

cancer drugs:

HIGH PRICES AND INEQUITY

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CANCER DRUGS: HIGH PRICES AND INEQUITY.

No es Sano Campaign. April 2018

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abbreviations.

CAR-T	Chimeric Antigen Receptor T-cells
CCAA	Autonomous Communities (from the Spanish Comunidades Autonomas)
CIPM	Inter-Ministerial Commission on Pharmaceutical Prices (from the Spanish Comisión Interministerial de Precios de los Medicamentos)
CLL	Chronic Lymphocytic Leukaemia
CNIO	Spanish National Cancer Research Centre (from the Spanish Centro Nacional de Investigaciones Oncológicas)
CORDIS	Community Research and Development Information Service
CT	Clinical Trials
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FIS	Health Research Funds (from the Spanish Fondos de Investigación en Salud)
GDP	Gross Domestic Product
ICO	Catalan Institute of Oncology (from the Spanish Instituto Catalán de Oncología)
INE	National Statistics Institute (from the Spanish Instituto Nacional de Estadística)
LSP	Laboratory Selling Price
MINECO	Spanish Ministry of Economy, Industry and Competitiveness (from the Spanish Ministerio de Economía, Industria y Competitividad)
MS	Multiple Sclerosis
MSSSI	Spanish Ministry of Health, Social Services and Equity (from the Spanish Ministerio de Sanidad, Servicios Sociales e Igualdad)
NCI	National Cancer Institute
OECD	Organisation for Economic Co-operation and Development
R&D	Research and Development
REEC	Spanish Register of Clinical Trials (from the Spanish Registro Español de Ensayos Clínicos)
REMS	Risk Evaluation and Mitigation Strategy
REPORT	Research Portfolio Online Reporting Tools
RRMS	Relapsing- Remitting Multiple Sclerosis
SEFH	Spanish Society of Hospital Pharmacy (from the Spanish Sociedad Española de Farmacia Hospitalaria)
SEOM	Spanish Society of Medical Oncology (from the Spanish Sociedad Española de Oncología Médica)
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UCLA	University of California Los Angeles
US	United States
WHO	World Health Organisation
YLDS	Years Lived with Disability

one.

INTRODUCTION

Curing cancer has become a priority for health systems and professionals from different fields, but, above all, for the patients that day in and day out face this disease that, despite advances, continues to be one of the main causes of death and impoverishment for many people and families both in Spain and abroad. Responding to this urgent need is essential and should be undertaken by guaranteeing the research, access to treatment, care and financial aid needed, relying on the collaboration and commitment of all the parties involved. States have the responsibility to ensure the right to health and provide universal access to adequate treatments. It is also their responsibility to guarantee the upkeep of healthcare systems, providing them with the human and technical resources that ensure quality of care in terms of equity and social justice.

The first section of this report reviews the problem of cancer in epidemiological terms, addressing the main treatments and exploring the conditions and barriers to accessing oncology drugs. The trend towards the high prices of the medication has direct implications on healthcare systems, notably increasing the drug expenditure and, in some countries, limiting patients' access to their medication. The cancer drug market has grown exponentially in recent years, and it is expected to continue to do so by virtue of a regulatory framework and intellectual property incentives that contribute to high prices. Likewise, it is essential to bring to light the need to invest more in biomedical innovation, which is a fundamental element in order to advance in the fight against cancer, and to value the huge contribution that patients altruistically give through their participation in oncology clinical trials.

Illustrating these aspects, the report addresses specific case studies that narrate the story of some drugs, from their very first stages up to their commercialisation, and it reveals, among other issues, the important public participation throughout the process and the lack of return on said investment after decades of commercialisation.

Finally, in light of that revealed, it draws a series of conclusions that will enable changes to be made in the current system; these are put forward for consideration.

There were also limitations when preparing this report due to the difficulty in accessing information regarding real prices, research costs, patents, pharmaceutical and clinical trial expenses and more. In terms of the case studies, the results do not pretend to be transferable to all current drugs, but they do place value on scientific research in public centres and non-profit centres throughout the world, which are essential for the present and future advancement of healthcare technology. With its limitations, the purpose of this report is to go into depth in the aforementioned aspects and to prove that there is a need to review the current biomedical R&D system and the access to medicines.

two.

THE PROBLEM OF CANCER

2.1. SOME IMPORTANT FACTS

The word cancer conveys a serious worry and an important challenge. First of all, for patients, who day-in, day-out face a disease that, despite all the advances, continues to be one of the main causes of death, loss of quality of life and impoverishment. It is also so for the family and friends that accompany the patients throughout this process, the doctors that work to cure them and the researchers that fight to discover the best medication and therapies for today's and tomorrow's patients.

Cancer is proof of the scope and consequences of an illness that exceeds the limits of medical attention and influences other social, economic and cultural variables that come in and play an enormously important role (1).

In 2012, 14.1 million new cases were registered in the world and it is estimated that 8.2 million people died from cancer related issues, of those some 4.3 million (more than half) were premature deaths. It is calculated that in 2030, 21.6 million new cases will have been reached(2) and in 2035 the number of deaths produced by tumours will increase to more than 14 million people(3). The percentages are distributed as follows: middle and low income countries account for 65% of cancer-related deaths globally, and 75% of premature deaths (2). This group of countries faces the greatest barriers to diagnosis and treatment of the disease, mainly due to the weakness of their health systems, the lack of specialists, the lack of preventive policies and the lack of access to treatments due to their high prices (3,4).

Furthermore, it is estimated that more than 100,000 children die from cancer each year,

mainly in low and middle income countries (3), where health structures are scarce and diagnosis arrives too late, when the prognosis for the disease is worse. The geographical distance from hospitals means that families have to use many resources in order to get there (transport, accommodation, leaving work and their homes, etc.) and this is often an expense that they cannot take on. This, together with the direct costs for hospital stay and medicines, unaffordable for many families, limits access to effective treatments in the appropriate time and place or push children to abandon their treatments earlier than they should. Moreover, many hospitals do not have adequate facilities and equipment, and essential medication is not always available (5).

In terms of the type of cancer, lung cancer causes the most deaths globally, followed by bowel cancer. In men, prostate cancer is the most common, but it is also the most controlled. In the case of women, breast cancer is both the highest cause of death and the tumour with the highest years lived with disability (YLD) rate (6). With regards to regions, 70% of cancer deaths are concentrated in Africa, Asia and South and Central America. Although cancer is categorised as a non-communicable disease, it can be stated that cancers due to viral infections, such as those caused by the Human Papillomavirus or by the Hepatitis C virus are responsible for 20% of the deaths in low and middle income countries (7,8).

In Spain, cancer has become the second biggest cause of death, behind cardiovascular diseases (9). According to data from the National Statistics Institute (INE), in 2016, 27.5% of deaths (112,939 deaths) were due to tumours, particularly lung tumours (22,187 cases) and bowel tumours (15,802 cases); followed far behind by pancreas cancer (6,789), breast cancer (6,477)

and prostate cancer (5,752)(10). Per sex, tumours were the first cause of death in men, and the second cause in women. In terms of age groups, cancer was the main cause of death for those between 1 and 14 years (some 28.4% of deaths) and those aged between 40 and 79 (44.5%) (9).

With regard to incidence, in Spain 247,771 new cases were registered in 2015 (148,827 men and 98,944 women) (11). Per type of cancer, bowel cancer was the most commonly diagnosed (41,441), followed by prostate and lung cancer. Out of all the new cases of cancer detected in Spain in 2015, prostate cancer was the most common among men and breast cancer was the most common among women (**figure 1**). The projections for Spain predict 315,413 new cases for the year 2035 (12).

This data reflects the impact of a disease on the population, but behind that there are many people that face the consequences of a disease that can be disabling and that has a huge impact on households and for the system. Cancer creates poverty and worsens those situations of greater vulnerability in which there is already a risk of suffering from it, whilst having direct consequences on the economy of households. From a labour perspective, cancer can be a double-edged sword: the illness and the exclusion from the job market (13).

In countries such as the US, it is calculated that in 2017 some 1.7 million new cases will have been diagnosed and, data from 2014 shows that cancer patients pay approximately 4 billion out of their pockets on cancer treatments (14).

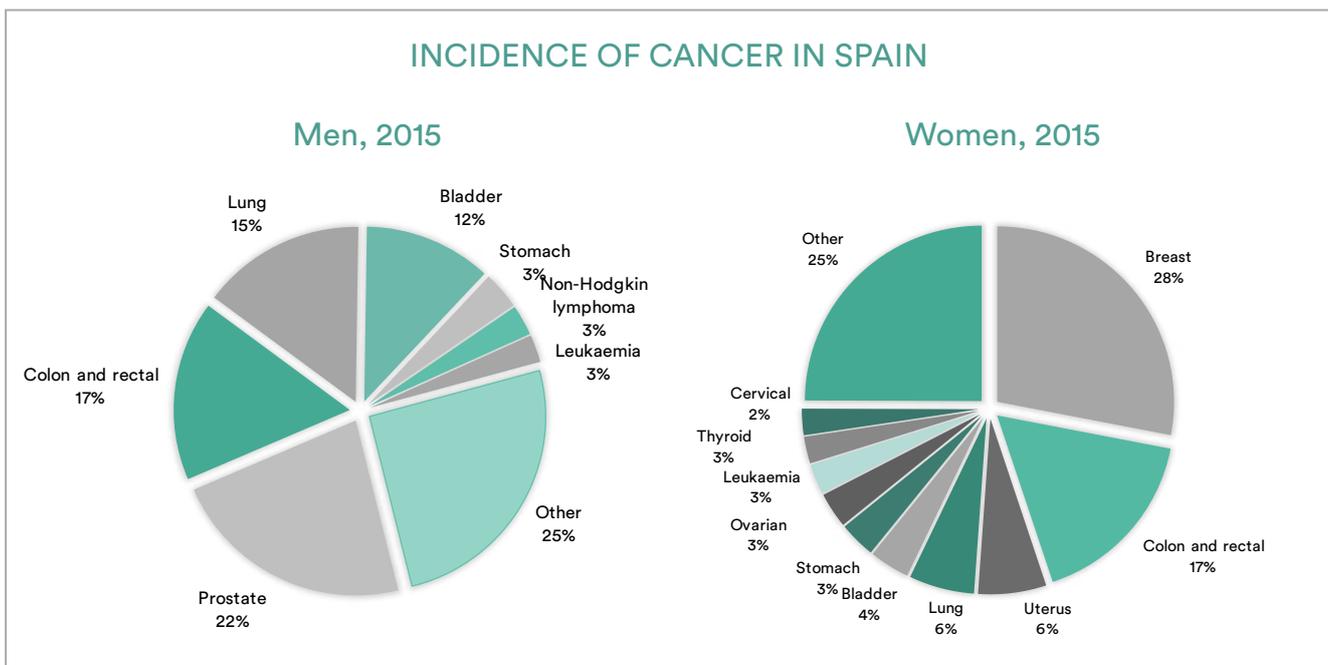


Figure 1. Incidence of Cancer in Spain. Percentage of registered new cases in 2015 per sex and type of cancer. Source: REDECAN (Spanish Cancer Registries) (11). Prepared by the authors.

Associations warn that not even health insurances enable cancer patients to cover the costs of the treatment they need, at times due to the high co-payments or directly because the insurance does not cover that treatment. However, in addition to the direct costs, there are indirect ones which are far more difficult to quantify, that are linked to the loss of employment, the accommodation costs in places near to where treatment is provided, specialised transport to medical appointments, childcare or care of dependants, etc. (14).

It is calculated that in Spain some 25,000 people with cancer are at risk of social exclusion each year as a result of the disease (1); a figure which represents almost a third (27.7%) of the total diagnosed in the active population in Spain in 2017. On the other hand, each year a total of 9,832 unemployed people are diagnosed with cancer, of which more than half (5,232) do not receive any financial aid, meaning that low income families are forced to decide, for example, between paying the bills or buying medication (1,15). Regional inequalities can also be added to this: in the Canary Islands, 60% of households do not have the means to cover the extra costs caused by the disease; in Andalusia this figure is 52% and in the Basque Country it drops to 18.9%.

2.2 NEW CANCER THERAPIES

Cancer is a multi-causal and multi-factorial disease which presents itself in diverse ways and it must be approached in a multi-disciplinary and comprehensive way, addressing prevention (including early diagnosis screening) up to treatment (surgery, radiotherapy or pharmacological treatment), palliative care and the psychological and social support of the patients and their families.

This chapter will focus solely on cancer drugs, although just as some medical societies have stated recently, when talking about cancer, it is not just treatment that should be included, but also the epidemiological, diagnostic, preventative and screening aspects and the defining of the population at risk (16). **Table 1** shows a summary of the main types of cancer drugs with some examples. Far from being an exhaustive list, the aim of this summary is to help to understand what the main treatments are and the way in which they act.

Knowledge of the genetic and molecular alterations that are caused when tumours and metastasis develop, as well as the development of drugs which serve to balance out said alterations, have allowed for research in more specific therapies (17). This is the case for the new biological therapies, which have resulted in an advance in tumour treatment, allowing for the treatment to be more selective in the attack of the tumour and improving patients' quality of life.

In this respect, CAR-T (Chimeric Antigen Receptor T-cells) therapies have recently appeared which modify the patient's immune system in order for it to have the ability to precisely attack the tumour cells.

These are therapies that open new paths of treatment but that also must be evaluated in terms of clinical results and safety, as such more evidence is still needed (18,19).



CHEMOTHERAPY

By means of different mechanisms, these drugs are able to provoke alterations in cells that may lead to cell death. In short, they indiscriminately destroy all those cells that quickly reproduce, as is the case with tumour cells.

Examples: Cisplatin, Fluorouracil, Doxorubicin, Paclitaxel, Docetaxel.



HORMONOTHERAPY

The drugs in this group work by modifying the way hormones work with the aim of stopping the growth of tumours classed as hormone-dependent, meaning that they depend on certain hormones in order to grow. Fundamentally, they are drugs aimed at breast and prostate cancer, as well as ovarian cancer, endometrial cancer and neuroendocrine tumours.

Examples: Tamoxifen, Anastrozole, Abiraterone, Enzalutamide, Fulvestrant.



BIOLOGICAL THERAPIES

Biological therapies include a group of treatments designed to act selectively on tumour cells with a determined characteristic and this gives them an improved profile of effectiveness and less side effects.

The mechanisms of action in biological therapies are varied and treatments are diverse. For example, immunotherapy makes the most of the capacity of the patient's immune system to fight against the cancer. Unlike other treatments available, immunotherapy does not aim to directly destroy the tumour cells, but rather its action involves stimulating and boosting the patient's antitumor immune response so that it attacks and destroys the tumour. The monoclonal antibody alemtuzumab and the new CAR-T therapies are examples of immunotherapy.

Another group of therapies, known as targeted therapies, aim to block the signals that the tumour cells need to grow or survive. These include drugs such as the monoclonal antibodies bevacizumab and trastuzumab.

Figure 2. Types of Cancer Drugs by their Mechanism of Action. Source: SEOM (20)

three.

ACCESS TO CANCER DRUGS

Access to safe, effective and quality drugs is a fundamental element in the structuring of the right to health¹. In the area of oncology, scientific advances have been very noticeable in recent years, especially due to the prevention strategies, early diagnosis and treatment to stop cancer (21). The word cancer currently leads us to think of a more hopeful scenario than it did a few decades ago, but there are still many people in the world that cannot access the medication they need. Although it is true that cancer is a disease which requires a comprehensive approach, pharmacotherapeutic treatment is crucial and determining in many cases.

Thus, fulfilling the 2030 target of a one-third reduction of premature deaths globally, caused by chronic diseases including cancer (22), included in the framework of the Sustainable Development Targets, perhaps sounds like a long way off for too many people who see how certain tumours (which have effective treatment available) become insuperable diseases.

This is the example of diseases such as acute lymphoblastic leukaemia. This type of leukaemia is one of the most common among children and it has the best prognosis if it is treated in time (23). However, the impossibility of accessing curative treatment sentences children that live in low and middle income countries to death. A child diagnosed in Portugal has a 90% chance of still living 5 years after being diagnosed. A child born in China, Ecuador or Mexico

does not have the same luck: they would have a less than 60% chance of surviving. This is shown by the recently published CONCORD study (3), which also indicates the impossibility of estimating survival in some developing countries where cancer registers are non-existent (24) and even carrying out a civil register or a death rate is a complicated task. This is particularly accentuated in the continent of Africa where there are still armed conflicts and wars going on which started decades ago (25). The absence of data is a reflection of health systems with scarce resources, with low coverage and that are tremendously fragile. It is estimated that in the world's poorest countries, five-year survival in children diagnosed with leukaemia may be less than 20% (26).

When talking about cancer, this same pattern can often be seen, both on a worldwide level, as well as within each country. Worldwide and country-wide social and economic inequalities, even in the richest countries, mark out a clear survival gap. The likelihood of a patient surviving colon cancer, or of a women surviving breast cancer, is highly dependent on where they live (3) and it is strongly associated to a guaranteed access to early diagnosis and effective and appropriate treatment, framed within a high quality health system which attends to the population's needs. More than 30 countries in Africa and Asia do not even have radiotherapy services available (27).

¹ El reconocimiento del Derecho a la Salud se remonta a la Carta de las Naciones Unidas (1945), la Declaración Universal de Derechos Humanos (1948) y la Constitución de la Organización Mundial de la Salud (1948). Este derecho también se plasma en el Pacto Internacional de Derechos Económicos, Sociales y Culturales (1966), que recoge en su artículo 12.1 el derecho de toda persona al disfrute del más alto nivel posible de salud física y mental (242). La OMS en su Constitución, además, insiste en la necesidad de garantizar la disponibilidad, accesibilidad, aceptabilidad y calidad de establecimientos, bienes y servicios de salud para el ejercicio de este derecho (12).

In Nigeria, for example, there are no oncologists and the most basic chemotherapy is limited, both in the public and private sector (28). Available treatments are unaffordable for patients who have to pay out of their own pockets for the price of medication. The lack of adherence to treatments in these environments is another great problem. Although patients may start their treatments, the cost of medication and healthcare services turns out to be too much and many patients tend to abandon their therapies. If you are diagnosed with cancer, your likelihood of surviving depends on your postcode (29).

3.1 HIGH PRICES: A GLOBAL BARRIER TO MEDICINES ACCESS

The trend of the high prices of drugs has established as one of the main barriers to accessing treatment (30). In the case of cancer, as in other cases, the high prices of oncology treatments or new immunotherapies reveal that we are facing a global problem, which is a consequence of the current innovation system. A system that is more interested in protecting intellectual property rights than in guaranteeing innovation that is in the public's interest, despite the calls from professionals, scientific societies, experts and even some leaders, verbalising their opinions with phrases such as "patients before patents" (31,32).

In recent years, the average price of new cancer drugs has shot up, reaching exorbitant figures. Numerous studies portray this growth. Some authors have valued the average price increases of oncology medication at more than 10% per year since 1995 (33). Other studies calculate that, from 2003 to 2013, the average

The problem with the high prices has been exposed many times by different international campaigns, often led by the patients themselves.

This is the case of Patients for Affordable Drugs (39), an independent organisation that aims to achieve the political change that is necessary in the US in order to lower the price of drugs; or the Union for Affordable Cancer Treatment (UACT) (40), a movement that brings together patients with cancer, their families and friends, healthcare professionals and researchers that are also concerned about the high prices. This union fights to achieve access to care and treatment for cancer that is available and accessible for everyone that needs it.

price of these drugs multiplied by two, from 4,500 dollars to more than 10,000 dollars per month of treatment (34,35). Annually, this is an increase from 54,000 to 120,000 dollars per year for treatment.

Although it is true that low income countries are those that most suffer from the consequences of the high prices to access medication, this is not a problem that is exclusively confined to those countries.

In the United States, where the price of cancer drugs between 2011 and 2016 increased by 88% (36,37), the drugs are, simply, beyond the reach of many families that have to choose between their health, or covering the costs of other basic needs. In a letter in 2015, scores of doctors (38) supported an independent group of patients with the aim of lowering the prices of oncology medication. In this they stated, alongside other evidence, that in 2014 all new cancer drugs approved by the American agency, the

Food and Drug Administration (FDA), had a price over 120,000 dollars a year, which implies a cost of 25,000 to 30,000 dollars for families; more than half of the average household income.

In Europe, as in the rest of the world, the price of new medication increases each year, threatening the sustainability of the healthcare systems, and making it more difficult for the most vulnerable to access treatments for diseases such as cancer. A study carried out in 2016 by the European Society for Medical Oncology (ESMO) in 48 European countries concluded that the high price is a factor that contributes significantly to the inequities in accessing cancer drugs in our continent (41) and it highlights large disparities in access in European countries that are closely linked to the economic development levels of the country and its income per capita.

Thus, it shows how countries in Eastern Europe, with much lower incomes suffer more shortages, they have a lower availability of drugs and their citizens have to assume larger expenses for their oncology treatment. In short, there is a direct consequence for patients to access the drugs that they need. For example, in countries such as Serbia, Slovakia, Croatia, Bosnia, Bulgaria, Macedonia and Poland, much of the medication to treat melanoma and renal cancer are not even included in the national list and, when they are, they are not reimbursed, meaning that patients have to pay for 100% of the treatment (41).

Spain is one of the countries in the OECD with the greatest healthcare coverage and access to drugs (42). However, according to data from the Spanish Ministry of Health (MSSSI) from 2016, 4.4% of the Spanish population cannot buy the medication prescribed by their doctor for economic reasons, (43); this converts to more than 2 million people.

Despite this revealing fact, there may still be the perception that the problem of the high price of innovation is far removed from countries like ours, with good healthcare coverage. However, other variables must be taken into account. According to the recent report from the Spanish Ministry of Health, antineoplastic drugs account for 11.5% of the total hospital drug expenditure and, specifically, monoclonal antibodies² experienced an expenditure increase of 13% between 2014 and 2015 (44).

This increase in drug expenditure forces cuts to be made in other areas in a healthcare system with limited resources. Cancer disease requires comprehensive care, beyond the treatment with drugs, which implies other medical specialities, services and levels of care (45). All those essential areas may be financially displaced in a scenario in which it is estimated that the area of oncology will continue to grow and will involve a more than 20% share of the hospital market (46).

In recent decades, medical innovation has substantially improved the lives of millions of people around the world. The challenge now will be for those improvements to reach everyone, leaving no one behind (47).

² According to the ATC Classification System: antineoplastic drugs (group L01) and monoclonal antibodies (group L01XC).

four.

THE ONCOLOGY MARKET

Cancer drugs make up one of the groups of medications with the highest prices and they illustrate a global problem. In the US the average price for new cancer drugs has multiplied by 10 in 15 years (38). In 2012, chronic myelogenous leukaemia experts from around the world warned of the high and “unsustainable” prices of these medications (48).

This progressive increase is an issue that concerns many public authorities, doctors, patients and researchers, and some studies suggest that the current pricing models are not rational, but rather they reflect what the market will bear (49). Besides, some of these drugs provide limited added therapeutic value. An article published recently in the British Medical Journal (50) concluded that more than half of cancer drugs approved in Europe between 2009 and 2013 do not present enough evidence that supports a significant clinical benefit in terms of survival or quality of life. In the US, a study published in 2014 showed that 48 of the new cancer drugs approved by the FDA between 2002 and 2014 only improved the patient's total survival rate by slightly over two months (51). Although it is very important to prolong the life expectancy of cancer patients by as much as possible, what seems questionable is that such high amounts of money are paid for these results, when these prices are already unaffordable for 20% of the Western population (52). This situation challenges the regulatory agencies criteria for approving drugs, in some cases without having clear evidences of its safety and effectiveness (50,53).

In Spain, a review of 40 highly priced oncology therapies, employed for the treatment of 13 tumours, showed that the total survival rate compared to the alternative was less than 3 months in 26 of the 34 therapies evaluated, and of the 6 that were not evaluated there was no information available in this regard. However, in 22 of the 40 therapies studied, there was an added cost of over 15,000 euros and, for example, 6 of those had increased costs of between 30,000 and 60,000 euros with a total increased overall survival of between 2 and 3.7 months (54).

In 2012, some doctors and the Memorial Sloan-Kettering Cancer Center (55) took the decision to not administer Zaltrap® to their bowel cancer patients and to continue with an alternative therapy due to the limited value added that was provided at double the price.

In 2014, it was considered that in 5 years (the year 2019), the global expenditure on medication would increase by 30%, to a large extent due to cancer drugs and immunosuppressives (36,37). The global expenditure on oncology treatments went from 107 billion dollars in 2015 to 113 billion dollars in 2016, and it continues to be the therapeutic area with the highest volume of sales (56). Furthermore, the oncology market is anticipated to grow between 6% and 9% a year until 2021, when the sales volume will reach 147 billion dollars (37).

4.1 PHARMACEUTICAL EXPENDITURE IN SPAIN

In Spain, the composition of the pharmaceutical market has been varying considerably in the past five years. At present, it is the hospital market that directs its growth and it is estimated that this will continue over coming years until reaching 11.3 billion in 2021, some 19% more than in 2016, largely because of new therapies and indications arising (46).

In 2017, the total expenditure on hospital drugs in Spain was 6.448 billion euros (57), which implied a growth of 3.3% compared to the previous year.

In 2015, 39% of this expenditure was due to 15 drugs (**Table 1**), four of which (trastuzumab, rituximab, bevacizumab and imatinib) are classified as antineoplastic drugs (group L01) (44). Farmaindustria states that in 2014, the expenditure on cancer medications was greater than 1.6 billion euros; almost 11% of the Spanish National Health System's total drug expenditure and 2.7% of the total spending on public healthcare (58,59).

Forecasts indicate that, despite biosimilars appearing, the oncology market will continue to grow as a result of new launches and indications and more immunotherapies being available.

Therapeutic group	Active Ingredient	Drug Expenditure* (LSP, million euros)	% of Total Expenditure
Antivirals	Sofosbuvir and Ledipasir	557.8	7.5
Antivirals	Sofosbuvir	364.2	4.9
Immunosuppressants	Adalimumab	303.7	4.1
Antivirals	Ombitasvir, Paritaprevir and Ritonavir	230.2	3.1
Immunosuppressants	Etanercept	174	2.3
Immunosuppressants	Infliximab	170.7	2.3
Antivirals	Simeprevir	162.3	2.2
Antineoplastics	Trastuzumab	136.7	1.8
Antineoplastics	Rituximab	121	1.6
Antineoplastics	Bevacizumab	118.1	1.6
Immunoglobulins	Inmunoglobulin intravenous (IgIV)	118	1.6
Antineoplastics	Imatinib	115.7	1.6
Immunostimulants	Interferon beta 1a	112.8	1.5
Antivirals	Tenofovir disoproxil y emtricitabine	112.5	1.5
Antihæmorrhagics	Factor VIII	106	1.4
	Total	2,903.7	39

Table 1. Fifteen Main Active Ingredients that Hospitals Spent the Most on, year 2015. Source: Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSI) (44). *LSP: Laboratory Selling Price.

Oncology has positioned itself as the most relevant therapeutic area in the hospital market, representing a share of 23.8% (46). It is a sector that has seen the average price of drugs have duplicated between 2011 and 2015. Whilst in 2011 the average price of a drug³ was 290.50 euros, in 2015 this figure was 593.50 euros (44).

4.2. HOW ARE PRICES FIXED?

The question about what determines the establishing and scaling of the prices of cancer drugs is essential and it has very few truly explicative answers. The pharmaceutical industry justifies the high prices because of the need to meet the high research costs. However, establishing the prices of drugs is a process that responds to criteria that seems arbitrary, and there are increasingly more opinions voiced about the way they are excessive and unsustainable (41,48). For some authors, it responds to a spiralling situation whereby the price of a drug has a constant annual increase with regards the previous year. New medication would adapt to the moment, establishing its price based on the market base (60). For others, there is more weight behind the reference price theory, whereby prices of new medication are established in line with the prices of existing therapy, adding an increase of 10-20% (33).

The current global system of establishing prices encourages the industry to mark the prices of the new, patented-protected medications in terms of what the market can withstand in order to obtain the maximum profit possible. Although this is the way of establishing prices in open exchange and competitive markets, it is worth questioning whether it is also the correct way of doing so in oligopolies where the main buyer is the State and with products that are essential for people's survival.

On the other hand, the current system encourages that, firstly, prices are negotiated in countries as they are in the US, guaranteeing the highest initial price that does not require a governmental agreement, in order to then individually negotiate in each country. This strategy gives way to the sequential launching of new medication (65), starting with the large markets and delaying entering into small markets and those with lower prices. For example, within Europe, pharmaceutical companies tend to delay requesting the authorisation of new drugs in Belgium, where prices are lower, and instead they generally start in countries that can pay more, with the aim of the external reference price⁴ not lowering (66). These prices are published without discounts⁵, so there is always the risk that the reference price is not true and more is being paid in some countries than in others (65). Thus, the prices of these drugs are different among high income countries, and variations can oscillate between 28% and 388% (67).

³ Average LSP of a formulation, for example, a vial.

⁴ In Europe in 2010 a voluntary collaboration project was put in place between countries with the aim of sharing the national prices of medication. The programme is called EURIPID and it contains data regarding the official prices of drugs that are reimbursed with public money, and that are published pursuant to the Transparency Directive 89/105/EEC.

⁵ In Spain, for example, laboratories are obliged to apply reductions to the maximum industrial price of medication for purchases made by the National Health Service's healthcare services and the pharmacy offices, apart from generic drugs or those that make up part of the groups to which the reference price system applies(243).

Price/ unit (tablet or vial)	South Africa (€,2017)	India (€,2017)	Austria (€,2013)	Spain (€,2013)	France (€, 2013)	UK (€,2013)
Abiraterone acetate	nd	2.03 €	27.50 €	nd	27.50 €	25.08 €
Bendamustine	nd	88.15 €	301.20 €	nd	273.81 €	283.28 €
Bevacizumab	188.20 €	340.30 €	1,338.00 €	1,272.90 €	1,088.80 €	1,085.10 €
Bortezomib	nd	171.70 €	1,166.00 €	1,120.10 €	1,043.90 €	894.91 €
Erlotinib	nd	4.33 €	68.97 €	68.18 €	67.45 €	63.84 €
Lapatinib	nd	nd	17.64 €	14.49 €	16.58 €	11.80 €
Lenalidomide	nd	2.03 €	260.72 €	250.78 €	165.16 €	184.88 €
Nilotinib	1.15 €	nd	23.34 €	24.16 €	24.25 €	25.50 €
Sorafenib	nd	0.81 €	35.70 €	30.44 €	28.83 €	31.24 €
Trastuzumab	716.29 €	790.04 €	690.00 €	596.52 €	536.87 €	478.22 €

NOTE: Price (LSP)/ unit (tablet or vial)

ND: No data available. This may be because the medication is not available, or because data regarding the price is not available.

Table 2. Price per Unit of Some Oncology Drugs in South Africa, India, Austria, Spain, France and the United Kingdom (UK). Source: Vogler et al. 2016 and Tomlinson et al. 2017 (67,68).

Table 2 shows the price per unit of some drugs in different countries. From this data it can be seen that, among other countries, Spain generally pays more than France or the United Kingdom and that, specifically, drugs such as trastuzumab have higher prices in South Africa than in Europe.

These strategies and dynamics are backed up by a market model that prevents the competition, through the shield that the current system of drug patents offers which, contrary to what it may seem like, has not always existed. In the US it was introduced at the beginning of the 20th century, and in Europe it started to appear in Germany and France in the 1960s and 1970s. In Spain it did not appear until the beginning of the 1990s (69).

The reasoning behind patenting biomedical innovations is based on the idea of rewarding the inventor or developer, with the aim of continuing to motivate investments in R&D, and to guarantee the recovery of the costs and a reasonable profit. As stated by some authors (69,70), the price established under the protection of the patent should cover said costs and profits. However, in reality it is not possible to know the real research costs as they are kept secret. Added to the commercialisation protection given by the patent monopoly, is the exclusivity of data and other incentives, such as supplementary protection certificates or legislation on orphan drugs. All of this allows companies to place themselves in a dominant position in the market, which allows them to establish the maximum price that the buyer can pay (69,71).

This give rise to imbalances between buyers and providers, has a direct impact on the public health system budget and allows the abuse and misuse of companies' dominant position that has nothing to do with rewarding innovation.

The system of giving incentives for innovation should have the aim of public and private research to generate innovations that society considers as priority and at the lowest possible cost (72,73). This is particularly true when data from the EFPIA (European Federation of Pharmaceutical Industries' Associations) shows that only 16% of total sales were allocated to research (74) and 21% to production (75) in pharmaceutical companies, whilst the gross profits⁶ of the largest companies in the sector are over 23% (76,77).

In developing countries, people struggle to pay for these products at prices far higher than the average income per inhabitant. In a situation in which there are no competitors, buyers are at the mercy of a sole provider that becomes the owner of the product and the holder of the patent (7). Of the 8.8 million deaths from cancer in the world these days, approximately 70% take place in developing countries (78).

This is a figure that would justify far more governments to make use of mechanisms, such as compulsory licenses, that would allow for the exploitation of a patent without the holder's consent for public interest⁷. In the field of oncology, a very well-known case of a compulsory license is that of sorafenib, a renal cancer drug. In 2012, the Indian authorities gave Natco Pharma Ltd. the green light to start to manufacture and sell the drug in the country (79). Another notable case that has taken place recently is that of Colombia, where the government has given a declaration of public interest over the drug Imatinib; which has led to the original price of the drug being lowered substantially (80).

On the other hand, in the quest to protect the market niche of a patented drug, the industry often resorts to strategies that avoid or delay the availability of generic or biosimilar drugs, which also multiplies the negative effects of the high prices (61). For this, it is common to find laboratories having large lawsuits with the aim of preventing generic drugs appearing as soon as their patent expires. However, there are other, more elaborate means, such as the pay-for-delay⁸.

⁶Gross profit or profit before tax (244).

⁷This is one of the flexibilities that the World Trade Organization Agreement allows regarding TRIPS (Trade-Related Aspects of Intellectual Property Rights). The same is also included in the Spanish Law on Patents, in Section 95.

⁸This strategy takes advantage of the Hatch-Waxman Act, passed by the US Congress in 1984, in order to encourage the production of generic drugs, and for which the first authorised generic drug has a 6 month grace period with exclusivity on the market. The laboratory that produces the branded drug also has the possibility of bringing out its own generic drug ("authorised generic") during the first 180 days of the generic drug's grace period, thus competing with its sales. With this threat on the table, the branded drug laboratory pays the producer of the generic to delay bringing the generic onto the market, in exchange for the promise of not competing with the authorised generic. By doing this, the manufacturer of the patented drug extends their period of exclusivity and the manufacturer of the generics gains an income in exchange for obstacles being in their way for the future launch.

In the US, the imatinib example illustrates this strategy. The laboratory reached a pay-for-delay agreement with Sun Pharma, a generics manufacturer, for them to delay the imatinib generic entering the market for 6 months after the patent had ended in July 2015. When it came onto the market in February 2016, it did so with a minimally lower price than the branded drug: 140,000 dollars/year, compared to the branded imatinib's 145,000 dollars/year. As the biosimilar was able to enjoy a six month period of exclusivity, the company could establish the price that it wanted and for 12 months, after the patent had expired, both laboratories upheld the high prices of imatinib thanks to this duopoly agreement (61). In Europe, in 2005 the European Commission fined AstraZeneca 60 million euros for the improper use of the patent system with the aim of blocking or delaying generics of omeprazol entering the market. The Commission concluded that they had abused their dominant position (81).

The pharmaceutical industry defends that the high prices of the innovations are inevitable due to the need to recover the R&D expenses involved in bringing a new molecule onto the market. Although this is an issue which is questioned by many due to the lack of transparency (73) in the data provided by the laboratories (72). According to a study from the Tufts Center for the Study of Drug Development in Boston (US)(82) the cost of developing a new drug reaches an average of 2.8 billion dollars. This is a figure that is accepted by the industry, although it is questioned due to the lack of methodological transparency and disclosure of data (83)⁹.

THE PRICING ARBITRARINESS: THE CASE OF IMATINIB

Imatinib (Glivec®, from Novartis) came onto the market in 2001 to treat chronic myelogenous leukaemia. In the US it cost around 2,200 dollars a month, which had been established using the price of interferon as a reference; this was the common treatment for this disease. At that point, a year of Imatinib treatment cost around 26,000 dollars. In 2016, it reached 146,000 dollars. It grew between 10 and 20% each year (61). When the patent expired in 2015, the laboratory had accumulated sales of 48 billion dollars (62).

It should be noted that the price of generic drugs is between 126-216 dollars per patient per year (63); that the research costs had been partly covered by public budgets; and that the laboratory invested less than 1 billion dollars in clinical trials (64). Taking into account the drug's yearly turnover, this figure was covered in the first year. Therefore, from that moment on the prices could have been nearer 100-200 per person/year and not above 20,000-100,000 dollars per patient per year.

On its part, the DNDI (Drugs for Neglected Diseases Initiative) calculates the cost of developing a new molecule to reach a maximum of 170 million dollars, also taking into account for the losses in unsuccessful molecules (84).

⁹In 2013, the CEO of GlaxoSmithKline acknowledged that the justifying of the high prices because of the R&D costs, then estimated at 1 billion dollars, was "one of the industry's big myths" (245).

The nature of the research costs may be very diverse and, on occasions, complex and it depends on the type of innovation. In other words, it depends if it is an active drug derivative, or on the other hand, a completely innovative drug.

In any case, different studies prove that in this development process the high proportion of

public investment in biomedical research must also be taken into account (85–87), this implies taking away costs from the calculations of the price of posterior R&D (69).

Thus, a study that analyses the clinical trials started between 2006 and 2013- registered in the ICTRP (International Clinical Trials Registry Platform) from the WHO- portrays that in the

PRICE-FIXING IN SPAIN

In Spain, establishing the prices of drugs is a process that begins with the Inter-ministerial Commission on the Price of Drugs (CIPM) from the Ministry of Health. The Commission, presided by the Ministry of Health, is also made up of representatives from the Ministry of Finance, the Ministry of the Economy, three Autonomous Communities and three others as observers. The CIPM is responsible for deciding the reimbursement or financing of each drug and of establishing a maximum industrial price (this price is proposed by the industry) and a financing price for the National Health System. In the case of hospital medication, this price is then renegotiated in each Autonomous Community, or even in each hospital. It must be pointed out that the three representatives from the CCAA and the three observers rotate every 6 months. This makes it difficult to monitor and participate in decision making, despite them being the ones to pay the pharmaceutical bill.

On a regional level, the final price depends on the negotiation process between the authorities and the pharmaceutical companies, by means of different types of agreements, applying public procurement procedures.

Generally speaking, the final price of hospital drugs approved by the CIPM is lowered through these negotiations. But if these initial prices approved by the CIPM are very high, these negotiations in health centres and health services allow for a very moderate adjustment. Thus, the price defined by the CIPM decisively influences the price that will finally be paid for the drug.

Recently, the regulation, composition and agreements of the CIPM have been published. This is a step forward towards improving the transparency, although it is insufficient despite the repeated requests from scientific societies, professional and social groups and recently the Court of Audit (91). This, in its latest report on the MSSSI's economic activity stated the non-existence of procedures about functions and responsibilities with regards to pharmaceutical policy, as well as the lack of evaluation criteria for the inclusion of drugs in the pharmaceutical provision and establishing of its prices. Congress has recently insisted that the government takes on its recommendations (92).

group of high income countries, 51.6% of the trials were not financed by the industry (87). Another piece of research outlines that of the total global R&D investments in health carried out, 60% come from the business sector, 30% from the public sector and approximately 10% from other sources (including private, non-profit organisations) (86).

In the specific field of oncology, a recent study notes that the average cost of developing a new cancer drug is 648 million dollars. Using this figure as a reference, and taking into account that the average profit generated by a drug reaches 1,654.4 billion (88), it is estimated that in less than four years, companies recover their investment and generate an income from commercialisation that is 10 times more than that spent on R&D.

Not knowing the cost of a drug and the mechanisms used to establish its price are elements that force a deep reflection about the lack of transparency in a sector which often receives transfers and reimbursements from the State. As citizens, we pay the bill with our taxes, but the current system still lacks many mechanisms that guarantee an adequate accountability (32) regarding the expense it involves for the Spanish treasury. In this regard, with innovative drugs, and specifically with cancer drugs and therapy, there is still a lot of work to do.

At the same time, this opacity reaches the price agreements in each country, where the confidentiality clauses (89) prevent us from having knowledge of the real price of drugs.

In the case of Spain, where the Autonomous Communities pay, this gives rise to price differences between regions and even among hospitals, which has repercussions on the sustainability of the system.

This is a situation in which questions about the costs and prices of drugs do not have an answer, nor do other relevant aspects such as, for example, clinical trials and the publishing of their results (90).

In short, all these issues are favoured by a regulatory environment, at a national, European and international level, which does not allow for the approach of the current unbalance between business profits and public interest (70). Added to this is the intellectual property incentive system which encourages the generation of a situation of high prices and huge profits.

EU experts have warned about this issue and, in their latest report, called for the adoption of transparency measures, including the knowledge of the real prices and costs of R&D, the review of the current innovation model based on patents and market exclusivity and the study of alternative mechanisms to encourage research (72). The oncology sector is currently anticipated to be the most profitable area in a context in which the pharmaceutical industry maintains its global growth (33,56,93).

INTELLECTUAL PROPERTY INCENTIVES

Patents and data and market exclusivity make up the main incentives for innovation in cancer drugs granted by States and regulatory agencies.

Patents as an intellectual property incentive are considered as a form of recognition for the invention. They prevent third parties from manufacturing, reproducing, selling or using, in the case of procedures, the patented technology, apart from with the patent holder's authorisation or granting. There are numerous and varied patents surrounding a drug, affecting all processes, from basic research to its indications. They are bestowed by intellectual property or national or international patent offices and each patent is valid for 20 years from the moment it was requested (94). Thus, it is common to find drugs protected by a hundred patents that have accumulated over the years, from the active ingredient to the indications or pharmaceutical forms, creating a true protective architecture. Furthermore, the supplementary protection certificates (SPCs) allow for the patent on an active ingredient to be extended for a maximum of five years after the patent expires.

The Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement also include a certain degree of flexibility which enables, for matters of health, for public interest to prevail. In this regard, there are mechanisms, such as compulsory licenses, through which States can make governmental use of the intellectual property, or they can force the patent holder to license it to a third party in order to produce generic drugs for public health reasons (95,96).

However, in recent years, some countries have had to take on more restrictive conditions regarding the protection of intellectual property in the commercial negotiations with the US and Europe. These agreements, known as "TRIPS-Plus" allow for patents to be extended and for the exclusivity of data, they protect the secrecy of the negotiations and they limit the use of compulsory licenses, among other issues, putting the access to drugs at risks (97,98).

The regulatory agencies grant data and market exclusivity. All new medication authorised in Europe is granted eight years of data exclusivity and an additional two years of market exclusivity. This means that for 10 years from its authorisation, the drug is protected from competitors entering the market, generic drugs for example, and this can be extended for one year if new indications are approved during this time.

There is also a series of compensations and incentives that aim to encourage the research and development of paediatric drugs and drugs for rare diseases (orphan drugs). If a drug is designated as an orphan drug, it is granted 10 years market exclusivity, a tax reduction for clinical trials and scientific-technical assistance from the European Medicines Agency (EMA), and the possibility of carrying out a single, centralised procedure of orphan authorisation (99). In the case of paediatric drugs, they have a supplementary protection certificate extension of 6 months and 2 extra years of market exclusivity should it be classed as an orphan drug, as well as free scientific support (100).

five.

PUBLIC INVESTMENT IN CANCER R&D

Research and innovation are determining elements so as to ensure that society prospers in all fields. Biomedical R&D specifically, from its most basic and fundamental slant up to clinical research, is a starting point for a greater knowledge of diseases, their causes, consequences and dynamics; a greater advance in prevention and diagnosis; the incorporation of new, safer and more effective treatments; and the definition of improved strategies that contribute to improving the health and social well-being of everyone. And, in order to achieve this, it is essential to have a clear public commitment to the sufficient resources in order to guarantee a competitive, high quality science that is people-focused.

In Spain, the lack of funding in science and the reduction in resources destined for R&D is a recurring problem this decade, with notable effects in the public and private scientific sectors (101). In the public sector, the austerity policies resulting from the 2008 economic crisis weakened the science and innovation budgets and, despite the increase in attracting funding from European R&D programmes, these do not compensate for the reduction in resources.

In 2016 the total expenditure on R&D in Spain increased by 0.66% compared to the previous year, making up a figure of 13.26 billion euros. However, this figure is only 1.19% of the GDP, far below countries such as the United Kingdom (1.69%), France (2.25%) and Italy (1.29%) and it decreased for the fifth consecutive year. In the EU, the average that year was 2.03% (102).

Whilst the EU28 group currently invests 25% more in R&D than it did before the economic crisis, our economy invests 10% less (103). Spain has not recovered the 2008 investment levels. Furthermore, at present, the accumulated decline brings us back to the 2004 investment levels.

According to OECD data from 2014 (104), R&D in health¹⁰ in Spain made up 20% of the total R&D expenditure, some 2.5 billion euros. Of this, governmental institutions assumed 40% of the cost, nearly 1 billion euros (**figure 3**). The expenditure in R&D in the health sector in 2008 was 2.645 billion euros and it reached its maximum in 2010 (2.76 billion). In 2014, the 2008 levels had not even been recovered.

5.1 CANCER RESEARCH IN SPAIN

Just like in other fields, basic, translational and clinical research in oncology is essential (105,106) and their interrelationship and complementarity are of utmost importance. Just as many leading research groups acknowledge (107,108), maintaining this alongside an increase in public investment is not just fundamental but it is also a true necessity so as to advance in the fight against cancer.

In Spain, the first Oncology Congress took place in 1982 (106), but it took a few more years for research in cancer to really get going.

¹⁰ Pursuant to the OECD's NABS2007 classification (Nomenclature for the Analysis and comparison of Scientific programmes and Budget), this category includes everything related to the protection, promotion and recovery of human health. It includes the prevention and monitoring of infectious and chronic diseases, monitoring the state of health, promotion of health, occupational health, public health (management and regulation), health services, nutrition, food safety, medical attention for the at risk and vulnerable populations (246).

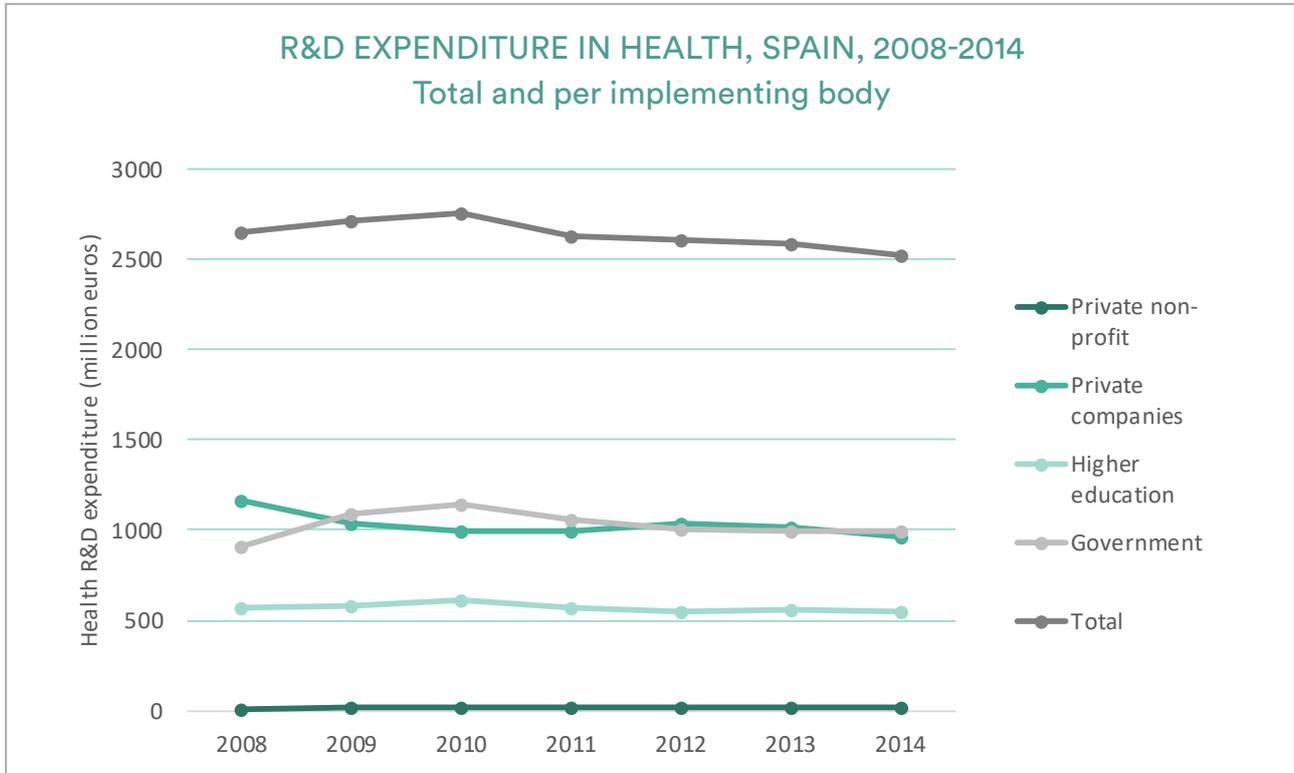


Figure 3. R&D Expenditure in Health in Spain 2008-2014. Total and per Implementing Body¹¹. Source: OECD (104). Prepared by the authors.

At the beginning of the 1990s industry collaborations started to spring up, the Spanish National Cancer Research Centre (CNIO) was created in 1998 (109) and specific research projects got under way with a public investment of around 500 million pesetas per year, which converts to about 3 million euros.

Today, 20 years later, the data about aid and final projects states that between 2009 and 2016, approximately 88 million euros was invested in cancer-related projects through aid from the

Spanish Ministry of Economy, Industry and Competitiveness (MINECO), in the SAF/biomedicine area¹².

Similarly, between 2008 and 2017, 143 million euros were invested through Health Research Funds (FIS) from the Strategic Action in Health from the Ministry of Health (MSSSI). The data also shows that two thirds of these funds was allocated to research centres in Madrid and Barcelona (**Figure 4**).

¹¹ According to the OECD classification, the “higher education” sector includes universities, schools and other higher education institutions, as well as research centres, research institutes and hospitals associated with research activity.

¹² Aggregate data regarding the financing of cancer programmes from the MINECO between 2009 and 2016 (both inclusive). See searching and analysis methodology (annex).

These lines of financing are the most representative in the field of biomedical R&D in Spain¹³. When compared with other sectors between 2010 and 2016, the main areas that received funds¹⁴ were cancer and molecular and cellular biology, with a total of 228 million in projects subsidised by the MINECO.

In terms of the contributions and/or loans to projects with companies in the Centre for the Development of Technology during the same period, oncology is the therapeutic indication with the largest investment of the 25 established, with 52 million.

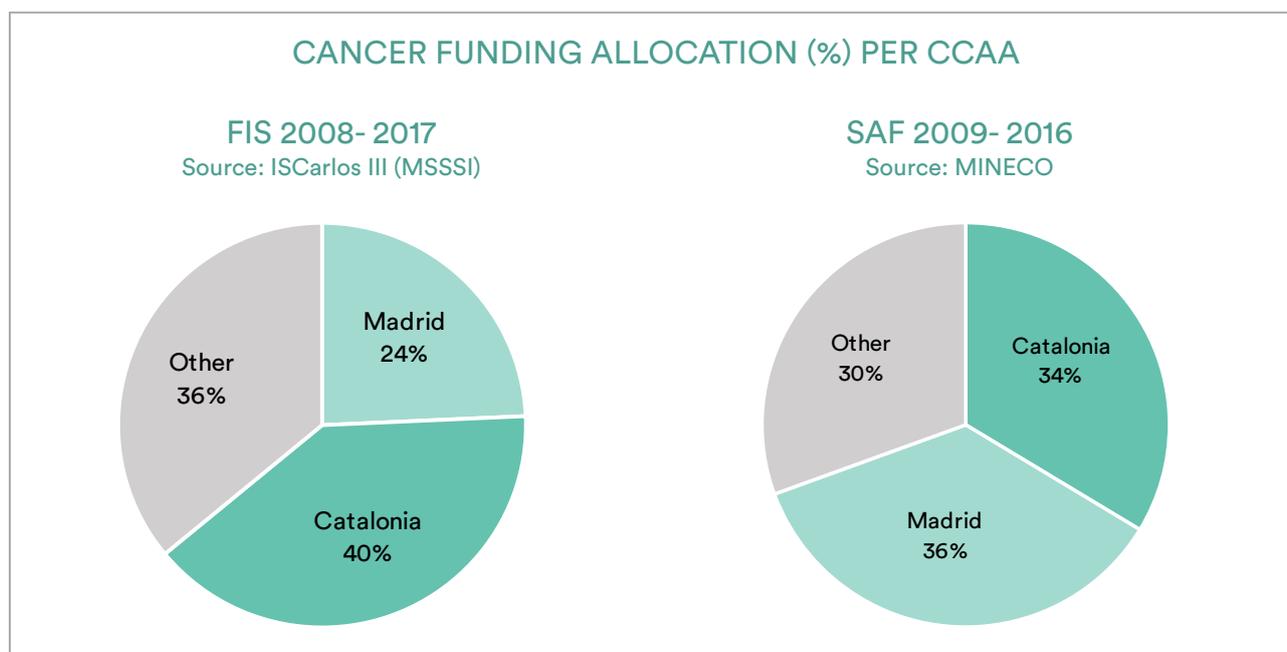


Figure 4. Allocation of FIS and SAF Funds per Autonomous Community. Source: data from Carlos III Health Institute (MSSSI) and the Spanish Ministry of Economy, Industry and Competitiveness (MINECO). Prepared by the authors.

¹³ This chapter only reflects the public investments in State-called for projects. On the one hand, managed by the Ministry of Health together with the Carlos III Health Institute through the Strategic Action in Health and, on the other hand, the MINECO through the State Scientific and Technical Research Plans. Investment in the CNIO and other public centres with their own budgetary lines is not added to this data, nor are the CCAA contributions.

¹⁴ This data makes up part of a report on Public Interest Criteria in Biomedical R&D in Spain, carried out by the Right to Health (Salud por Derecho) Foundation and will be presented in 2018.

With regards the EU Framework Programmes, it can be noted that Spain participated in a total of 277 cancer-related projects between 1998 and 2013 through the different EU multi-year projects and in line with data gathered from CORDIS¹⁵. Of these, 89 projects were financed between 2007 and 2013, making up a total of almost 430 million euros, of which more than 75 million was allocated to participating Spanish centres¹⁶ (110). According to the European Commission, between 2007 and 2013 a total of 1000 cancer-related projects were financed in Europe with a value of 1.5 billion euros. The European programme Horizon2020 which is currently being developed already has a total of 272 cancer-related projects, with a total allocation of 415 million euros (111).

If we compare with other countries, the investment in cancer between the US and the UK in 2007, for example, was over 1 billion euros annually (112). The average investment per capita in the US was 19.34 euros (112), whilst in Europe it was 3.45 euros. These are some differences that show how investment in science is valued as a public policy in the US and how it is one of the main driving forces in the development of medication and health technology. Spain is far behind these public investment figures, but it is also important to bring to light the presence of other types of investment that the report does not quantify, but that carry out an

essential role in many research centres and universities. This is the case of La Caixa Foundation (113) the Spanish Association for the Fight Against Cancer (AECC), (114) the Cris Cancer Foundation (115) or the BBVA Foundation (116), among others, as well as investment from the pharmaceutical industry itself (117).

On this line, and to complete the bigger picture with regards clinical research, Spain does stand out in terms of clinical trials dedicated to cancer. The first piece of data is obtained from the Spanish Register of Clinical Trials (REEC), which gathers 1,052 results regarding cancer-related clinical trials published since 2013 in Spain (a total of 3,200) and that, according to that reported, involved a total of 359,043 patients¹⁷.

In Spain, a third of all CTs are cancer-related, which is far above the European average of 24% (118). One of the key reasons behind this has been the passing of the Royal Decree on Clinical Trials 1090/2015 which, among other things, encourages them to be carried out in our country as it is one of the European Countries with a smaller time frame to start clinical research of a drug, some 139 days from the documentation being presented until being trialled by the first patient.

¹⁵ CORDIS is the European Commission's database comprising of the projects financed by European funds through the European Union Framework Programmes. FP5, FP6 and FP7 correspond to Framework Programmes in the periods 1998-2002, 2002-2006 and 2007-2013 respectively. Horizon2020, the current financing programme, has been in place since 2014 and will continue until 2020 with a budget of 77 billion euros (247).

¹⁶ Aggregate data on the financing of cancer-related programmes gathered from CORDIS. Programmes prior to FP5 are not reflected due to lack of complete data. See methodology (annex).

¹⁷ The Spanish Register of Clinical Trials collects the total number of patients involved in the trial. It should be highlighted that a large number of these are take place in multiple centres, involving patients from many other centres outside of Spain.

Spain was the fourth country in the European Union in terms of CTs in 2017, behind France, Germany and Italy and ahead of the United Kingdom, and 50% were developed by the pharmaceutical industry (118). On this point, two aspects must be highlighted. One the one hand, the National Health Service's patients' commitment to science, as their results ensure that developments are made with regards drugs and health technology that may benefit other patients in similar situations. Secondly, the altruism in their decision to participate in a trial which has an aim that goes beyond them and is at the service of society.

In this context of basic and applied research, numerous debates have emerged regarding the necessity to guarantee independence in these medical and institutional processes.

If the oncology market has a huge potential for the pharmaceutical industry, its interrelationship with doctors and institutions, especially during clinical trials, should include a complete series of guarantees.

In this ground, where the public space and private interest come together with the altruistic collaboration of patients, experts and doctors, it is essential to place focus on some aspects that deserve special care with regards individual-institutional-industrial relations, primarily highlighting the need for transparency in the rules of the game, scientific rigour and absence of conflicts of interest (105,119,120).

six.

CASE STUDIES

6.1. TRASTUZUMAB

Trastuzumab is a monoclonal antibody¹⁸ that acts on a type of tumorous cells that have a larger amount of a protein (or receptor) called HER-2 on their surface. This protein is responsible for the excessive growth of these cells, and thus, of the tumour. Therefore, these tumours are referred to as HER-2 positive. In the case of breast cancer, approximately 25% of cases involve HER-2 positive tumours. They are categorised by the fact that they tend to grow more quickly and have a higher possibility of relapse than those that do not have HER-2 in their cells (121–123).

Trastuzumab is able to recognise the HER-2 positive tumorous cells that grow uncontrollably. They attach to the HER-2 receptors on the surface, indicating to the immune system that it should destroy the tumorous cell. As a result the tumour stops growing. This drug is sold by Roche as Herceptin® and was approved by the FDA in 1998 and by the EMA in 2000. It is indicated for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer.

Since 2015, the WHO has included it in its list of essential medicines (124). However, cases such as Tobeka Daki (125) cast doubt on its accessibility in many countries, mainly due to its high price.

In Spain, the Inter-Ministerial Commission on Pharmaceutical Prices does not make public the negotiated price for hospital drugs in the National Health System. Regulations impede the reimbursement price approved at a State level for national health centres from being made public. According to public procurement publications from the Basque Country, a vial of trastuzumab bought in 2015 has a price of 507.04 euros (130). In line with reports published on the Spanish Society of Hospital Pharmacy Genesis Group website, this price varies slightly depending on the hospital¹⁹ (131–134). Using this data, the approximate cost of metastatic breast cancer treatment would be 12,000 euros per patient²⁰.

Trastuzumab biosimilars have started to appear in Europe. Ontruzant (Samsung Bioepis) was approved by the EMA in September 2017 (135) and there are another few in phase III and/or that have requested approval. The following figure among the latter: Mylan/Biocon, Celltrion, Pfizer and Amgen/Allergan (136–138). The price that Ontruzant will have in Spain is still unknown.

¹⁸ Antibodies are substances produced in our bodies by our immune system cells to fight against infections and other foreign agents. Monoclonal antibodies are antibodies that are synthesised in a laboratory and designed to recognise and attack specific tumour cells.

¹⁹ The price per vial of Herceptin® 150mg is 620.38 euros according to data from reports from the Hospital Virgen del Rocío and Hospital de Cabueñes, and 573.85 according to the ICO report (Catalan Institute of Oncology).

²⁰ These calculations only include the cost of the drug (trastuzumab) for a 70kg woman who receives an initial dose of 4mg/kg followed by a weekly 2mg/kg for 6 months.

THE TOBEKA DAKI STORY

Tobeka Daki was a South African activist who fought for the access to trastuzumab and who passed away from breast cancer in November 2016. Despite being a good candidate, she could never access treatment because of its high price: one year of treatment cost 5 times her annual salary. It is unknown whether or not this treatment would have saved her life, but what is known is that she was denied the opportunity to try it.

The leadership and commitment from this activist inspired the Tobeka Daki Campaign for Access to Trastuzumab which in 2016 launched the coalition Fix the Patent Laws²¹ (126) to ask for an improved access to this drug.

In South Africa trastuzumab costs more than 700 euros per vial in the public sector, far more than in other countries such as the United Kingdom or France (68), this is unaffordable for a country with such devastating statistics: more than 50% of the population live under the poverty line (127) and it is ranked 119 out of 188 in the Human Development Index (128).

Hundreds of women live with cancer and organisations from around the world came on board with Tobeka's fight to demand the pharmaceutical company to lower the price. A similar campaign, Campaign for Affordable Trastuzumab (129), is also under way in India.

In India, CANMAb, the Mylan/Biocon biosimilar has been available since 2014. Roche accepted a voluntary license, in order to avoid the Indian laboratory Biocon resorting to requesting a compulsory licence, lowering the price of trastuzumab in India at that point from 2,000 dollars to 1,300 dollars per vial, a price that in 2014 was still out of the reach of the majority of the population in India but that allowed them to keep the battle of the compulsory licence at bay (139,140).

THE HISTORY OF TRASTUZUMAB R&D

The relationship between the HER-2 receptor and breast cancer was proven in the 1980s, mainly thanks to research headed by Dennis Slamon, a scientist from the University of California Los Angeles (UCLA), who, together with his team at the National Cancer Institute (NCI), was able to prove that there was a correlation between the presence of this receptor and an increase in the aggressiveness of breast tumours (141).

²¹ Fix the Patent Laws is a coalition made up of the Médecins Sans Frontières' access to medication campaign (248), and Treatment Action Campaign, a South African organisation that had an important role at the end of the 1990s defending the access to VIH treatments. At present it fights to defend the right to health from different perspectives (249).

Years later, and thanks to collaborations established between Dr. Slamon and many other researchers, it was able to be demonstrated that the union between HER-2 specific monoclonal antibodies and the cells causing the tumour led to the tumour stopping to grow (141). Based on these advances, Genentech, a then biotech innovator, developed this new monoclonal antibody alongside the UCLA. But a change in management led Genentech to withdraw its support, stopping to finance the cancer research due to lack of profitability (142). Despite all of this, Dr. Slamon continued forward with the conviction that a promising path was being uncovered with the discovering of a drug that would cure patients²². In 1990, thanks to contributions from philanthropists Lilly Tartikoff and Ronald O. Pareman, and many other private individuals, the development of trastuzumab was kick started and the first clinical trials began (142). This same year, Roche bought 60% of Genetech (143).

After these first stages of clinical development, Genetech regained interest in trastuzumab, seeing that it could effectively be a promising drug, and the first clinical trial in humans took place in 1993. From 1989 to 1997, contributions from philanthropists totalled more than 13 million dollars, allocated to the UCLA, thus acting as a safety cushion from the economic downturns caused by Genetech's continuous coming and going.

In 2009, Roche completed the acquisition of Genetech (144) for 36 billion euros. These days, trastuzumab is still one of Roche's top sellers and, since it went on the market, has accumulated sales of a value of more than 65 billion euros.

TRASTUZUMAB AND THE SHIELD OF PATENTS

Trastuzumab illustrates an example of a drug that has a complex framework of patents that shield the medication in all its scopes. From the antibody itself to its methods of production, its indications, means of administration, tumour diagnosis techniques and even possible combinations with other drugs. We are witness to a drug that started to be patented in 1992, and still, in 2015 was registering new patents(145).

Of all of these, Genetech claims that it still has at least 40 ongoing patents on trastuzumab (146), through which it has had disputes with other companies as it tries to delay the entrance of biosimilars onto the market. There are also various patents that have renewed their validity through the introduction of small modifications. The monoclonal antibody, for example, was first patented in 1994 (147) and was patented 7 more times until 1998 (147).

²² The story of Herceptin® has been taken to the big screen with the film "Living Proof", starring Harry Connick Jr, based on the true story told in Robert Bazell's book "Her-2".

PUBLIC R&D INVESTMENT

Since the year 2000²³, 1694 projects on the study of trastuzumab have been financed with public funds in the US, adding up to more than 700 million dollars (148). Of these, 145 were allocated to the University of California System, with a total of 67.2 million dollars, and 102 to the National Cancer Institute with a total allocation of 76.8 million dollars. According to data published, in Europe there have been 12 trastuzumab projects since the year 2000 which total a public contribution of almost 14 million euros, of which over 2 million were allocated to Spanish centres²⁴ (110).

Much like in the preclinical stages, public contributions during the clinical development of trastuzumab were particularly relevant. The analysis of data obtained from American and European clinical trials (149,150), illustrates that (**figure 5**): of the 641 trastuzumab clinical trials²⁵ registered in Europe and the US from 2004 and 1998, respectively, almost half were carried out with non-commercial purposes and with funding coming from universities, research centres and non-profit foundations. Around a third (32%) of these trials were funded exclusively by the industry and 21% received a combination of funding, split between universities, research centres, foundations and the industry.

In the analysis per clinical stage of the trial, universities, public centres and foundations led and financed more than 50% of the phase II clinical trials, those in which the clinical efficacy and optimal dose is determined in patients. In terms of countries, the US notably held the highest amount of clinical trials, followed by China. In Spain, a total of 112 clinical trials have been registered since 2004, according to data from the American, European and Spanish registers of clinical trials. Of those, the Spanish Register of Clinical Trials, which started to register trials just 4 years ago, notes 11 trastuzumab clinical trials which, according to the information available, involved more than 3000 patients²⁶.

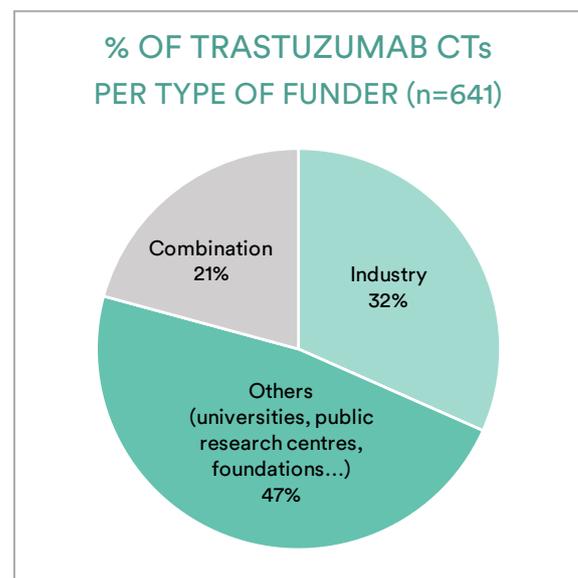


Figure 5. Percentage of Trastuzumab Clinical Trials per Type of Funder. Source: European and American clinical trials registers (149,150). Prepared by the authors.

^{23, 24} Investment data prior to the year 2000 is unknown. See the annex to consult methodology.

²⁵ See the annex to consult methodology.

²⁶ It is unknown how many of these patients participated in Spain. Data from the REEC does not consider this breakdown.

INDICATIONS AND ANNUAL SALES

Trastuzumab (Herceptin®) accounts for 18% of Roche's sales and 63% alongside bevacizumab in oncology sales. In 2017, the global sales of trastuzumab reached 7.014 billion Swiss francs, some 6 billion euros (151). According to data from the laboratory itself, since this drug was brought onto the market in 1999, the company will have accumulated more than 65 billion euros in sales (151–168) (**figure 6**). From 1999 to 2017 trastuzumab registered a constant increase in its sales, supported by later launches of its subcutaneous formulation.

As with other cases, the architecture of patents safeguards the laboratory's property and responds to a strategy that allows for the entrance of competitors on to the market to be delayed for a maximum period of time (169). The same happens when new formulas of the same drug come about, with different pharmaceutical forms or routes of administration. Although the trastuzumab patents may have expired, the new formulas will allow for the product to be protected again and to be differentiated from the new biosimilars on the market that still have the original intravenous formula, and thus are less attractive.

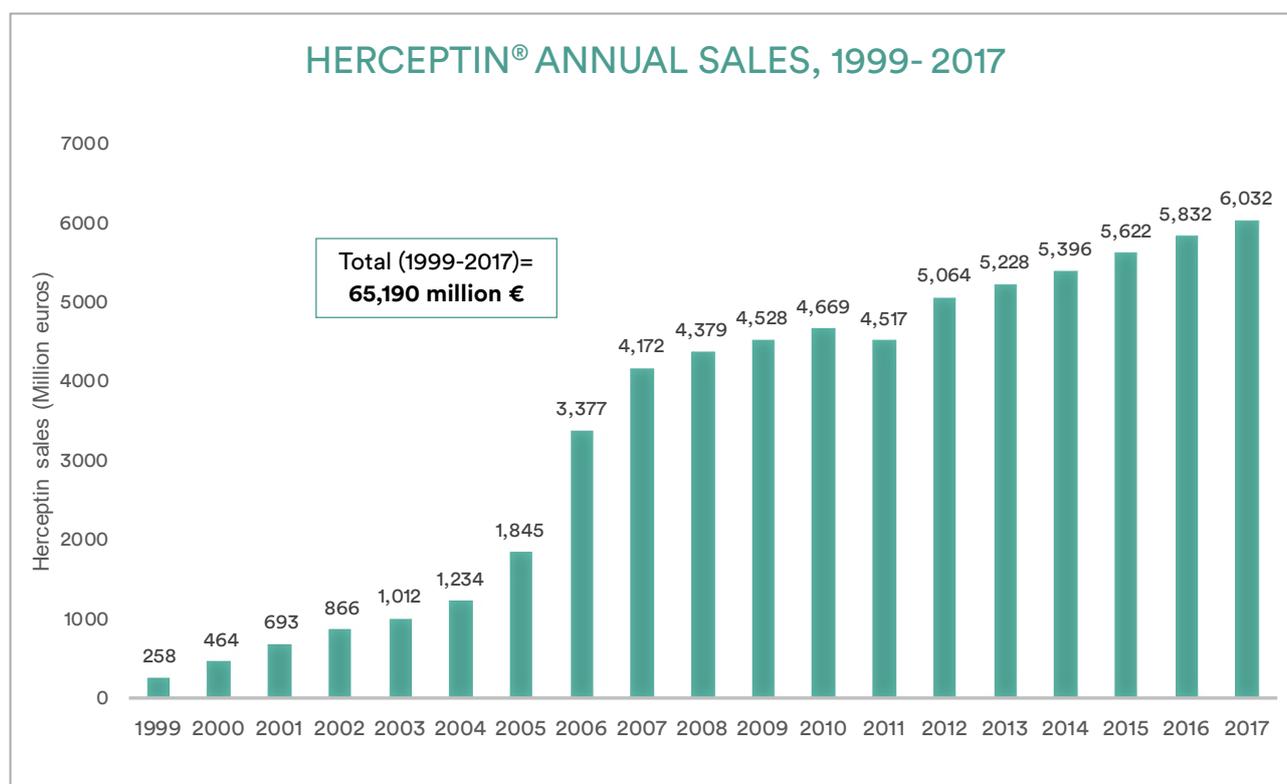


Figure 6. Total Sales of Herceptin® Since Its Approval (1999-2017) Source: Roche annual reports (151–168). Prepared by the authors.

6.2. ALEMTUZUMAB

Alemtuzumab, originally known as Campath-1H, was the first humanised monoclonal antibody²⁷; an advanced version compared to previous attempts and very promising for many researchers at the University of Cambridge who were having breakthrough discoveries in this area (170,171). This molecule was first used in the 1980s in the field of transplants. Its potential in leukaemia and autoimmune diseases was soon discovered and it was used to treat multiple sclerosis for the first time in 1991 (172,173).

Alemtuzumab was approved in Europe for the first time in 2001 for the treatment of chronic lymphocytic leukaemia (CLL) under the name of MabCampath® and marketed by Bayer-Schering. However, in 2012 it was withdrawn (174,175) and relaunched in 2013 as Lemtrada® for the treatment of relapsing-remitting multiple sclerosis (RRMS). It is marketed by Genzyme- Sanofi, and according to their last annual report, it will not lose its patent until 2027 (176).

Alemtuzumab for MS was approved later in the US due to its “questionable” safety profile. Upon its approval in 2014, the FDA created a special requirement in order to more carefully control the safety of the new drug and ensure the long term positive risk/benefit balance of the drug (177,178).

In Spain, Lemtrada® is authorised by the Spanish Agency of Medicines and Medical Devices (AEMPS) and reimbursed for hospital use. According to published reports²⁸ (179,180), the price per vial is 7,250 euros (LSP) and the cost for 2 years of treatment²⁹ is around 58,000 euros, at least a 15-fold increase per vial compared to the previous MabCampath® (table 3). The calculations carried out from the data available allow for us to estimate a difference of around 56,000 euros per treatment per patient. This would imply a saving of more than two million euros if patients with RRMS in Spain were treated with MabCampath®³⁰.

²⁷ Type of antibody produced in a laboratory through the combination of a human antibody with a small portion of a monoclonal mouse or rat antibody.

²⁸ The price of Lemtrada® is not published on the Spanish Ministry of Health website (Inter-ministerial Commission on the Price of Drugs). The price of MabCampath® is published (around 1200 euros/vial according to a 2008 agreement) (250).

²⁹ Calculation undertaken based on the treatment regimen for RRMS treatment, considering the initial administration of 12mg/day for 5 days (course 1) and, 12 months later, a second course of 12mg/day for 3 days (179), after which the patient is monitored for 4 years.

³⁰ Calculation carried out based on the following assumptions: in Spain there are 36,800 RRMS patients (80% of all MS patients). If all the RRMS patients were treated in the same year in Spain, the system would have to pay:

- MabCampath®: 1277.45 euros/treatment x 36,800 Pt.= 47,010,160 euros

- Lemtrada®: 58,000 euros/treatment x 36,800 Pt.= 2,134,400,000 euros

Brand name (alemtuzumab)	Indication	Price (LSP)	Formulation	Price (LSP) / vial	Dose (mg/day)	Days / course	TOTAL (€)
MabCampath®	RRMS	1,197.61 €	30mg/ ml 3 vials 1 ml sol inf	399.20 €	12	5 (course 1) 3 (course 2)	1,277.45 €
	RRMS	1,173.66 €	10 mg/ ml 3 vials 3ml sol inf	391.22 €	12	5 (course 1) 3 (course 2)	1,251.90 €
Lemtrada®	RRMS	7,250	10 mg/ml 1 vial 1.2 ml conc sol inf	7,250.00 €	12	5 (course 1) 3 (course 2)	58,000 €

Table 3. Estimation of the Price of Complete Alemtuzumab Treatment (Drug Only) in Multiple Sclerosis Using MabCampath® or Lemtrada®. Source: SEFH and MSSSI.

MS is one of the most common neurological diseases among 20-30 year olds (181). In global terms, it affects more than 2 million people. In Spain, some 46,000 people suffer from this disease, and the average age at which it is diagnosed is 35 (182); one of the highest in the European Union.

Depending on the course of the disease, it is classified into different types. Relapsing-remitting multiple sclerosis (RRMS) is the most frequent (around 80% of MS). It takes this name as it is characterised by its unpredictable attacks of symptoms, 'relapses', that repeat throughout the duration of the disease.

At present, there is still no cure for MS. The treatments that currently exist aim to delay or stop the disease, acting on the acute relapses, alleviating symptoms and reducing the number of relapses or the evolution of the disease.

Recently, the FDA (March 2017) and the EMA (January 2018) have authorised a new drug, ocrelizumab (Ocrevus®, from Roche), which seems to have a superior effect to other drugs. In the US the price is established at 65,000 dollars per year (183). In Spain, the reimbursement and price established is still pending (184).

THE CAMPATH® / LEMTRADA® CASE

Through Milstein and Köhler's pioneering research on monoclonal antibodies in the mid-1970s, the immunologist Herman Waldmann, also at the University of Cambridge, started to apply these findings to the area of transplants. With funding from the MRC (Medical Research Council, United Kingdom), in 1980 Waldmann was able to develop an antibody called Campath® (from Cambridge Pathology). The rights to develop Campath® were given to the British Technology Group (BTG), which at the time was a public company that licensed and marketed this finding.

After the first clinical trials in patients, in 1985 the BTG licensed the rights to develop and commercialise the drug to Burroughs Wellcome, who continued with the development of Campath® alongside the University of Cambridge (185,186). Later work, also by Waldmann, improved the original molecule and its results. Campath-1H was tested that same year on the first patient, and in following years it was studied for the treatment of other diseases such as lymphomas, leukaemia, rheumatoid arthritis and multiple sclerosis. Clinical trials for multiple sclerosis (MS) began in 1991. Years later Wellcome transferred the development and commercialisation rights to Leukosite and ILEX, and in 1999 they established a supply contract for the manufacture of alemtuzumab with Schering. In 2001, alemtuzumab (MabCampath®) was approved in Europe for the treatment of chronic lymphocytic leukaemia (CLL).

Throughout this whole time, alemtuzumab trials on MS continued to take place at the University of Cambridge, and in 2002 they had data from 58 patients (187). These trials were carried out almost entirely with public funding. Funding from the industry came about in

development phases II and III. As reported by the University of Cambridge, this investment was just under 2 million pounds sterling (188). Private investment came at the hands of an agreement with ILEX, until this company was acquired by Genzyme in 2004, making it the licensee and holder of the development and commercialisation rights of alemtuzumab.

Schering, which was part of the alemtuzumab commercialisation agreement for CLL, was acquired by Bayer in 2006. Bayer-Schering transferred those rights to Genzyme, but reserved the right to co-promote the development of alemtuzumab in MS (189). After two years of intense negotiations, in 2011, the French company Sanofi bought Genzyme for 20 billion dollars. The agreement came through a Contingent Value Rights (CVR) (190) structure, through which the Genzyme investors received additional payments for alemtuzumab sales pursuant to a series of milestones.

That negotiations were framed by the discussion regarding how much economic profit alemtuzumab could generate once its indication had been approved in MS. The debate was mainly based around its price: if the price of alemtuzumab for MS was the same as it was for CLL, some 7,000 dollars per treatment, the profits anticipated by Sanofi would not be reached (185). Furthermore, the MS market was moved by other figures: the average price of competitor MS treatments in the US was 36,000 dollars per treatment. Sanofi needed to find a way of differentiating the price of alemtuzumab for MS from that of alemtuzumab for CLL so that it was in line with the price of existing treatments.

In 2012, Sanofi withdrew MabCampath® (alemtuzumab for CLL) from the market, claiming it was for “commercial reasons” (174,191). Regardless of how the future of alemtuzumab in MS would be, the drug had already generated sufficient profit from its sales in the field of oncology. This same year, Sanofi submitted a new application to FDA and EMA for the approval of alemtuzumab for MS. An article in *The Lancet* (191) already showed concern for the possible price increase of the drug for MS and the supply problems that CLL patients being treated would face after Campath® was withdrawn from the market.

More than a year later, in 2013, this price increase was confirmed when alemtuzumab was approved by the EMA for MS treatment as Lemtrada® (192,193). The current price per vial of Lemtrada® is 15 times greater than the price of MabCampath®. The cost of the complete MS treatment with Lemtrada® in Spain comes to 58,000 euros(179), whilst in the case of MabCampath® it would be around 1,200 euros³¹.

THE ZENAPAX®/ ZINBRYTA® CASE

The Campath®/ Lemtrada® case is not the only one in the history of MS. There is a similar case with the drug daclizumab: Zynbryta® (Biogen), previously sold as Zenapax® (Abbie).

Daclizumab, once again, represents the history of a drug developed in the public sphere and manipulated by the industry for their own interests. Just as with the case of alemtuzumab, daclizumab was initially approved by the FDA in 1997 as Zenapax® for acute transplant rejection, and the EMA approved it in 1999 (194). Later research proved its effectiveness in MS. In light of this new market perspective, the medication was voluntarily withdrawn in 2009 (195) to then be relaunched in 2016 as Zynbryta® at a price 6 times higher.

The EMA has recently recommended the immediate suspension and withdrawal of daclizumab for MS, after having detected serious inflammatory brain disorders throughout the world. Biogen has already requested the withdrawal of the drug and the suspension of clinical trials (196,197).

³¹ Calculation based on data published from the agreements establishing prices from the Inter-ministerial Commission on the Price of Drugs.(250)



Figure 7. History of alemtuzumab 1980-2018. Prepared by the authors.

PUBLIC R&D INVESTMENT

A search with the defined methodology, similar to the previous case (148), gives the result of 337 projects assigned to this drug in the US since 1993 that total more than 156 million dollars from public American funds. Of all of these, 35 were allocated to the Ohio State University³², with a total funding of more than 20 million dollars, and 30 projects to the National Cancer Institute, through the Basic Science and Clinical Science Divisions, with funding of more than 21 million dollars.

Much like in the preclinical stages, public contributions during the clinical development of alemtuzumab were particularly relevant. The analysis of the data obtained from the American and European registers of clinical trials (149,150) illustrates this fact (figure 8): 70% of the clinical trials registered were carried out with non-commercial purposes and with funding from universities, research centres and non-profit foundations. Only 13% of these trials were exclusively financed by the industry. The pharmaceutical industry would have had greater participation in the phase III studies, whilst the weight of the first clinical phases falls mainly on universities, public research centres and non-profit foundations.

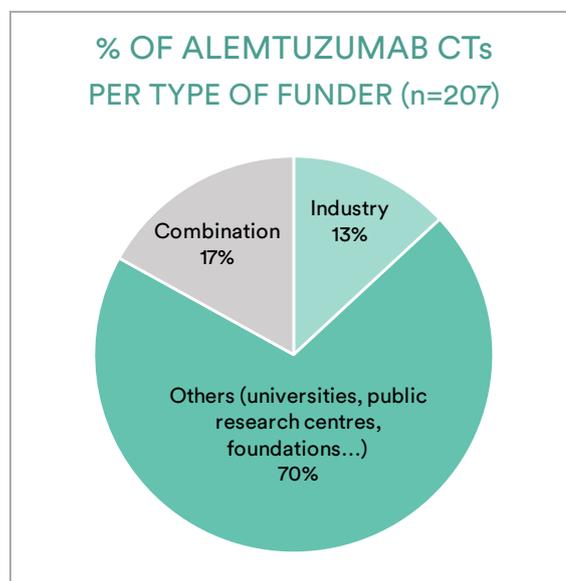


Figure 8. Percentage of Alemtuzumab Clinical Trials per Type of Funder. Source: European and American clinical trials registers (149,150) Prepared by the authors.

Since 2013, the REEC has registered 4 clinical trials of the drug Lemtrada® that, according to the information available, involved more than 200 patients³³. Of these 4 trials, 3 are aimed at the study of the drug in RRMS, but incorporating data from European and American databases, since 2004 in Spain a total of 16 clinical trials on alemtuzumab have been registered.

³² The main researcher, who appears in 26 of the 35 projects at Ohio State, is John C. Byrd, who, according to data reported in TAGGS(251), between 1991 and 2018 has received more than 32 million dollars for cancer research.

³³ It is unknown how many of these have participated in Spain. This information is not available in the REEC.

INDICATIONS AND ANNUAL SALES

Pursuant to the EMA's registers, (198), Lemtrada® was authorised in September 2013 for the treatment of adult patients with active disease, based on their symptoms or scan results.

Annual Sanofi reports, available in the US, Europe and Japan, state that the most recent patent registered will expire in September 2027.

Lemtrada® generated 474 million euros in sales in 2017, 425 million in 2016 and a total accumulation of 1.178 billion euros in sales since its authorisation for MS in 2013 (176,199–202) (figure 9). Sanofi reported a gross global profit of 12.160 billion euros in the first half of 2017(202).

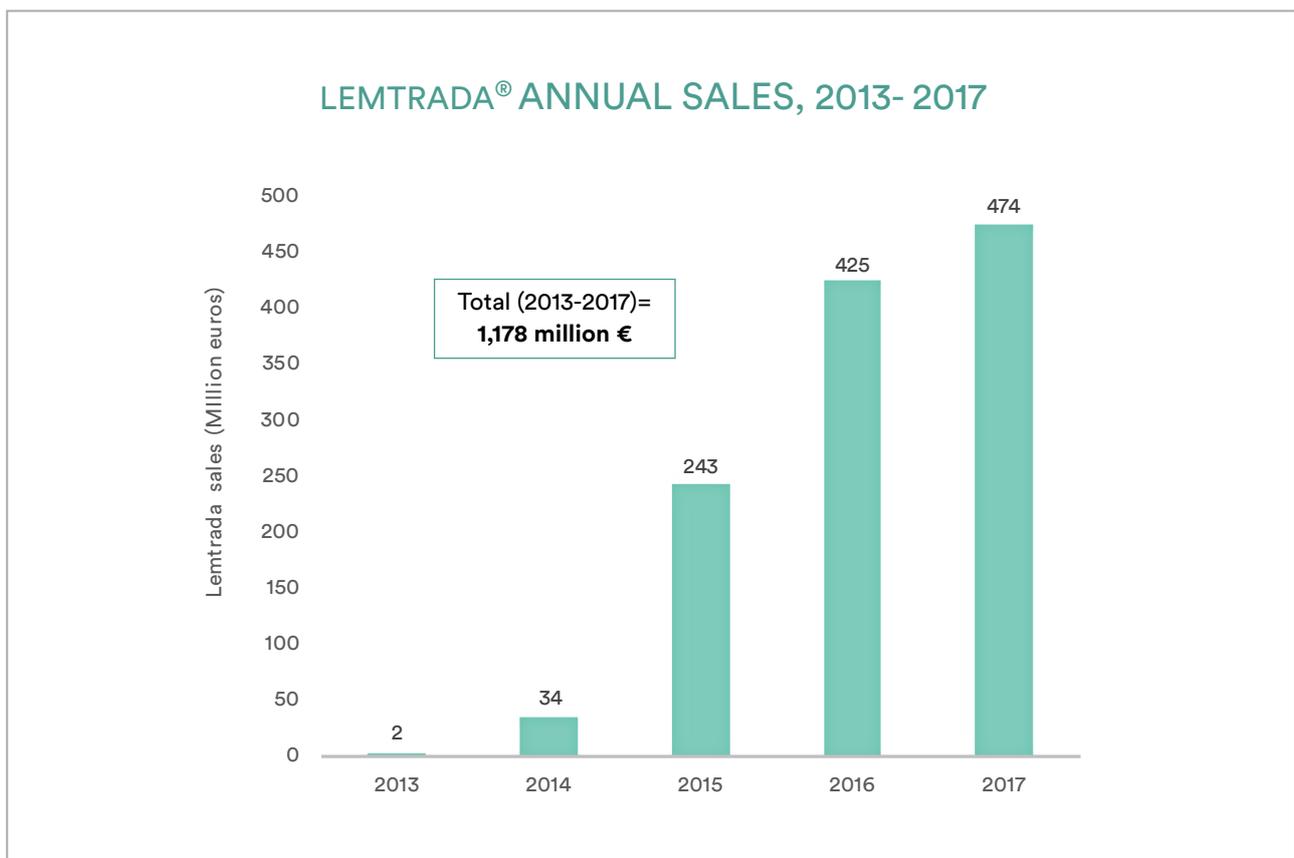


Figure 9. Lemtrada® Sales Since Its Authorisation for Multiple Sclerosis (2013-2017). Source: Sanofi- Genzyme annual and financial reports (176,199–202). Prepared by the authors.

6.3. BEVACIZUMAB

Bevacizumab (Avastin®) is a monoclonal antibody used in the treatment of different types of cancer. It blocks the action of a receptor known as the vascular endothelial growth factor (VEGF), which is responsible for blood vessels forming around the tumour. By stopping these from forming, the vascularisation that “feeds” the tumour is reduced, and hence so is its growth.

This drug was first authorised in the US in 2004 and was later approved by the EMA in 2005 for the treatment of bowel cancer. Since then, the indications approved have risen, and these days bevacizumab is authorised for the treatment of breast cancer, non-small cell lung cancer, kidney cancer, bowel cancer and ovarian cancer. Furthermore, it is used “off-label”³⁴ for the treatment of age-related macular degeneration (AMD), an eye disease which slowly destroys the sharp, central vision; a use that has been studied ever since the drug was researched, but that has never been approved.

Regarding bevacizumab and some of its indications, doubts have arisen from the regulatory agencies. In the US, in 2011 the FDA decided

to suspend its use for metastatic breast cancer after not finding enough evidence regarding its benefit/risk balance (203). In Europe, however, this indication is still approved, although it was also reviewed in 2010 and some limitations of its use and combination with other drugs were introduced.

In Spain it is authorised by the AEMPS and all of its indications are authorised for hospital use. Pursuant to the information available (204), the price (maximum LSP) per vial (25mg/ml 16ml) is 1272.89 euros. In lung cancer, for example, the approximate price per cycle of treatment is 3,341.34 euros, leading to a total of almost 58,000 euros per year of treatment³⁵.

According to the latest annual Roche report, the most recent patent will expire in Europe and the US in 2020 (157), but Mvasi, the Amgen biosimilar, was approved in September in the US and has just been approved in Europe (205). Other biosimilars are already available in some countries such as India and Russia, but potential losses are not expected to be more than 2 billion dollars for 2022, thus maintaining its position as one of the main 10 cancer drugs (56).

³⁴ “Off-label” is the practice of using drugs differently to that which they are approved for, whether that be for a different age group, disease, dosage or means of administration that is different to the official indication when there are no therapeutic alternatives. It is regulated in Spain by Royal Decree 1015/2009 of 19 June (252).

³⁵ Price calculated for a treatment with a regimen of 15mg/kg every 3 weeks administered to a person weighing 70 kg.

MACULAR DEGENERATION Y THE AVASTIN®/ LUCENTIS® CASE

In 2007, in Europe a new drug was approved: ranibizumab (Lucentis®) for age-related macular degeneration (AMD), the first cause of blindness in people over 65 years in high income countries. The new drug is, in fact, a modification of bevacizumab (Avastin®) and it has a very similar mechanism of action preventing the formation of new blood vessels and cellular growth, in this case of the retina, therefore improving visual sharpness.

Both bevacizumab and ranibizumab were developed by Genentech/Roche and both are marketed by Roche in the US. However, outside the US, ranibizumab is commercialised by Novartis, who also had data exclusivity until 2015 (206).

Treatment with the intraocular application of bevacizumab was widely studied, demonstrating evidence of its safety and efficacy through studies financed by public bodies. However, the company did not ask the regulatory agencies, those responsible for authorising the commercialisation including said application,

for the inclusion of a new indication for bevacizumab. The current regulatory system does not allow for authorisation to be requested from an agent that is different to the pharmaceutical company. This situation means that, for commercial interest, new applications are not approved for many medications that would be useful in certain indications (207).

As such, the appearance of ranibizumab in 2007 launched a specific and determined alternative for the treatment of macular degeneration. With the indication now officially authorised, the price of the treatment with this drug will also be significantly “differentiated”, reaching a price of up to 100 times more than the intraocular application of bevacizumab (180,208).

According to public procurement data from the Basque country (209,210), in Spain the price per dose of bevacizumab for intravitreal application is around 3 euros, whilst the cost for a dosage of ranibizumab is up to 132 euros (table 4). Although it is true that these amounts do not consider for the cost of resources when preparing bevacizumab, the price increase is pronounced enough to continue anticipating

Drug	Formulation	Price (LSP)	Price/vial	mg/ vial	Dose (mg/ dose)	TOTAL (€/ dose)
Avastin®	25 mg/ml 4 ml 1 vial concent soluc	262.43 €	262.43 €	100	1.25	3.28 €
	25 mg/ml 16 ml 1 vial concent soluc	965.38 €	965.38 €	400	1.25	3.02 €
Lucentis®	10 mg/ml 1 vial 0.3 ml sol inject	792.92 €	792.92 €	3	0.5	132.15 €

Table 4. Estimation of Price/Dose of Avastin® and Lucentis® in ARMD. Data: Basque Government. Contract resolutions 2014 and 2017. Prepared by the authors

an economic relationship which encourages the off-label use of this drug in AMD.

The comparisons in terms of efficacy and safety are similar in the bevacizumab and ranibizumab alternatives in all the reports consulted from the health services and hospital boards of pharmacy (211). Moreover, in 2012 a technical report compared ranibizumab and bevacizumab in AMD and it concluded that both drugs were equally effective, they have a similar safety profile and the same convenience (frequency and routes of administration), but that ranibizumab involved a significant additional cost with far higher impacts on hospital and National Health System budgets (208).

This fact was reported in Italy by the consumers organisation Altroconsumo, after considering that an artificial differentiation of the products could have been promoted contrary to the competition and with the aim of steering the demand towards a more expensive use. Consequently, in 2014 the Italian Competition Authority (ICA) fined Roche and Novartis laboratories 90.6 and 92 million euros respectively.

In Spain, the Organisation of Consumers and Users (OCU) requested explanations from the Spanish Ministry of Health, Social Services and Equity (212) and reported the case to the National Commission of Markets and Competition (CNMC) (213) which opted to dismiss it. Years later, in January 2018, the Italian Competition Authority's actions were endorsed by the Court of Justice of the European Union (CJEU) (214), after the Italian Council of State had requested its opinion after the laboratories' appeal.

In France, the Minister of Health, Marisol Touraine, authorised the use and reimbursement of bevacizumab for AMD in 2015. In Spain, some sources reveal an estimation of a low consumption of ranibizumab compared to bevacizumab, and this coincides with data published by the MSSSI in 2016 (44).

Bevacizumab was the second most sold product in 2016 (6,783 billion Swiss francs, and the most sold in the field of oncology), with a 16% increase in global sales, followed by trastuzumab. Ranibizumab was in 7th place with 4% of sales.

PUBLIC R&D INVESTMENT

American public investment in bevacizumab from 2001 to 2017 comes to more than 341 million dollars, split between 1864 projects. Of all of these, the institution that received the most over said time period was the National Cancer Institute, through its Basic Science and Clinical Science divisions, with a total funding of almost 50 million dollars split between 77 projects (148). In Europe, 12.5 million euros have been invested in projects related to bevacizumab since 2006 (110).

The contribution from public and private non-profit institutions in the clinical development of bevacizumab is particularly relevant. An analysis from the data extracted from the American and European registers of clinical trials (149,150) shows that only 24% of clinical trials were undertaken with commercial aims and with funding exclusively from the industry.

However, more than half (53%) were carried out with non-commercial purposes and with funding from universities, research centres and non-profit foundations (**figure 10**).

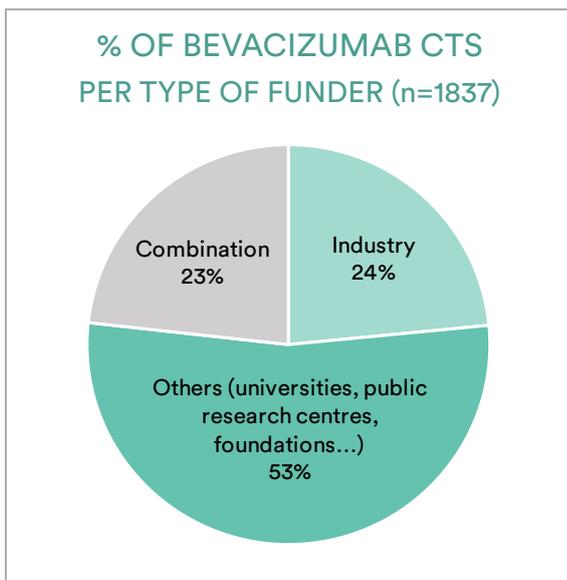


Figure 10. Percentage of Bevacizumab Clinical Trials per Type of Funder. Source: European and American clinical trials registers (149,150). Prepared by the authors.

In terms of countries, the US notably held the highest amount of clinical trials, followed by China. Data from the American, European and Spanish CT registers show that in Spain a total of 190 clinical trials have taken place since 2004. Of these, the Spanish Register of Clinical Trials reports that 29 bevacizumab clinical trials have taken place since 2013, involving more than 12,700 patients.

ANNUAL SALES

Bevacizumab is, alongside trastuzumab, the most sold Roche oncology medication worldwide. Since 2004, the accumulated sales of bevacizumab now surpass 61 billion euros (**figure 11**) and, despite the imminent loss of the patent, it is expected that sales will remain relatively stable until 2022 (56).

The drug has numerous indications and that thus widens its market and impacts on the sales figures. In the 12 years since its approval in 2004, 11 different indications have been approved. Furthermore, in 2018 the combination of bevacizumab with atezolizumab was also added to treat renal cell carcinoma and non-small cell lung cancer.



Figure 11. Annual Avastin® Sales Since Its Authorisation and Approved Indications (2004-2017). Source: EMA and Roche annual reports. Prepared by the authors.

6.4. NEW CAR-T THERAPIES

In the last few months two new very promising therapies have been approved in the United States which fall into the category of the Chimeric Antigen Receptor T-cells (CAR-T) therapies. These therapies are based on the genetic modification of the patient's own T lymphocytes³⁶

to get them to destroy specifically the tumour cells. To do this, a sample of the patient's blood is taken, their T lymphocytes are isolated and are modified in a laboratory. After this modification, the cells, which are put back into the patient, recognise and link to the surface of the tumour cells, causing a response which destroys them (215). Therefore, this is not a case of usual drugs, but rather of a therapeutic process (**figure 12**).

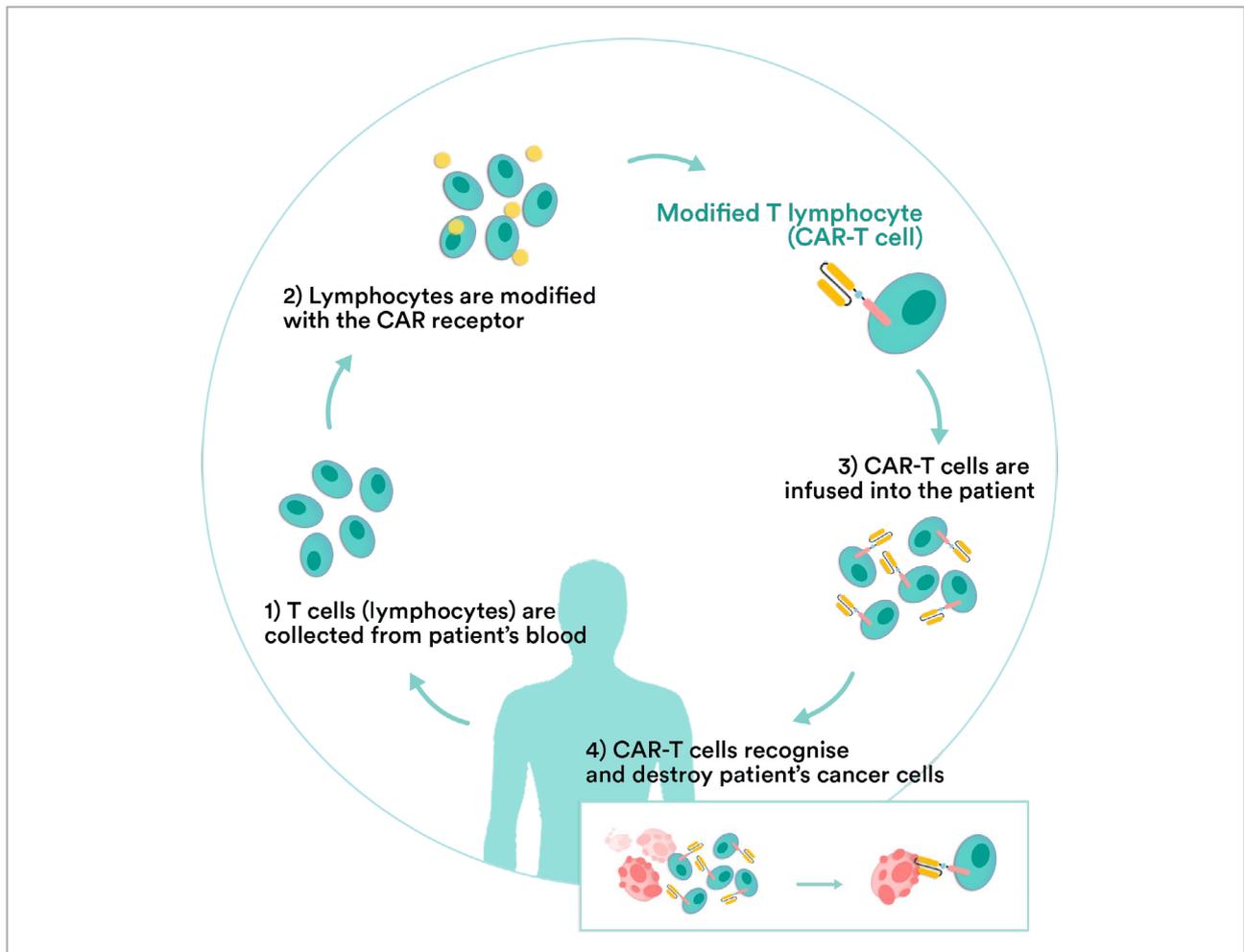


Figure 12. Chimeric Antigen Receptor T-cell (CAR-T) Therapy Process. Source: Authors own. Adapted from the MSK Cancer Center (216).

³⁶The T lymphocytes or T cells are a type of white blood cell that make up part of the immune system. They are called "T" because they are originated in the thymus gland.

In August 2017, Kymriah (tisagenlecleucel) became the first CAR-T therapy approved by the FDA for the treatment of acute lymphoblastic leukaemia (ALL) in children and young people up to the age of 25 that do not respond to conventional therapies or that suffer a relapse (15-20% of patients) (217).

ACUTE LYMPHOBLASTIC LEUKAEMIA

Acute lymphoblastic leukaemia (ALL) is a type of blood and bone marrow cancer whereby an excessive and uncontrolled amount of white blood cells and lymphocytes are produced. These leukaemia cells quickly invade the blood and can spread to other parts of the body such as the lymph nodes, liver, spleen, the central nervous system (brain and spinal cord) and the testes (in men). This affects the immune system, causing frequent infections, anaemia and easy bleeding, in addition to other symptoms.

ALL is the cancer that is most commonly diagnosed in children and it represents approximately 25% of all cancer diagnosis in children under 15. In Spain, around 39 new cases per million children between 0-14 years are detected each year (218).

Until now, treatment has been mainly based on chemotherapy and, in cases of relapse, bone marrow transplants are undertaken. The prognosis is better in children than in adults (23).

A few weeks after tisagenlecleucel was approved, in mid-October 2017, Yescarta (axicabtagene ciloleucel) was approved. This is the second CAR-T therapy, this time for a Non-Hodgkin lymphoma in the adult population known as diffuse large B-cell lymphoma.

The approval of these new treatments in the United States has generated a lot of hope in the field of immunotherapy but, at the same time, great concern, not only regarding the side effects on patients (217), but also with regard to the exorbitant initial price in the US: 475,000 dollars per treatment for tisagenlecleucel and 373,000 dollars for axicabtagene ciloleucel. These prices stand out when some of the main researchers behind the development of these therapies have acknowledged that the cost is no greater than 15,000 dollars (219).

Added to that is the fact that with these new personalised therapies, far fewer patients have undergone clinical trials. For these cases, their approval is based on two clinical trials that had the participation of: 63 patients for tisagenlecleucel (ELIANA trial) (220) and 101 patients for axicabtagene ciloleucel (ZUMA-1 trial) (221). On the other hand, the monitoring of the patients' response to treatment is barely greater than 12 or 8 months, respectively (19,220–223), which forces a prudent reading of the results at present.

On the other hand, the lack of transparency (224) regarding the data and the criteria upon which the prices of these therapies have been decided create extremely relevant information gaps that, due to confidentiality, will be left unanswered for patients, researchers, clinicians and regulators.

PUBLIC R&D INVESTMENT

The development of T lymphocytes against tumours gained its first results in 1988 in the US, through the pioneering research by Dr. Steven Rosenberg, oncologist and researcher at the National Cancer Institute, and the first CAR-T cell was developed in 1993 in Israel at the hands of Dr. Zelig Eshhar (228).

From then, numerous institutions and research centres have continued to commit to this field. Much of the research has been undertaken in public centres. One of the countries that has invested the most is the US, through the National Institutes of Health (NIH)³⁷. According to the data available, since 1998 the NIH will have funded 982 projects in the US, with an allocation of 370 million dollars related to research on Chimeric Antigen Receptor T-cells therapies³⁸.

The first CAR-T trials for the treatment of tumours were carried out on ovarian cancer and, later, in infant neuroblastomas, with funding from Australian and US health institutes.

Despite these first trials being disappointing in terms of their efficacy (229), the trials continued and up until the end of 2016 some 220 CAR-T cell trials had been registered, 188 of which are ongoing (230).

NON-HODGKIN LYMPHOMA

Lymphoma is a cancer of the cells in the lymphatic system and is differentiated from other types of leukaemia as it first appears in the lymphatic tissue (spleen, tonsils, lymph vessels, etc.) and not in the blood flow.

Malignant lymphomas are called Non-Hodgkin lymphoma (NHL), so as to differentiate them from Hodgkin's lymphoma (Hodgkin's disease), which has different clinical characteristics and a good prognosis. The NHL incidence in Spain ranges between 30 and 70 new cases per million inhabitants per year, and it more commonly affects adults.

Diffuse large B-cell lymphoma is the most common type of Non-Hodgkin lymphoma (around 30% of all NHL), and it is within the most aggressive group of NHL. The symptoms are variable and unspecific (fever, night sweats, weight loss, fatigue, infections, etc.) and the treatment varies depending on the patient, although it normally involves chemotherapy, and in some cases, radiotherapy (225–227).

³⁷ The US Department of Health and Human Services RePORT database (148) delivers the results of 546 projects between 2006 and 2017 which add up to 300 million dollars. Of these, the institution that had been allocated the most over those years was the National Cancer Institute through their Division of Basic Sciences that received 28 million dollars. Meanwhile, the University of Pennsylvania has been allocated 21 million dollars in the past 10 years. Moreover, the website Grantome, which gathers information about the NIH funding to different institutions, has data from pre-2006. Between 1992 and 2006 there were a total of 605 projects assigned to 24 American institutions. The investment data, which appears from 1998 to 2006, states that a total of more than 70 million dollars was split over those years in 418 projects. (see methodology in annex).

³⁸ The 10 institutions that received the most money between 2006 and 2017 were the Memorial Sloan Kettering Cancer Center, the Baylor College of Medicine, the University of Pennsylvania, the National Cancer Institute, the University of Texas, the University of California, the Fred Hutchinson Cancer Research Center, the Dana-Farber Cancer Institute, the Wistar Institute and the University of Minnesota with a total of almost 220 million dollars (148,241).

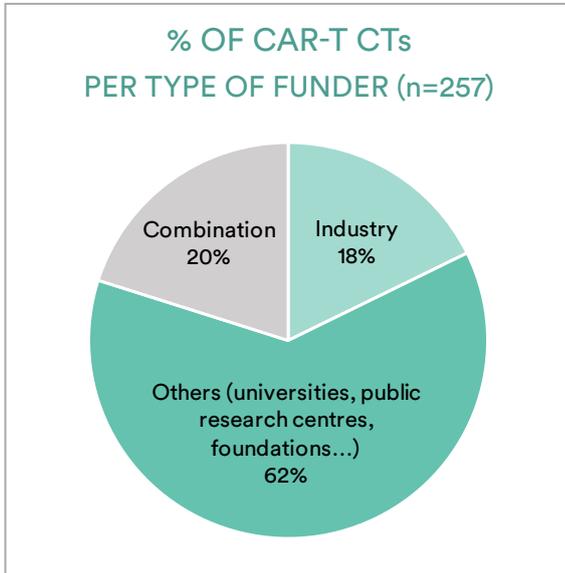


Figure 13. Percentage of CAR-T Therapy Clinical Trials per Type of Funder. Source: European and American clinical trials registers. Prepared by the authors.

Much like with the previous drugs, the CAR-T trials are being funded with large contributions from public and private non-profit organisations. According to the trials reviewed, only 18% of clinical trials were undertaken with commercial purposes and with funding exclusively from the industry, and 20% had a combination of industry and non-industry funding. However, 62% were carried out with non-commercial purposes and with funding from universities, research centres and non-profit foundations (**figure 13**). The phases in which the main differences can be seen are phase I and phase I/III, moments in which there is a greater amount of public investment, as has been so with the previously reviewed cases (149,150).

ARI PROJECT

Project ARI was born from Ari Benedé's initiative; a young woman diagnosed with ALL who passed away on 2 September 2016. This initiative has achieved the mobilisation of resources for research and home-care for a value of 1,134,584 euros coming from 56 companies, 23 foundations and associations and 1,477 individuals (231).

It was set up two years ago with the aim of continuing biomedical research in cancer and developing a CAR-T for the Clinic; a hospital that had been studying this therapy for more than 20 years (232).

The CAR-T trial has, thus far, treated 10 patients diagnosed with acute lymphoblastic leukaemia (ALL) that had not responded to conventional treatment (231) and has evaluated the safety and efficacy of their own therapeutic process. Carrying out this trial with their own CAR-T makes Hospital Clinic one of the very few European centres that are able to offer this therapy (232).

The majority of the trials are being carried out in the US and China. In Europe, they take place above all in the United Kingdom, Germany and France. In Spain, two are being carried out: the first in the framework of a multi-centre tisagenlecleucel trial at the Hospital San Joan de Deu and the second in the framework of the Project ARI at the Hospital Clinic de Barcelona (231). This is not a lot when compared to other countries and other drugs. However, Project ARI represents an opportunity for the development of new cell therapies with public funds.

THE CAR-T MARKET

The arrival of the first CAR-T therapies brings with it extremely important business operations.

TISAGENLECLEUCEL

This is a therapy with its origins at the University of Pennsylvania³⁹ and the Children's Hospital of Philadelphia, after more than two decades of research spearheaded by Dr. Carl June (233,234). In 2011, the advances demonstrated caught the eye of the industry, and in 2012 the pharmaceutical company Novartis signed an agreement with the University of Pennsylvania, through which the company was granted the exclusive worldwide licence for 20 million dollars. Information published by the university states that this agreement allowed for a centre to be built which has the capacity to treat 400 patients a year (235). In total, the company claims to have invested 1 billion⁴⁰ dollars in the development of these new therapies, however there are no registers or evidence to back this up.

AXICABTAGENE CILOLEUCEL

The second FDA approved therapy was born from the NCI in the US, where not only was a fair share of the basic research undertaken⁴¹, but the first adoptive cellular therapy clinical trial also took place here in 2010 with funds from the NCI itself and from the NIH (236).

From then, conversations started with Kite Pharma (237,238), an American biopharmaceutical company, and the first cooperative R&D agreement between the company and the Government was finalised in 2012. These agreements allowed for up to 6 licences to be exclusively granted to Kite from the NCI and more than a dozen patents on adoptive cellular therapies were established (239).

In August 2017, Gilead Sciences acquired Kite for a value of 11.9 billion dollars. This multi-million dollar operation placed the pharmaceutical company in a new market and thanks to this, the Kite investors considerably increased the value of their shares (240), which raised from 17 dollars in 2014 to 50 dollars at the end of 2016. It was expected that this new therapy would lead Kite to generate sales of between 1 and 2 billion.

Kite had reached an agreement with the Government so as to obtain the licence for the development of axicabtagene ciloleucel in exchange for royalties of around 5% of the sales from the product derived from the patent. The surprising thing is that this licence does not exist because the derived treatment was not patented by the NCI as it, seemingly, considered that it did not have good enough commercial prospects (240).

Although this section only outlines the work of two companies, many other centres and public institutions are working on these therapies. Their promising effects on certain tumours is generating a market which, in light of the data, is anticipated to be expensive and competitive.

³⁹ In the past 10 years the University of Pennsylvania will have received public American funding for a total of almost 30 million dollars spread between 87 CAR-T projects (148).

⁴⁰ The No es Sano Campaign sent a letter to Novartis in 2017 asking about the criteria for establishing the price of tisagenlecleucel and the R&D expenses, among others. In their reply, the company spoke of an investment of 1 billion, although there was not a breakdown of the information in this regard.

⁴¹ Between 1998 and 2017, the National Cancer Institute received more than 28 million dollars from American NIH which was split among 59 CAR-T projects (148).

seven.

CONCLUSIONS Y RECOMMENDATIONS

The purpose of this report has been to provide some facts regarding the access and funding of cancer drugs both in Spain and abroad. However, whilst being aware of the scale of the problem and the difficulty in accessing a lot of data, this report has limitations which have not allowed for some important aspects to be explored more in depth, such as the impoverishment of many people and families due to the disease or to further expand on other elements, such as the equity regarding access for patients in all the Autonomous Communities.

This report is focused on cancer drugs and the results gathered, confined to the specific cases outlined, prove that the public participation in the development of drugs is more common than that assumed among professionals and citizens. This participation is extremely important, both in the pre-clinical and clinical phases.

The first chapters show the specific aspects regarding the investment in biomedical innovation, the global and Spanish market and the key elements that make it more difficult to access these medications. The case studies chosen are of drugs that illustrate how some of the so-called “blockbusters”⁴² have been developed, how the different global pharmaceutical market dynamics behave and the repercussion of the current incentives and intellectual property system. Below, the conclusions of this report are set out in four differentiated blocks.

1.

HIGH PRICES OF CANCER TREATMENTS

The price of cancer drugs grows continuously and sustainably, placing oncology as one of the main areas of the market in this industry. The high prices are a barrier for citizens, jeopardising the resources available in the public system, which has limited economic capacities.

The variables upon which the price of a drug are based on are difficult to objectively analyse given the lack of transparency with regards the research and production costs.

The differences noted in the price of medication between different countries strongly suggest the hypothesis that prices are established by the pharmaceutical industry in relation to an analysis of each market and its capacity to pay.

RECOMMENDATIONS

- ✚ Change the current drug price fixing system in such a way that decisions regarding prices are underpinned by objective criteria, based on real and audited research and production costs plus a reasonable profit.
- ✚ Incorporate transparency measures and eliminate commercial conflicts of interest regarding the decisions on price adopted on a global level and, with regards to Spain, those taken by the Inter-Ministerial Commission on Pharmaceutical Prices in a way which information is accessible for citizens on its website.

⁴²“Blockbuster” is the name given to best-selling drugs.

- ✚ Make negotiations more transparent, as well as monitoring the investment in all those medications that are subject or not to an expenditure ceiling, with a high budgetary impact and with prices that are not entirely justified.

2.

FINANCING, BIOMEDICAL R&D RETURN AND INCREASE OF THE INVESTMENT

In the case studies presented, public R&D investment is very important in relation to the total investment, encompassing both basic and clinical research. Furthermore, it has been ascertained that the majority of industry investment is provided in the most advanced phases of clinical development.

Biomedical R&D investment in Spain is far below the European averages, although interest in basic and also clinical research in cancer has been seen to be growing thanks to scientific interest and patients' commitment and huge contribution to improving the knowledge of this disease.

This report confirms the advance in research and development in therapies thanks to the combination of efforts from different research groups. Group and collaborative work synergies have a high social value; hence the public access to data and results from projects funded with public money should be a priority.

RECOMMENDATIONS

- ✚ Boost the development of cancer drug research models with predominantly public money which facilitates separating the cost of research from the final price of the drugs and which, among other aspects, will give way to affordable prices.
- ✚ Link public funding in research to conditions that, for the generation of public assets, guarantee the future accessibility, affordability, availability and exploitation of data and efficiency of the product or technology of the product that is transferred, licensed or patented as a result of said funding. Likewise, these safeguards on the future exploitation of the drug should be extrapolated to the clinical trials in public centres.
- ✚ Spain needs to increase its commitment to science and the amount of human and material resources that are necessary for it to recover the importance it deserves. Moreover, the public biomedical research agenda should prioritise the needs of the population's health, also including R&D in diseases that are not as profitable in a commercial sense.

3.

TRANSPARENCY, EVALUATION OF RESULTS AND ACCOUNTABILITY

This report brings to light the impossibility to access the agreements on established prices between Governments and the industry for drugs for hospital use.

Spanish registers, as well as the information available regarding the financing of biomedical R&D projects, need to improve. Current mechanisms do not allow for a systematic knowledge of the patents linked to projects with public funding, nor the publications nor clinical trials. On the other hand, the Spanish Register of Clinical Trials (REEC) does not incorporate the results of trials and it provides very incomplete registers of the studies registered.

It highlights the essential, independent evaluation of the safety, quality and efficiency of the drugs, reserving accelerated approval process of exceptional circumstances.

At present, pharmaceutical expenditure is published as aggregate data, with three distinguished subgroups: hospital pharmaceutical expenditure, pharmaceutical and healthcare products with medical prescriptions (pharmacies) and healthcare products without medical prescriptions. It is also shown aggregated per Autonomous Community and per mutual company. The pharmaceutical expenditure per drug and hospital and the data of the number of patients treated per Autonomous Community are unknown.

RECOMMENDATIONS

- ✚ Measures regarding transparency should urgently be taken in Spain regarding the publication of price dossiers and the Inter-Ministerial Commission on the Pharmaceutical Prices decisions, as well as those from expenditure ceiling agreements.
- ✚ The transparency of data and the registering of this by the Public Administrations regarding funding granted to R&D, patents obtained with said funding and related publications and clinical trials needs to advance. Likewise, the Spanish Register of Clinical Trials (REEC) should incorporate the results of all trials, whether positive or negative.
- ✚ It is a priority to improve the current pharmaceutical expenditure accountability systems in order to discover and better analyse the incremental expense of hospital pharmaceutical invoices.

4.

INCENTIVES TO INNOVATION OR AN ABUSE OF INTELLECTUAL PROPERTY?

Business strategies have been proved that, when faced with the opportunity of adding a new indication, prefer to go back and patent and relaunch a product under a new brand for purely commercial reasons.

A complex architecture of patents can be witnessed surrounding a single drug, with the aim of protecting profits and delaying the entrance of biosimilars onto the market. Plus, there are evergreening practices on old patents, for example, through the introduction of new ways of administering the drug.

RECOMMENDATIONS

- ✚ Develop mechanisms that control and sanction the abuse of competition, evergreening strategies (the possibility of patenting old drugs again) or actions that delay biosimilars or generic drugs entering the market, by increasing the novelty requirements for the patenting of new molecules.
- ✚ If the current model of patents generates medication surcharges, an alternative innovation model should be promoted with fair, controlled prices that could lead to lower pharmaceutical expenditure. This could be exercised in such a way that when distributing the healthcare budget, a greater investment could go towards research in health priorities, prevention, promotion and care and the improvement of health and social services, including the long term care services that are so necessary for many families.
- ✚ Review the current intellectual property incentives model in pursuit of promoting innovation alternatives that go beyond patents.
- ✚ Review the current model of transferring technology from public institutions to the private sector with regards to key aspects: 1) partially reserving the public property of sold patents and 2) avoiding exclusive licences.

eight.

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annex 1.

GLOSSARY OF TERMS

ACTIVE INGREDIENT. The raw material, substance or mixture of substances that provide the pharmacological effect.

ADHERENCE. The degree of therapeutic compliance in which a patient acts in accordance with the dose, the dose regimen and the time frame prescribed by the medical professional.

ANTIBODIES. Substances that are produced in our bodies and that act as a part of our immune system to fight against infections and other foreign agents. They are also known as immunoglobulins (Ig).

ANTINEOPLASIC. Cancer drug that prevents the development or growth of malignant tumour cells that may produce the tumour or cancer (neoplasm).

BASIC RESEARCH. Research that aims to collect and gather information in order to build a foundation of knowledge that is added to previous existing knowledge and, in the case of the study of new drugs, from which clinical research can be based.

BIOSIMILAR. Biological drug that is equivalent in quality, efficacy and safety to the original biological drug or reference product and that has the same routes and regimen of administration.

CANCER. Group of diseases that are characterised by the development of abnormal cells, which uncontrollably divide, grow and spread in any part of the body.

CHEMOTHERAPY. Therapy that uses drugs which, by means of different mechanisms, cause the indiscriminate destruction of all those cells that reproduce quickly, as is the case with tumour cells.

CLINICAL TRIALS. Experimental studies of a drug to evaluate its safety and effectiveness. They are divided into 4 phases: phase 1) the safety and behaviour of the drug is evaluated in individuals (less than 100); phase 2) the efficacy is tested and data regarding dose and safety in patients is collected (between 100 and 200); phase 3) the safety and efficacy is evaluated in real conditions of use and compared to the available therapeutic alternatives. This is carried out in a larger number of patients (from several hundred up to thousands) and is the basis for the future approval of the drug; phase 4) studies that are undertaken after commercialisation to control the onset of side effects in the long term or those that had not been previously noted (pharmacovigilance). Furthermore, they can act as a way of exploring new indications or formulations.

COMPULSORY LICENCES. Mechanism designed under the TRIPS (intellectual property) Agreement flexibilities through which States can make government use of a patent, or they can force the patent holder to license it to a third party in order to produce generic drugs for public health reasons.

CONFLICTS OF INTEREST. Situation in which an individual and their actions are unduly influenced by a secondary interest, generally of an economic or personal nature.

FORMULATION. Process through which an active ingredient is incorporated in the final preparation ready for its administration.

GENERIC. Drug that has the same composition and pharmaceutical composition as the original or reference drug, and that has been proven to be equally effective and safe.

HORMONOTHERAPY. Therapies that work by modifying the way hormones work with the aim of stopping the growth of tumours that they depend on certain hormones in order to grow.

HUMANISED MONOCLONAL ANTIBODY. Type of antibody produced in a laboratory through the combination of a human antibody with a monoclonal antibody from a mouse or rat.

OVER-MEDICATION. Excessive or unjustified use of drugs in diseases or vital processes.

IMMUNOSUPPRESSANT. Chemical substance that causes the immune response to be suppressed or its complete inhibition.

IMMUNOTHERAPY. Group of biological therapies that makes the most of the capacity of the patient's immune system to fight against the cancer.

INCIDENCE. Number of new cases of a disease in a determined population within a specified period of time.

INDICATION. Description of the disease that is going to be treated by a drug and the public for which it is intended.

INTELLECTUAL PROPERTY. Collection of private rights recognised for an individual's intentional creations.

LIST OF ESSENTIAL MEDICINES. Medicines guide drawn up by the World Health Organization which includes more than 400 drugs that are considered as essential to respond to the main public health needs on a global scale.

MONOCLONAL ANTIBODY. Antibody that is synthesised in a laboratory and designed to recognise and attack specific tumorous cells.

MONOPOLY. A pharmaceutical laboratory's exclusive right to commercialise a drug.

MORTALITY RATE. Number of deaths in a determined population and period of time.

OLIGOPOLY. Market situation in which the number of sellers is very reduced, as such they control and dominate the sales of certain products as if it were a monopoly.

PHARMACEUTICAL PATENT. Collection of exclusive rights given by a State to the inventor of a new pharmaceutical product or technology that is susceptible of being commercially exploited for a limited period of time.

PHARMACOTHERAPY. Application of drugs to prevent and treat diseases.

POST-AUTHORISATION STUDY. Studies that are undertaken once the drug has been authorised and commercialised. This includes phase IV trials.

RADIOTHERAPY. Cancer therapy in which a high-dose radiation is administered to destroy the cancer cells and reduce tumours.

T LYMPHOCYTES. Type of white blood cells (lymphocytes) that are part of the immune system which are capable of recognising and activating an immune response which allows for the infected or malignant cells to be directly or indirectly destroyed. They are called "T" because they are originated in the thymus gland.

THERAPEUTIC ALTERNATIVE. A drug with a different composition that is used to treat the same disease with similar clinical effects.

THERAPEUTIC GROUP (ATC SYSTEM). Drug classification system according to its pharmacological effect, therapeutic indications and chemical structure.

YEARS LIVED WITH DISABILITY (YLD). Expression of the loss of health of an ill or disabled person of a determined severity and duration. This is calculated by multiplying the number of cases, the average duration of the disease and a factor that reflects the severity on a scale of 0 (optimal health) to 1 (death).

RECEPTOR. Molecule found on cells surface that is able to recognise and unite to other molecules that come from the outside of the cell with the purpose of generating a response.

EVERGREENING. Strategy which, by means of different mechanisms, allow for the patent of a drug which is about to expire to be extended.

BIOLOGIC THERAPIES. Group of treatments designed to act selectively on tumour cells with determined characteristic which gives them an improved profile of efficacy and safety.

TARGETED THERAPIES. Group of therapies that aim to block the signals that the tumour cells need to grow or survive.

TUMOUR. Abnormal tissue mass that appears when cells multiply more than they should or when do not die when they should. Tumours may be benign (non-cancerous) or malignant (cancerous). This is also called neoplasm.

ADDED THERAPEUTIC VALUE. The differential clinical benefit that a drug provides compared to an existing therapeutic alternative.

annex 2.

METHODOLOGY

Below is a brief description of the sources of information and databases used in the study of public funding and clinical trials, as well as the search strategy used for each case study and the process for extracting data.

All the searches were carried out between September and October 2017. The definition of the criteria of inclusion/exclusion and doubts or disagreements were solved by those that participated in the search, extraction and analysis of the data.

A. PUBLIC FUNDING

NIH RePORTER

The RePORT project (Research Portfolio Online Reporting Tools) (148) is an initiative from the US government's Department of Health and Human Services (HHS) that include a series of tools, including the RePORT Expenditures and Results Tool (RePORTER). RePORTER is a repository of the projects financed by the NIH which also includes information regarding the publications and patents associated to each project.

Search strategy

RePORTER search for projects with NIH funding was undertaken between September and December 2017 using the website's advance search engine. The resulting projects were downloaded in a .csv format and analysed using Microsoft Excel 2016.

For this, the following search criteria was employed:

1. All the fiscal years were selected. The field "fiscal year" allows for the years from 1985 to 2018 to be selected.
2. In the field "text search" the following syntax was introduced:
 - a. TRASTUZUMAB: trastuzumab OR Herceptin®.
 - b. ALEMTUZUMAB: alemtuzumab OR Campath®. Campath® was used rather than Lemtrada® given that the events of interest regarding the alemtuzumab R&D took place before Campath® was withdrawn and Lemtrada® entered the market.

c. BEVACIZUMAB: "bevacizumab OR Avastin®"

d. CAR-T: "chimeric antigen receptor" OR "axicabtagene ciloleucel" OR tisagenlecleucel.

The data obtained could be underestimated given that it cannot be guaranteed that the list of projects obtained is exhaustive. RePORTER does not guarantee to have complete data from prior to 2008.

With the aim of gaining the total funding allocated to the projects, the columns "FY Total Cost and FY Total Cost (subprojects)" were used.

Furthermore, an analysis of the number of projects per research centre (organization name) was carried out, as was the calculation of the total amount assigned to each centre. The total sum of allocated funding and the number of projects per fiscal year was also obtained.

CORDIS

CORDIS (Community Research and Development Information Services) is a public repository with information regarding all European research projects. The website opened in 1994.

The Projects and Results Service (110) collects data regarding projects funded by the European projects: Horizon2020, FP7, FP6, FP5 and those previous up until 1990.

Search strategy

An advanced search was carried out using the Projects and Results Service in order to extract the data of biomedical cancer projects undertaken in Spain. To do this, the search was filtered with the following parameters: term: "cancer"; content types: "Project"; subject: "Medical biotechnology" and "Medicine and Health"; Country: "Spain".

The search results were downloaded in a .csv format. However, the information contained within the downloadable file did not include data regarding the funding nor information about the centres that coordinated or participated in the project.

The extraction of the data regarding the total cost, European funding, contribution to Spain, participating institutions in Spain and the location of these, was carried out manually from the web page to the spreadsheet.

A breakdown of the funding per participating centre was only found for those projects in the FP7 programme, as such the monetary contribution given to Spanish centres could only be established in part. In overview, projects prior to the FP5 programme were ruled out for not having information available regarding the cost of the project. Thus data related to programmes FP5, FP6 and FP7 was included. At the time of searching (October 2017), Horizon2020 projects were not portrayed.

GRANTOME

Grantome (241) is a project headed by a group of researchers based in Cleveland (United States). The website has data regarding projects funded by the National Institutes of Health (NIH) with a simple and intuitive interface.

The website allows users to view data in the form of graphs for free, which is a great advantage with regards other websites when it comes to obtaining a quick, easy and schematic approach to the public funding of the drugs of interest. By means of drop-down lists, it also allows users to filter by year, funder, institution that received the funding, type of funding, research centre or lead researcher. The main limitation is that the data and graphs cannot be downloaded free of charge, as such they cannot be subsequently analysed. At the same time, it must be clarified that the data regarding the projects is reliable but not complete. Grantome is a less exhaustive repository compared to the official ones (RePORTER) in terms of the number of projects and data reported from each project.

Search strategy

Grantome search for projects with NIH funding was undertaken between September and December 2017 using the website's simple search engine. For this, the names of the active ingredients were introduced:

“trastuzumab”, “alemtuzumab”, “bevacizumab” and “chimeric antigen receptor” for CAR-T.

Data was narrowed down and viewed by means of the resources available on the website (filters and graphic tools). The data of interest was extracted manually to an Excel file to be later analysed.

B. CLINICAL TRIALS

B.1. REGISTERS AND SOURCES

EUROPEAN CLINICAL TRIALS DATABASE (EUDRA CT)

In Europe, the clinical trials database (EudraCT) (149) from the European Medicines Agency includes information regarding the clinical trials of drugs undertaken in the European Union and the European Economic Area (EEA) from 1 May 2004.

From July 2014, the database has also included summaries of the results of the trials which are available to the public. In the case of trials carried out in the EU after 1 January 2015, all the results must be published, regardless of the positive or negative implications.

Search strategy

The search and filtering of clinical trials carried out in the European Union was undertaken manually.

For this, the term corresponding to the drug of interest was entered into the search engine, in our cases: “trastuzumab”, “alemtuzumab” and “bevacizumab” and “chimeric antigen receptor” OR “axicabtagene ciloleucel” OR “tisagenlecleucel”.

After this, the trials resulting from the search were downloaded page by page. The results were transferred one by one to an Excel database, only those results that fulfilled the inclusion criteria were included for their later analysis and those that did not were rejected.

The information regarding each clinical trial (CT) transferred to the Excel database included: Eudra identifier of the CT, name of funder, type of funding (commercial/non-commercial), CT phase, state, number of patients included in the CT, if it took place in Spain, and a comment was added should it have been necessary to add or clarify anything.

In order to simplify, the state in which the clinical trial was found was coded as follows: “ONG” were those that were still being undertaken (ongoing) or those that had been temporarily stopped (temporarily halted); “COMP” referred to completed trials (“completed”), terminated (“terminated”) and those that had ended prematurely (“prematurely ended”); finally, “withdrawn” included all those that had been withdrawn for any reason and this was stated in the database.

Inclusion/ exclusion criteria

TRASTUZUMAB

Those trials are included that in their point D (“IMP Identification”) included “Herceptin®”, “trastuzumab”, “subcutaneous trastuzumab” or a trastuzumab biosimilar (providing it was indicated as “trastuzumab”), providing that they were categorised in point D as “Test” (“IMP Role”).

All those CTs that did not fulfil the inclusion criteria were excluded, as were those that made reference to “trastuzumab emtansina” (Kadcyla®). Furthermore, those that fulfilled the inclusion criteria but also used “Herceptin®”, “trastuzumab”, “subcutaneous trastuzumab” or a trastuzumab biosimilar as comparators were also excluded. With this, the assumption was made that the aim of a clinical trial is to improve the effectiveness, safety, possible combinations and doses of the test drug and not to exclusively test a biosimilar.

ALEMTUZUMAB

Those trials are included that in their point D (“IMP Identification”) included “Lemtrada®”, “alemtuzumab” or a alemtuzumab biosimilar (indicated as “alemtuzumab”), providing that they were categorised in point D as “Test” (“IMP Role”).

Furthermore, those that fulfilled the inclusion criteria but also used “Lemtrada®”, “alemtuzumab” or a alemtuzumab biosimilar as a comparator were also excluded. With this, the assumption was made that the aim of a clinical trial is to improve the effectiveness, safety, possible combinations and doses of the test drug and not to exclusively test a biosimilar.

BEVACIZUMAB

Those trials are included that in their point D (“IMP Identification”) included “Avastin®”, “bevacizumab” or a bevacizumab biosimilar (providing it was indicated as “bevacizumab”), providing that they were categorised in point D as “Test” (“IMP Role”).

Furthermore, those that fulfilled the inclusion criteria but also used “Avastin®”, “bevacizumab” or a bevacizumab biosimilar as a comparator were also excluded. With this, the assumption was made that the aim of a clinical trial is to improve the effectiveness, safety, possible combinations and doses of the test drug and not to exclusively test a biosimilar.

CAR-T

It was observed that these therapies could be referred to with diverse terms with regards their treatment definition (for example, “CD19- cells”, “modified T-cells” etc.) Those trials were included that in their point D (“IMP Identification”) included “tisagenlecleucel”, “axicabtagene ciloleucel” or “chimeric antigen receptor”, and in the case of finding other terms, it was verified that they were synonyms before they were included.

AMERICAN REGISTER OF CLINICAL TRIALS (CLINICALTRIALS.GOV)

Clinicaltrials.gov (150) is a web page that gathers registers of the clinical trials (CTs) and observational studies of drugs and interventions for human use carried out in the United States. It has operated since February 2000 and was created as a consequence of the Food and Drug Administration Modernization Act of 1997 (FDAMA), through which the FDA required the U.S. Department of Health and Human Services (HHS), through the NIH, to establish a registry of the information of clinical trials funded both by the State and by private entities.

The website is maintained by the National Library of Medicine (NLM) of the National Institutes of Health (NIH) in the United States. All the information in the database is provided by the funders or the lead researchers of the clinical trials. Some of the trials take place in multiple centres and involve countries other than the US. However, not all the CTs undertaken in the US are included in this database, as they are not required to be registered by law. These are mainly those observational studies that did not involve the testing of a drug or device.

Search strategy

The search for clinical trials via the American registry was carried out manually and the filtering was completed using Microsoft Excel 2016.

For this, in the advanced search engine the term that corresponded to the drug of interest was entered in the section for indicating if it was an intervention or treatment (“intervention/treatment”), in our cases: “trastuzumab”, “alemtuzumab” and “bevacizumab”. For CAR-T therapies, the terms “chimeric antigen receptor OR axicabtagene ciloleucel OR “tisagenlecleucel” were introduced in the section “other terms”, as it was observed that these therapies could be referred to with diverse terms with regards their treatment definition (for example, “CD19- cells”, “modified T-cells” etc.) After this, the trials resulting from the search were downloaded in a .csv format and they were transferred to a database for the optimal handling. After successive filtering, only the results included for their later analysis were those that fulfilled the inclusion criteria and those that did not were excluded.

Exclusion/ inclusion criteria

TRASTUZUMAB

The database was filtered using:

- In the “intervention” category, only those classified as DRUG, BIOLOGICAL or RADIATION were selected.
- Of these, only those that in that category included the terms “trastuzumab” or “Herceptin®” were included.
- Those that made reference to “trastuzumab emtansina” were ruled out.

- In the case that “trastuzumab” and “trastuzumab emtansina” appeared, the CT was searched for on the website clinicaltrials.us using its registration number in order to determine if trastuzumab was only being used as a comparator.

Those CTs with empty fields were excluded. A CT which appeared as “no longer available” was also excluded as were those in which the number of participants was null or 0.

ALEMTUZUMAB

The database was filtered using:

- In the “intervention” category, only those classified as DRUG, BIOLOGICAL or RADIATION were selected.
- Of these, only those that in that category included the terms “alemtuzumab” or “Lemtrada®” were included.
- Those that had empty fields were ruled out, as were those which appeared as “no longer available” and those CTs in which the number of participants was null or 0.

BEVACIZUMAB

The database was filtered using:

- In the ‘intervention’ category, only those classified as DRUG, BIOLOGICAL or RADIATION were selected.
- Of these, only those that in that category included the terms “bevacizumab” or “Avastin®” were included.
- Those that had empty fields were ruled out, as were those which appeared as “no longer available” and those CTs in which the number of participants was null or 0.

CAR-T

These therapies could be referred to with diverse terms with regards their treatment definition. All those clinical trials resulting from the search were included as it was impossible to filter them without introducing bias and errors.

B.2. MERGING AND ANALYSIS OF DATABASES

After filtering and selecting the clinical trials, the European and American databases of each drug were unified in order to obtain global data.

For this, the variables and categories were unified and duplicated were eliminated.

1. UNIFYING VARIABLES AND CATEGORIES

Data were organised according to the following variables and categories:

- ID
- Name of funder
- Type of funding: categorised as “industry”, “others” and “combination”.
 - i. “Industry”: private industry with commercial purposes.
 - ii. “Others”: includes universities, foundations, research centres, NIH, federal agencies, etc. In the American database it was accepted that the NIH, federal agencies and private, non-profit foundations and organisations undertook trials without a commercial purpose and they were categorised alongside the European ones classed as “non-commercial” within this group.
 - iii. “Combination”: “Others” + “industry”
- Status: “ONG” (including “ongoing” and “temporarily halted”), “COMP” (including “completed” and “prematurely ended”) and “withdrawn”.
- Enrollment: number of patients included in the clinical trial.
- Clinical trial phase: I, I/II, II, II/III, III, IV.

2. ELIMINATING DUPLICATES

The American database has an “other IDs” field which collects other clinical trial identification numbers; as such duplicates were able to be detected.

The duplicates were detected, these were normally those undertaken in multiple centres, and it was verified that the data published in both coincided for the same trial.

If data was the same, the duplicate was eliminated from one of the databases, normally the European one, and a note of such was marked on the other.

If the data did not match up, it was unified in line with the following: If the number of patients did not coincide (enrolment), the data that indicated the largest number of patients was chosen (just as with the European database in the case of multi-country trials where the sample size did not coincide); or b) in the case that the funder (sponsor) did not coincide, this data was included separated with “/”.

3. ANALYSIS

El análisis was performed based on:

- Type of funding: number of clinical trials undertaken by “industry”, “others” or “combination”.
- Number of patients included in the trial: total number of patients.
- Trial phase: total of phase I, I/II, II, II/III and IV trials separated per type of funding.

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