoted in different but complementary ways: (a) cooperation between the government, business and public education for educating qualified human capital looking for competitive advantage; (b) provide physical capacities for developing new technologies which could result interesting for foreign investors; (c) create a sustainable way to finance public agencies able to invest in the public knowledge base required for the next round of innovation (104, 114).

4. Discussion

My findings suggest that the Spanish public health authorities are currently unable to capture the full efficiency on supply procedures for oncologic drugs. Efficiency is fundamental in health system. It is important to allocate resources properly with the purpose of avoiding unnecessary poor outcomes for cancer patients in terms of health, moral, experience or cost. Also, reaching the highest level of efficiency would prevent the SNS denying health improvement to Spanish citizens. Especially those treatments that could have been offered if a better management of the resources available to the national system and the other entities involved had been done (115).

The incidence of the disease in our country grows at a faster rate than the resources intended to palliate it. This situation compels the government to respond rapidly, due to budgetary liquidity emergencies caused by the country's political instability in the last few years since the crisis of 2008. Measures oriented in the "here and now" are established, with a short-term effect and which may continue to shut off the supplies, seeing that healthcare represents a weighty part of public spending (116, 117).

This kind of decisions constrains the equal access to health care, a right of Spaniards and an obligation of the Government and the World Medical Association (WMA), as it was retracted in the Helsinki Declaration of 1964 (118). For instance, the SNS has denied some oncologic treatments it considers cannot afford, such in the case of *nivolumab (Opdivo) combined with ipilimumab (Yervoy)* for advanced stages of melanoma in adults (119).

Authorities ought to move from the actual conjuctural policies to the structural ones, oriented in the long-term, setting multi-year budgets sufficiently robust to face a change in the legislature and maintain the social goal. In order to reach this challenge; demographic, population's health habits and technology diffusion should be studied in first place. Data collected would improve strategic planning extensive to the government and pharmaceutical industry actions.

The research done highly recommends to run new policies to five main aspects: (a) reconfiguration of price setting criteria; (b) standardize evaluation processes for a centralized decision method capable to ensure transparency and efficient flow of information; (c) drive new treatments purchases to Risk Sharing agreements; (d) public policies promoting innovation; (e) collaborative measures between the pharmaceutical industry and the public sector .

Not straying to the truth, until now, the Spanish government has launched some initiatives to fight against the lack of efficiency in the SNS. In 2017, The State Compact for Health Service (*Pacto de Estado por la Sanidad*), was proposed by the PP (*Partido Popular*) and supported by the opposition, the PSOE (*Partido Socialista Obrero Español*) and other minorities present in the Senate. Its purpose was taking action to reach significant stability and sustainability in the SNS. Due to the changes in government, the project remains as a preliminary agreement even now (29, 120, 121). Other measures have been taken, as modifications in law for promoting the national R&D and innovation, included in the *Real Decreto-ley 3/2019*. Despite of that, the measurements leave too much space for the imagination and in some aspects cast doubts on their real utility. For example, the new law proposes agreements with public research units, providing them a subsidy if the expected budget is lower or equal to 50.000€. The measure means a positive approach to innovative promotion, but it probably results insufficient since oncologic discoveries require huge investments. For instance, Roche, the pharmaceutical leading anticancer treatments in Spain, spent over 54 million on R&D in 2017 (122, 123).

The absence of precision in regulations and measures published by Spanish Government affects also to other aspects, like determining the value and innovation degree of a new treatment. The lack of guidelines makes harder for manufacturers to design projects which reach the social and economic expectative of authorities. On the other hand, evaluators have no objective reference to judge and giving rise to inefficient decisions and higher disparity between CC.AA health services. A great number of studies advert about the lack of proper evaluations used nowadays in Spain. This insufficiency is reflected on the efficiency the SNS' portfolio, fundamentally on anticancer drugs.. For example, *Ticagrelor*, a drug for treating hematologic illnesses costs 15.000€/QALY. On the other hand, *Lapatinib* for treating breast cancer has a 2.000.000€/QALY cost (and additional living month costs 60.996€) (88, 124, 125).

This case reflects there's still a long way to go in being an efficient national healthcare system. It is necessary to study the appropriate investments and place efficiency before saving. Moreover, successful strategic plans can be a source of long-term savings, especially in the marginal costs of cancer. Lastly we should emphasize the prevention programs promulgated by the Government are essential for stimulating SNS' efficiency: activating measures for cutting the potential number of people suffering cancer will be translated to (a) less treatment's cost on hospitals and drug

purchases; (b) a raise in welfare given that there would be more health population in the country. Those prevention actions might give especial importance to finish with smoking and nutrition education, especially in schools.

In conclusion, the study advocate Spanish public health authorities should review the national health policies with critical awareness from now on. A major implication from governors is necessary since actual reforms are not enough for complying with government obligations. At the end, even if literature suggests that high prices on oncologic drugs come from the industry, and it is; because every business final objective is making profits. However, it is the Spanish Government who has the responsibility of dealing with conflict of interests and guarantying fairness on health.

5. Conclusions

To conclude, this study pretends a change on mind in governmental priorities and encourages the Spanish public health system and the Spanish government to take action with the purpose of providing real solutions on this issue.

5.1. Final remarks and implications.

To achieve a more efficient healthcare system within the framework of cancer treatments, the current criteria for pricing must be questioned. The judgment must be limited in the short term and with excessive fixation in the cost. At the same time, to bet on a global vision in the long term, with a common methodology for all the autonomous communities. What could be expensive today, can be profitable tomorrow.

The concept of innovation must be defined because it must include the creation of the value that provides an oncological treatment to the patient. The benefits could go even further, since more people recover from cancer. It could signify an increase in quality of life, knowledge diffusion and source of savings. Widening the national healthcare challenges would lead to create a sustainable economic and social framework sufficiently attracting for investors who bet on the innovation growth in Spain. It is important to understand the financing of innovation as an investment and not as an expense.

Therefore, it is equally necessary to provide substantial, objective, measurable and clear health improvement results for all interested parties. Stipulating the correct guidelines, the SNS will be able to pay for the real value of the medicines, instead of paying for their cost.

5.2. Future research and limitations

The study has been limited by the confidentially agreements of meetings for price-setting. It is a constraint for finding out updated data about prices. Because of that, the prices of reference for oncologic drugs are from 2012. If, as this study suggests, transparency standards are applied; future research would be able to provide even more accurate solution for maximizing efficiency in the SNS.

One subject that remains to be explored is the influence of human judgement during MA evaluation and setting prices. Actually, human judge is the stronger driver in this type of decisions. I would find interesting to know to what extent common sense must influence the results of standardized decision models and partly subjected to mathematical variables. In that case, how could this measure is included objectively to reduce opportunity costs in decision-making?

6. References

1. Touryalai H, Stoller K. Global 2000 - The World's Largest Public Companies 2018. Forbes. 2018 June 6,.

2. WHO | Cancer [Internet].: World Health Organization [cited Feb 27, 2019]. Available from: http://www.who.int/cancer/en/.

3. Informe Anual, del Sistema Nacional, de Salud 2. Demografía y Situación de Salud.

4. Insituto Nacional de Estadística, (INE). Fallecidos por cáncer en España. 2019 Febrero.

5. Sociedad Española de Oncología Médica, (SEOM). Las Cifras del cáncer en España 2018. 2018.

6. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct 08,;388(10053):1659-724.

7. Prevención del Cáncer [Internet].; 2018 []. Available from: https://www.aecc.es/es/todo-sobre-cancer/prevencion.

8. Kobelt G, Jönsson L, Mattiasson A. Cost-effectiveness of new treatments for overactive bladder: The example of tolterodine, a new muscarinic agent: A Markov model. Neurology and Urodynamics. 1998 Dec 30,;17(6):599-611.

9. Villar FJA, Oliva J, Velasco M, Zozaya N, Antoñanzas MRL, Bastida JL. Costes directos e indirectos del cáncer en España. Cuadernos económicos de ICE. 2006(72):281-309.

10. Badia X, Tort M. La carga del cáncer en España. Madrid: Omakase Consulting, Bristol-Myers Squibb España; 2018.

11. Ministerio de Sanidad, Servicios sociales e Igualdad. Gobierno de España. Informe Anual del Sistema Nacional de Salud 2017 2018.

12. Ekwueme DU, Chesson HW, Zhang KB, Balamurugan A. Years of potential life lost and productivity costs because of cancer mortality and for specific cancer sites where human papillomavirus may be a risk factor for carcinogenesis—United States, 2003. Cancer. 2008 Nov 15,;113(S10):2936-45.

13. Real Decreto-ley 16/2012, de 20 de abril, de medidas urgentes para garantizar la sostenibilidad del Sistema Nacional de Salud y mejorar la calidad y seguridad de sus prestaciones. Régimen Local. Esquemas. 2012 April 24,:19.

14. Blay L, Louro J, Barata T, Baré M, Ferrer J, Abad JM, et al. Variabilidad en la práctica de la cirugía mamaria en mujeres participantes en el programa de cribado poblacional de cáncer de mama. Cirugía Española. 2019 February 1,;97(2):89-96.

15. About Cancer: Surgery [Internet].; 2015 [updated 04/29/; cited Mar 2, 2019]. Available from: https://www.cancer.gov/about-cancer/treatment/types/surgery.

16. ¿Qué es la cirugía? - Tratamiento contra el cáncer [Internet]. [cited Mar 2, 2019]. Available from: https://www.aecc.es/es/todo-sobre-cancer/tratamientos/eleccion-tratamiento.

17. Chemotherapy to Treat Cancer [Internet].; 2015 [updated 04/29/; cited Mar 3, 2019]. Available from: https://www.cancer.gov/about-cancer/treatment/types/chemotherapy.

18. Anon. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011 Jun;14(2):113-23.

19. ¿Qué es la quimioterapia? [Internet]. [cited Mar 4, 2019]. Available from: https://www.aecc.es/es/todo-sobre-cancer/tratamientos/quimioterapia/que-es-quimioterapia.

20. Porras-Alonso E, Salom-Coveñas C, García-Teno M, Gutiérrez-Bayard L. Cambios en la vascularización de la mucosa faringolaríngea tras radioterapia y quimioterapia concomitante observados con imagen de banda estrecha. Descripción de dos casos. Revista ORL (Ediciones Universidad de Salamanca / Sociedad Otorrinolaringológica de Castilla y León, Cantabria y La Rioja). 2019;10(1):87.

21. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA: A Cancer Journal for Clinicians. 2014 Jul;64(4):252-71.

22. Radiation Therapy [Internet].; 2019 [updated January 8,; cited Mar 4, 2019]. Available from: https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy.

23. de Francisco ALM, Macía M, Alonso F, García P, Gutierrez E, Quintana LF, et al. Onco-Nefrología: cáncer, quimioterapia y riñón. NEFROLOGÍA. 2019 Mar.

24. Immunotherapy to Treat Cancer [Internet].; 2018 [updated November 28,; cited Mar 4, 2019]. Available from: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy.

25. Sociedad Española de Oncología Médica, (SEOM). La inmunoterapia del cáncer - SEOM: Sociedad Española de Oncología Médica 2019. . 2015 May 12,.

26. Bustos Fiore A, Gutiérrez AB, Acosta LG, Segura Cros C, Ramos de la Rosa, R. Inmunoterapia en oncología: un nuevo desafío radiológico. Radiología. 2019 March 1,;61(2):134-42.

27. Redondo B, Moliz C, Alonso M, Paz-Ares L, Praga M, Morales E. Inmunoterapia en el cáncer: grandes expectativas en el mundo de la oncología, pero un motivo de preocupación renal. Nefrología. 2019 /01/01;39(1):94-6.

28. Ministerio de Sanidad, Servicios Sociales e Igualdad, Agencia Española de Medicamentos y Productos Sanitarios, (AEMPS). INFORME DE POSICIONAMIENTO TERAPÉUTICO PT/V2/15042015. 2015 Abril 9,.

29. Álvarez Cabo D, Antoñanzas F, Arocena I, Gómez P, Martínez-Olmos J, Rivero A, et al. Propuesta de criterios para una adecuada financiación de los medicamentos innovadores. 2018 Noviembre.

30. Director-General. WHO Executive Board 144th Session, Provisional Agenda item 5.7. Medicines, vaccines and health products: Cancer Medicines.

31. Lu ZJ, Comanor WS. Strategic Pricing of New Pharmaceuticals. The Review of Economics and Statistics. 1998 February 1,;80(1):108-18.

32. Solà-Morales O, Volmer T, Mantovani L. Perspectives to mitigate payer uncertainty in health technology assessment of novel oncology drugs. Journal of Market Access & Health Policy. 2019 Jan;7(1):1562861.

33. Hirschler B. GlaxoSmithKline boss says new drugs can be cheaper. Reuters. 2013 -03-14.

34. David H. Howard, Peter B. Bach, Ernst R. Berndt, Rena M. Conti. Pricing in the Market for Anticancer Drugs. The Journal of Economic Perspectives. 2015 Jan 1,;29(1):139-62.

35. Light DW, Kantarjian H. Market spiral pricing of cancer drugs. Cancer. 2013 Nov 15,;119(22):3900-2.

36. Abboud C, Berman E, Cohen A, Cortes J, Deangelo D, Deininger M, et al. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013 May 30,;121(22):4439-42.

37. Fox E. How Pharma Companies Game the System to Keep Drugs Expensive. Harvard Business Review. 2017 -04-06T16:00:48Z.

38. Cherny N, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Ann Oncol. 2016 /08/01;27(8):1423-43.

39. Trott P. Innovation management and new product development: Economics and Market Adoption. In: Innovation management and new product development. 5th ed ed. Harlow: Prentice Hall; 2012.

40. Anderson R. Pharma industry gets high on profits. BBC News. 2014 -11-06.

41. Pauwels K, Huys I, Casteels M, Simoens S. Industry Perspectives on Market Access of Innovative Drugs: The Relevance for Oncology Drugs. Frontiers in pharmacology. 2016;7:144.

42. Au R. The paradigm shift to an "open" model in drug development. Applied & Translational Genomics. 2014 Dec 1,;3(4):86-9.

43. Goldacre B, Lane S, Mahtani KR, Heneghan C, Onakpoya I, Bushfield I, et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. BMJ. 2017 Jul 26,;358:j3334.

44. Lipton SA, Nordstedt C. Partnering with Big Pharma—What Academics Need to Know. Cell. 2016 Apr 21,;165(3):512-5.

45. Haukos D. IMS Institute for Healthcare Informatics. Global Oncology Trend Report: A review of 2015 and Outlook to 2020. 2016 Jun. Report No.: 40.

46. Anonymous Constitution of the World Health Organization. International Health Conference; June 19-22, 1946; New York: ; June 22, 1946.

47. Cómo se regulan los Medicamentos y Productos Sanitarios en España, 2014).

48. Rao A. Entry and Investment Decisions in the Pharmaceutical Industry [dissertation]. University of Chicago; 2015.

49. Medicines Approval System. Marketing Authorisations for Medicinal Products within the EU [Internet]. []. Available from: http://www.hma.eu/medicinesapprovalsystem.html.

50. Bere N. Lifecycle of a medical product. How are medicines evaluated at the EMA. https://www.ema.europa.eu: ; Sep 25, 2018.

51. Documento aprobado por la Comisión, Permanente de Farmacia del, SNS, 21 de Mayo de 2013. Propuesta de colaboración para la elaboración de los informes de posicionamiento terapéutico de los medicamentos.

52. Boletín Oficial del Estado. Real Decreto Legislativo 1/2015. Boletín Oficial del Estado A-2015-8343. 15 July 25,;I:19.

53. Artells JJ, Campillo-Artero C, Meneu R, Peiró S. Trayectorias adaptativas en las decisiones de autorización, cobertura y precio de los nuevos medicamentos. Una aproximación cualitativa centrada en los tratamientos oncológicos. Gestión clínica y sanitaria. 2015 Nov,;17(2):52-8.

54. WHO | Cost-effectiveness analysis for health interventions [Internet].: World Health Organization [cited May 11, 2019]. Available from: https://www.who.int/heli/economics/costeffanalysis/en/.

55. Cost-effective (n.d.). Medical Dictionary. [Internet].; 2012 [updated May 11,;]. Available from: https://medical-dictionary.thefreedictionary.com/.

56. Owens D. Interpretation of cost-effectiveness analyses. Journal of General Internal Medicine. 1998 Oct;13(10):716-7.

57. Prieto L, Sacristán JA, Antoñanzas F, Rubio-Terrés C, Pinto JL, Rovira J. Análisis coste-efectividad en la evaluación económica de intervenciones sanitarias. Medicina Clinica. 2004;122(13):505-10.

58. Reglamento interno de la Comisión Interministerial de Precios de los Medicamentos (CIMP), (July, 2017).

59. Cherny N, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Ann Oncol. 2016 /08/01;27(8):1423-43.

60. Pauwels K, Huys I, Casteels M, Simoens S. Drug shortages in European countries: a trade-off between market attractiveness and cost containment? BMC health services research. 2014 Sep 26,;14(1):438.

61. Frakt A. To Reduce the Cost of Drugs, Look to Europe. The New York Times. 2017 -12-21T11:15:59.476Z.

62. OncologyPro Group. ESMO Drives EU-level Action to Tackle Shortages of Essential Medicines. 2019 Apr 09,.

63. Rodríguez A, Arenas m, Lara PC, López-Torrecilla J, Algara M, Conde A, et al. Are there enough radiation oncologists to lead the new Spanish radiotherapy? Clinical and Transnational Oncology. 2019 Apr 3,;21:1-10.

64. Brosa F, Agustí E. Els sistemes de pagament de la sanitat pública a Catalunya, 1981-2009. 1st ed. ; 2009.

65. Catalá-López F, Ridao M, Alonso-Arroyo A, García-Altés A, Cameron C, González-Bermejo D, et al. The quality of reporting methods and results of cost-effectiveness analyses in Spain: a methodological systematic review. Systematic reviews. 2016 Jan 7,;5(1):6.

66. Oyagüez I, Frías C, Seguí MÁ, Gómez-Barrera M, Casado MÁ, Queralt Gorgas M. Eficiencia de tratamientos oncológicos para tumores sólidos en España. Farmacia Hospitalaria. 2013 Jun 1,;37(3):240-59.

67. Lamata F, Gálvez R, Sánchez-Caro J, Pita P, Puigventós F. Medicamentos: ¿Derecho Humano o Negocio? 1ª ed. Diaz de Santos; 2017.

68. O'Hagan P, Farkas C. Bringing Pharma RD back to health. USA: 2009.

69. Bernal I, Iráizoz E. Medicamentos para el cáncer: altos precios y desigualdad. Campaña NoEsSano Abril 2018. Creative Commons; 2018 April ,.

70. Florido F, García-Agua N, Martín Á, García AJ. Crisis, gasto público sanitario y política. Rev Esp Salud Pública. 2019 Feb 22,;93.

71. Artells JJ, Peiró S, Meneu R. Barreras a la introducción de una agencia evaluadora para informar la financiación o la desinversión de prestaciones sanitarias del Sistema Nacional de Salud. Rev Esp Salud Pública. 2014 April,;88(2):217-31.

72. Pérez E. La compra pública innovadora en salud. 2018 -06-04T00:00:00+02:00.

73. Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future. Front Pharmacol. 2017 -4-04;8.

74. Rovira J, Espín J, García L. Experiences and Impact of European Risk-Sharing Schemes Focusing on Oncology Medicines. 2011 January,.

75. Adamski J, Godman B, Ofierska-Sujkowska G, Osińska B, Herholz H, Wendykowska K, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC health services research. 2010 Jun 7,;10(1):153.

76. Russo P, Mennini FS, Siviero PD, Rasi G. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. Ann Oncol. 2010 /10/01;21(10):2081-7.

77. Navarria A, Drago V, Gozzo L, Longo L, Mansueto S, Pignataro G, et al. Do the current performance-based schemes in Italy really work? "Success fee": a novel measure for cost-containment of drug expenditure. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015 Jan;18(1):131.

78. Abellán Perpinán JM, Garrido García S, Martínez Pérez JE, Sánchez Martínez FI. Evidencia de los acuerdos de riesgo compartido como fórmula de cobertura de nuevas tecnologías sanitarias [dissertation]. Universidad de Murcia; 2010.

79. Kamakura WA. Cross-Selling. Offering the Right Product to the Right Customer at the right Time. Journal of Relationship Marketing. 2008;6(3-4):41-58.

80. Dudas y certezas sobre los techos de gasto máximo. El médico interactivo. 2015 -07-24T12:17:05+02:00.

81. María Concepción Peñate Valentín, María del Carmen Sánchez Carreira. La compra pública innovadora. Análisis regional de la experiencia española. Investigaciones Regionales. 2018 Jan 1,(40):79-107.

82. European Commission - Research & Innovation. Cross-cutting issues: Innovation Procurement. In: EU, editor. H2020 Online Manual.

83. Holleman MS, Uyl-de Groot CA, Goodall S, Van der Linden N. Determining the Comparative Value of Pharmaceutical Risk-Sharing Policies in NoneSmall Cell Lung Cancer Using Real-World Data. Value in Health. 2019;22(1):0034.

84. Puig-Junoy J, Meneu R. Aplicación de los contratos de riesgo compartido a la financiación de nuevos
medicamentos. Gestión clínica y Sanitaria. 2005;7(3).

85. Badia X, Prior M. Innovative agreements with the pharmaceutical industry: "pay for performance". Farmacia hospitalaria : organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria. 2010 Mar;34(2):53.

86. Maynou-Pujolras L, López-Casanovas G, editors. Comparativa de los Sistemas de Evaluación de Medicamentos: Evidencia Europea. ¿Es necesaria una unificación de los criterios de evaluación? ; 2016.

87. Campillo-Artero C, Ortún V. Cost-effectiveness Analysis: Why and How. Rev Esp Cardiol. 2016 /04/01;69(04):370-3.

88. Salvador Peiro. In: La generación de evidencia en salud pública como base para establecer políticas sanitarias. Unpublished; 2015.

89. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices—Modeling Studies. Value in Health. 2003;6(1):9-17.

90. Phillips L, Bana e Costa C. Transparent prioritisation, budgeting and resource allocation with multi-criteria decision analysis and decision conferencing. Ann Oper Res. 2007 Oct;154(1):51-68.

91. Caro JJ, Brazier JE, Karnon J, Kolominsky-Rabas P, McGuire AJ, Nord E, et al. Determining Value in Health Technology Assessment: Stay the Course or Tack Away? PharmacoEconomics. 2019 Mar;37(3):293.

92. Freire S.M., Nascimento A., de Almeida R.T., editor. A Multiple Criteria Decision Making System for Setting Priorities. 1st ed. Singapore: Springer; 2018.

93. Oliva J, Puig-Junoy J, Bernal E. Evaluación económica de medicamentos: experiencias y vías de avance. Una visión complementaria. Gaceta Sanitaria. 2008 Jul 1,;22(4):358-61.

94. Gonzato O, Gronchi A. The evolving role of patient advocates in rare cancers: opportunities and challenges. Expert Review of Pharmacoeconomics & Outcomes Research. 2019 Jan 2,;19(1):1-3.

95. Gispert B. Las farmacéuticas lideran la solicitud de patentes españolas en Europa. La Vanguardia. 2019 -03-13T01:00:19Z.

96. Joseph E. Stiglitz. Prizes, not patents. Post-autistic Economics Review. 2007 May 18,(42):48-9.

97. Trott P. Innovation management and new product development: Managing Intellectual Property. In: Innovation management and new product development. Prentice Hall; 2012.

98. Juan J. Fuga de cerebros. La Vanguardia. 2019 -04-14T22:28:30Z.

99. Las farmacéuticas en España, entre los mayores generadores de empleo europeos. Diariomedico.com. 2018 -07-19T15:12:19+02:00.

100. Basu P, Joglekar G, Rai S, Suresh P, Vernon J. Analysis of Manufacturing Costs in Pharmaceutical Companies. J Pharm Innov. 2008 Mar;3(1):30-40.

101. Goldberg RM, Wei L, Fernandez S. The Evolution of Clinical Trials in Oncology: Defining Who Benefits from New Drugs Using Innovative Study Designs. The Oncologist. 2017 Sep;22(9):1015-9.

102. La asistencia sanitaria vuelve a ser universal en España. Correo Farmaceutico. 2018 July 30,.

103. Real Decreto-ley 7/2018, de 27 de julio, sobre el acceso universal al Sistema Nacional de Salud. Boletín Oficial del Estado (BOE). 2018 July 30,;I:19.

104. López I Casasnovas G. Políticas públicas y economía de la innovación en sanidad. 2017 Jan 1,.

105. European Comission. Council of the European Union: Proposal for aregulation of the European Parliament and of the Council L on health technology assessment and amending Directive 2011/24/EU ST 5844 2018 INIT. Jan 31, 2018; Brussels: .

106. Lambán P. La evaluación común de tecnología sanitaria se aprobará tras las europeas. Redacción Médica. 2019 Jan 18,.

107. Código sanitario. Códigos electrónicos. Edición actualizada a 30 de abril de 2019. 4, 1992).

108. Ley 14/1986, de 25 de abril, General de Sanidad. Revista de administración sanitaria siglo XXI. 1986 April 25,:481-526.

109. Externalities. BusinessDictionary. [Internet].; 2019 [updated May 12,; cited May 12, 2019]. Available from: http://www.businessdictionary.com/definition/externalities.html.

110. Social Cost. BusinessDictionary. [Internet].; 2019 [updated May 12,; cited May 12, 2019]. Available from: http://www.businessdictionary.com/definition/social-cost.html.

111. Lozano I, Rondán J, Vegas JM, Segovia E. Sustainability of the Health System: Beyond Cost-effectiveness Analyses. Revista Española de Cardiología (English Edition). 2016 Sep;69(9):880-1.

112. del Llano Señarís J, Rovira Forns J, Albarracín Medina G. La medicina individualizada en Oncología: evaluación del impacto sanitario y económico para garantizar el acceso y la sostenibilidad financiera del sistema de salud. In: Instituto Roche, editor. Medical Economics. La evaluación económica en Farmacogenómica Oncológica y Hematológica. Spanish Publishers Associates S.L.; 2009. p. 11-28.

113. Del Llano J, Oteo A. ¿Qué son los outcomes y para qué sirven? Farmacoterapia basada en resultados. Farmacia Hospitalaria. 2010:5-12.

114. Lazonick W. The Innovative Enterprise and the Developmental State: Toward an Economics of "Organizational Success" [dissertation]. Boston: University of Massachusetts; 2011.

115. Cylus J, Papanicolas I, Smith PC, editors. Health system efficiency: How to make measurement matter for policy and management. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2016.

116. López CM. La carga del cáncer y la incidencia: una carrera contrarreloj. Revista Española de Economía de la Salud. 2018:228-35.

117. Bernal-Delgado E, Campillo-Artero C, García-Armesto S. Oferta sanitaria y crisis: financiamos los bienes y servicios según su valor o caemos en la insolvencia. Informe SESPAS 2014. Gaceta Sanitaria. 2014 Jun 1,;28(S1):69-74.

118. The World Medical Association. Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Journal of International Biotechnology Law. 1964 Jun:73-6.

119. Fernández Carrasco C, Romo Martín B. Ipilimumab en el tratamiento del melanoma avanzado. Farmacología, eficacia y seguridad. 2015 Jun 1,.

120. El PP propone en el Parlamento un pacto por la sanidad más allá de ideologías [Internet].; 2019 [updated -03-29T12:47:55Z; cited Apr 28, 2019]. Available from: https://www.lavanguardia.com/politica/20190329/461321665168/el-pp-propone-en-el-parlamento-un-pacto-por-la-sanidad-mas-alla-de-ideologias.html.

121. Arganda C. Pacto por la Sanidad: PP y PSOE dan en el Senado los primeros pasos. DiarioFarma. 2017 -01-25T20:23:02+00:00.

122. Jefatura del Estado. Real Decreto-ley 3/2019, de 8 de febrero, de medidas urgentes en el ámbito de la Ciencia, la Tecnología, la Innovación y la Universidad. Boletín Oficial del Estado. 2019 Feb 9,:19.

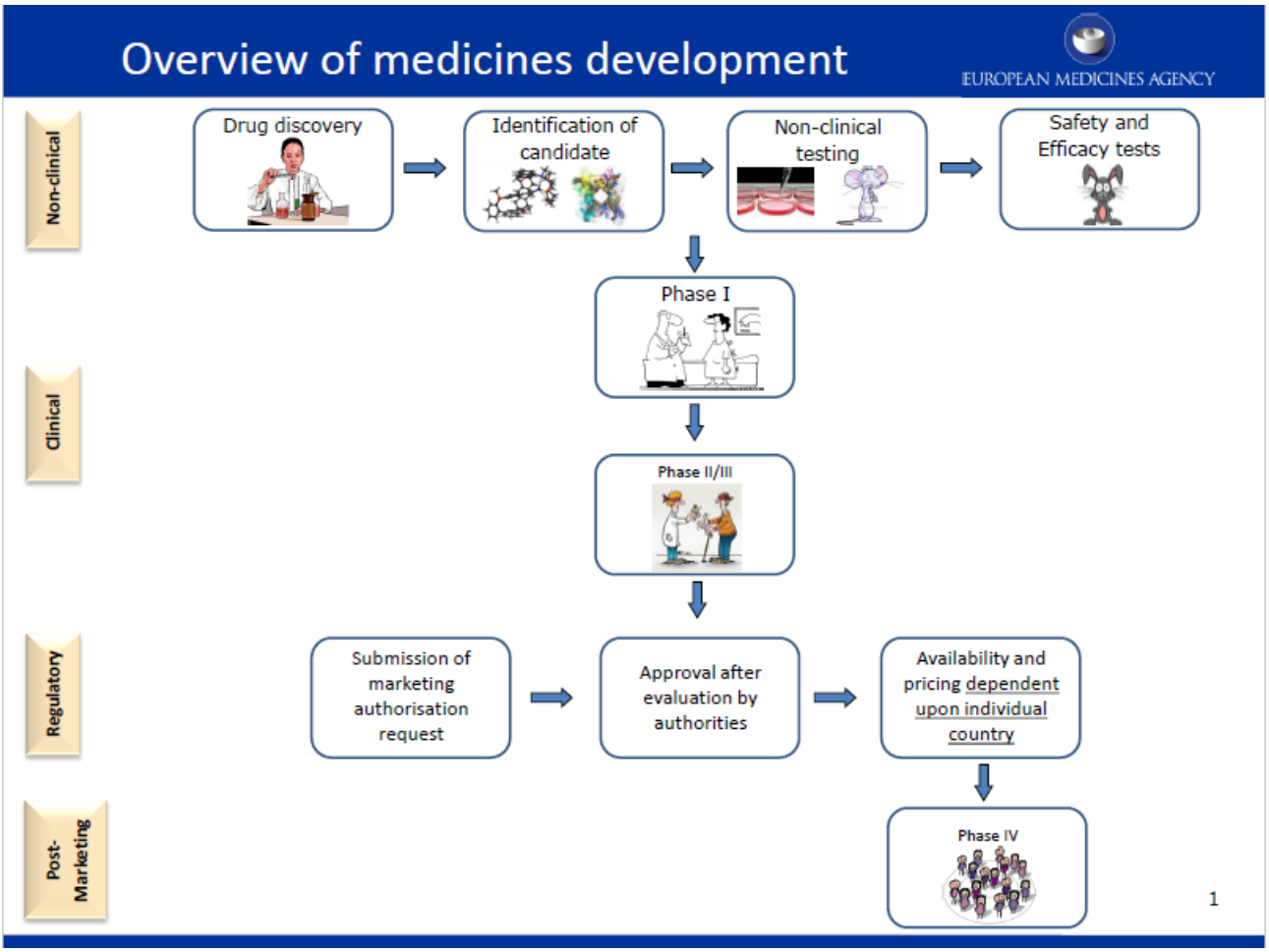
123. Roche Farma: Transparencia. Transferencias de valor de Roche España en 2017 [Internet]. [cited Apr 28, 2019]. Available from: https://www.roche.es/es_es/Roche_Farma/transparencia.html.

124. López Sendón, J.L., Heras, M., Carrera Hueso, F.J. et al. PharmacoEcon Span Res Artic. Análisis coste-efectividad del uso de ticagrelor frente a clopidogrel en el tratamiento del síndrome coronario agudo en España. PharmacoEconomics Spanish Research Articles. 2015 Nov,;12(4):137-46.

125. Vademecum. Ticagrelor [Internet]. Vademecum: ; 2018 [cited Apr 28, 2019]. Available from: https://www.vademecum.es//principios-activos-ticagrelor-b01ac24.

Appendix

Appendix 1- Medicine's development before setting prices



Appendix 2 -Initial fragment of IPT Report of nivolumab (Opdivo® in combination with ipilimumab (Yervoy) in advanced melanoma

INFORME DE POSICIONAMIENTO TERAPÉUTICO

Informe de Posicionamiento Terapéutico de nivolumab (Opdivo®) en combinación con ipilimumab (Yervoy®) en melanoma avanzado

IPT, 59/2018. V1

Fecha de publicación: 8 de noviembre de 2018†

El melanoma es la forma más agresiva de cáncer de piel. La tasa ajustada de incidencia de melanoma en España es de 5,2 por cada 100.000 habitantes/año (1). Aproximadamente, la mitad de los casos afecta al grupo de edad comprendido entre los 35 y 65 años, con una mediana de edad en el momento del diagnóstico de 44 años y una incidencia máxima a partir de los 65 años. La incidencia se ha visto incrementada en las últimas décadas de manera continua y afecta a todas las edades (2). El 95% de los casos son melanomas cutáneos, siendo de "novo" un 75% de ellos, mientras que el 25% restante lo hace sobre un nevus previamente presente. El pronóstico del melanoma depende en gran parte del estadio en que se encuentre. Aproximadamente el 85% de los melanomas diagnosticados son localizados, siendo solo un 5% los que se diagnostican en estadio metastásico de inicio. La tasa de supervivencia para los pacientes con enfermedad localizada y tumores de ≤ 1 mm de Breslow, es mayor del 90%. El porcentaje de pacientes con estadio avanzado se sitúa en torno a un 15% de los pacientes diagnosticados de melanoma (3-5). La enfermedad avanzada no solo conlleva asociados síntomas físicos, sino que supone también un sufrimiento emocional para el enfermo. El tratamiento establecido para el melanoma avanzado incluye cirugía, radioterapia y/o terapia sistémica. La resección total de metástasis aisladas y restringidas a un único lugar anatómico puede, en algunos casos, prolongar significativamente la supervivencia. La radioterapia paliativa estaría indicada en el alivio sintomático de las metástasis cerebrales, tejido óseo y vísceras. La terapia sistémica consiste en:

- Inmunoterapia: nivolumab, ipilimumab y pembrolizumab.
- Quimioterapia: dacarbazina, fotemustina, o medicamentos que, aunque carecen de la indicación en melanoma, son utilizados en mayor o menor medida en nuestro entorno, como temozolomida o carboplatino-paclitaxel.
- Terapia dirigida frente a BRAF y MEK: vemurafenib, dabrafenib, trametinib y cobimetinib.

NIVOLUMAB (OPDIVO®)

Nivolumab en monoterapia o en combinación con ipilimumab está indicado para el tratamiento del melanoma avanzado (irresecable o metastásico) en adultos (6). Un Informe de Posicionamiento Terapéutico evalúa el uso de nivolumab en monoterapia para el tratamiento de melanoma avanzado (7). El presente informe se centrará en la terapia de combinación de nivolumab + ipilimumab.

Según lo establecido en ficha técnica, solamente se ha establecido un aumento de la supervivencia libre de progresión (SLP) y la supervivencia global (SG) para la combinación de nivolumab con ipilimumab respecto a nivolumab en monoterapia en los pacientes con baja expresión de PD-L1 en el tumor (6).

Nivolumab se presenta como concentrado de 10mg/ml para solución para perfusión en viales de 4 y 10 ml (6). Mientras que ipilimumab se presenta como concentrado de 5 mg/ml para solución para perfusión en viales de 10 y 40 ml (8).

La dosis recomendada es 1mg/kg de nivolumab, administrado por vía intravenosa durante 30 minutos cada 3 semanas para las primeras 4 dosis en combinación con 3 mg/kg de ipilimumab administrado por vía intravenosa durante 90 minutos. Después se continúa con una segunda fase en la que se administran como monoterapia 240 mg de nivolumab cada 2 semanas durante 30 minutos, por vía intravenosa o 480 mg cada 4 semanas durante 60 minutos por vía intravenosa. El tratamiento se debe prolongar mientras se observe beneficio clínico o hasta que el paciente no tolere el tratamiento (6). No se recomienda la escalada de la dosis ni su reducción. Puede que sea necesario el retraso o la suspensión de la dosificación de acuerdo con la seguridad y la tolerabilidad individual. Cuando se administra nivolumab en combinación con ipilimumab, si se interrumpe la administración de uno de los medicamentos el otro también se debe interrumpir (6).

Farmacología

Nivolumab es un anticuerpo monoclonal humano de tipo inmunoglobulina G4 (IgG4) (HuMAb) que se une al receptor de muerte programada 1 (PD-1) y bloquea su interacción con PD-L1 y PD-L2. El receptor PD-1 es un regulador negativo de la actividad de los linfocitos T, que se ha visto que está implicado en el control de la respuesta inmunitaria de los linfocitos-T y es crucial en el mantenimiento de la homeostasis inmunitaria en condiciones fisiológicas (6).

Ipilimumab es un anticuerpo monoclonal humano (IgG1κ) inhibidor del punto de control inmunológico CTLA-4 (Cytotoxic T Lymphocyte Antigen-4). Ipilimumab bloquea las señales inhibitorias de las células-T inducidas a través de la vía CTLA-4 y aumenta el número de células-T efectoras que se movilizan para dirigir un ataque inmune dirigido a las células-T contra las células tumorales (8).

La combinación de nivolumab (anti-PD-1) e ipilimumab (anti-CTLA-4) produjo una mejora en la respuesta antitumoral en melanoma metastásico. En modelos de tumores singénicos murinos, el doble bloqueo de PD-1 y CTLA-4 dio como resultado una actividad antitumoral sinérgica (6).

Eficacia

Los datos clínicos de eficacia de nivolumab en combinación con ipilimumab para el tratamiento del melanoma avanzado (irresecable o metastásico) en adultos provienen de un ensayo clínico fase 2 (CheckMate 069) y un ensayo clínico fase 3 (CheckMate 067). Este último compara ipilimumab en monoterapia con el régimen combinado y con nivolumab en monoterapia, aunque sin preespecificar la comparación entre el régimen combinado y nivolumab. Sin embargo, para el posicionamiento de esta combinación, el interés se centra precisamente en su comparación con la inmunoterapia estándar, representada por nivolumab en una de las ramas de este ensayo.

Estudio principal: CheckMate 067 (Fase III)

El estudio CheckMate 067 fue un ensayo clínico fase III, doble ciego que incluyó pacientes adultos con melanoma irresecable confirmado o melanoma metastásico. Los pacientes fueron aleatorizados para recibir nivolumab en combinación con ipilimumab, nivolumab en monoterapia, o ipilimumab en monoterapia (9,10).

Se incluyeron pacientes en estadio III o IV según el sistema de estadificación American Joint Committee on Cancer (AJCC), con estado funcional ECOG 0 o 1 y que no habían recibido tratamiento sistémico previo para el tratamiento del tumor. Sí se incluyeron pacientes que habían recibido tratamiento adyuvante o neoadyuvante

† Fecha de adopción de la fase I del informe por el GCPT: 25 de septiembre de 2018.

Appendix 3 - Public health and pharmaceutical expenditure per inhabitant according to political ideology study period and type of Autonomous Community according to GDP. Conservative (PP) vs. progressive (PSOE) (70)**.**