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CICLO XXXI

COMPLEX SYSTEMS FOR THE ECONOMIC EVALUATION OF HEALTHCARE IN ONCOLOGY

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CHAPTER 1

INTRODUCTION AND AIM OF THE STUDY

1.1 Introduction

The Health Economy is a discipline that studies input and output variables within a health system to assess their sustainability through an economic evaluation model (*Figure 1*). The birth of this interdisciplinary science is commonly associated with the publication of a paper entitled "Towards the definition of health economics" by Selma Muskin in 1958 [1]. In this manuscript, Muskin was the first underlining that investments in the health system may have long-term beneficial consequences for the entire community [1].

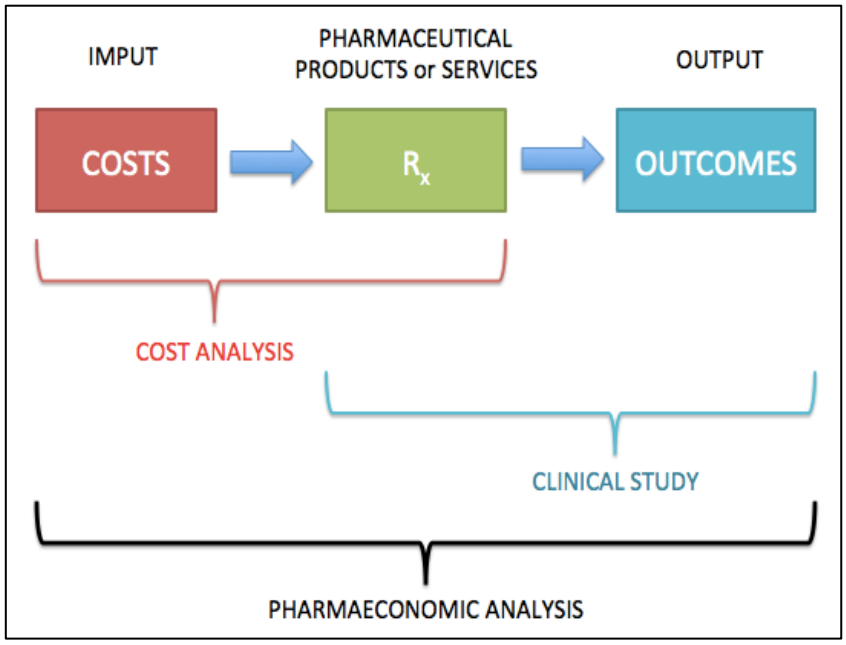

Figure 1. *Structural model of Pharmacoeconomics.*

Successively, Kenneth Arrow published in 1963 a manuscript entitled "Uncertainty and the welfare economics of medical care", thus extending Muskin's view in this setting.

In the last 50 years, Health Economy has been enriched by the development of novel technical tools, which have represented a milestone essential to cost-effectiveness analysis

of emerging medical technologies. These progresses parallel with the global economic changes encurred from 1989 to 2018, characterized by globalization and rising of newly industrialized markets worldwide, which have contributed to the creation of a huge diversity of methodological techniques to assist resource allocation processes.

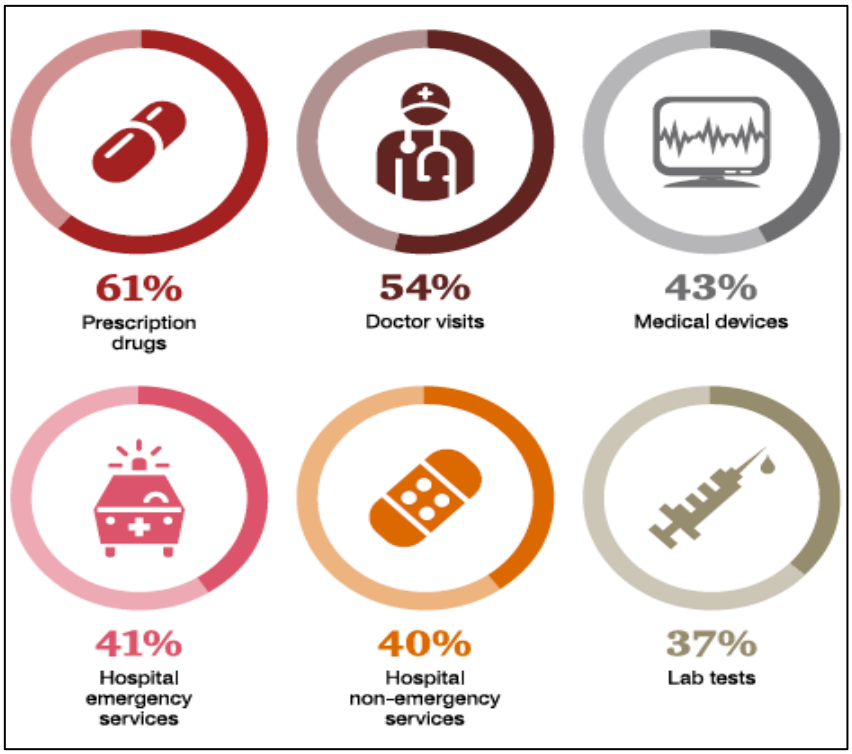

Figure 2. *Cost distribution in the Health System [2]*

The evolution of Health Economy has also led to the development of algorithms and tools aimed to predict the future cost of the health system in the different sub-settings. This analysis has become absolutely fundamental in order to guide the allocation of economic resources and to guarantee the access to cure for all patients. An annual increase of + 4.1% in healthcare costs is expected up to 2021, unlike the 1.3% increase [2] that has been up to now, due to the aging of the population, technological development in the medical field, increase in labor costs in the medical field and the introduction of new generation drugs.

Pharmacoeconomics is a branch of health economics elected to evaluate the costs of drugs used in the treatment of the various clinical pathologies associated with their relative

survival benefit. The necessity of developing a specific branch of Health Economy dedicated to the evaluation of drug costs has become crucial in the next two decades due to the introduction of a series of technologically more advanced (but even progressively more expensive) agents in different medical settings. This has led to the evidence that drug costs represent the most relevant expense in the health system, thus underlining the need for a careful evaluation (*Figure 2*).

In this discipline, efficiency and planning are two characteristic elements to evaluate a choice in the medical-clinical field. Through efficiency we want to achieve full economic sustainability using the fewest available resources, while with programming we choose priorities knowing the alternatives available.

Health Care can be considered as a complex system [3]. Indeed, differently from mechanical systems that are characterized by the possibility of controlling the outputs through the manipulation of single components, Health Care system is dynamic and includes networks of elements (i.e. hospitals, rehabilitation departments, patients and families). These components can interact nonlinearly on different scales (patients, families, hospitals and Governement). For example, pay-for-results and value-based payment models, aimed to optimize health care at lower cost may suggest aggressive treatments without considering their impact on life expectancy and relative toxicities. Differently from expectations, these payment models did not lead to benefits in terms of mortality [4] and spending [5]. In the same view, the development of clinical practice guidelines aimed to increase the quality of Health assistance and to reduce the variations among different centers have not had an impact in reducing the socioeconomic disparities reported, for example, in treating patients with diabetes [6]. Otherwise, the introduction of clinical practice guidelines have been associated with an increase in the cost of management of patients with multiple chronic conditions [7].

Among all the medical disciplines, Oncology is the one where the increase in costs has been an important element, due to the introduction of new molecular target drugs that have represented a change of game in the therapeutic scenario, improving cancer patients' life expectancy and their quality of life (*Figure 3*).

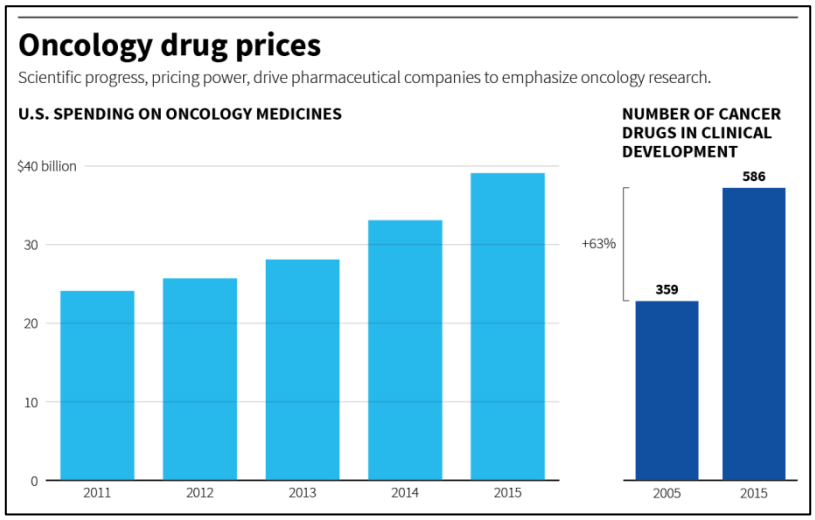

Figure 3. *Rapid increase of costs due to the introduction of novel oncological drugs [2]*

Compared to this excellent result in clinical terms, the problem of the increasing economic impact due to the high costs of targeted and immunotherapeutic drugs has raised in order to guarantee the access to patient care and the economic sustainability of the health system.

In this regard, in 2013, Amy Abernethy created the term "Financial Toxicity" referred to the problem related to the cost of new therapies that can significantly influence the patient's financial balance, causing a reduction of both quality of life and access to care due to economic reasons (*Figure 4*) [8].

This increase in the oncological expenses is not only related to the introduction of new drugs but also due to the absence of an agreement between pharmaceutical companies and the Government concerning price stabilization, causing an increase in private insurance policies of 170% from 1999 to 2011 [9]. The difficulties in reaching an agreement not only

lead to an increase of insurance policies but also can cause delays in the approval and clinical applicability of emerging drugs, with direct and indirect consequences on patients' Quality of Life.

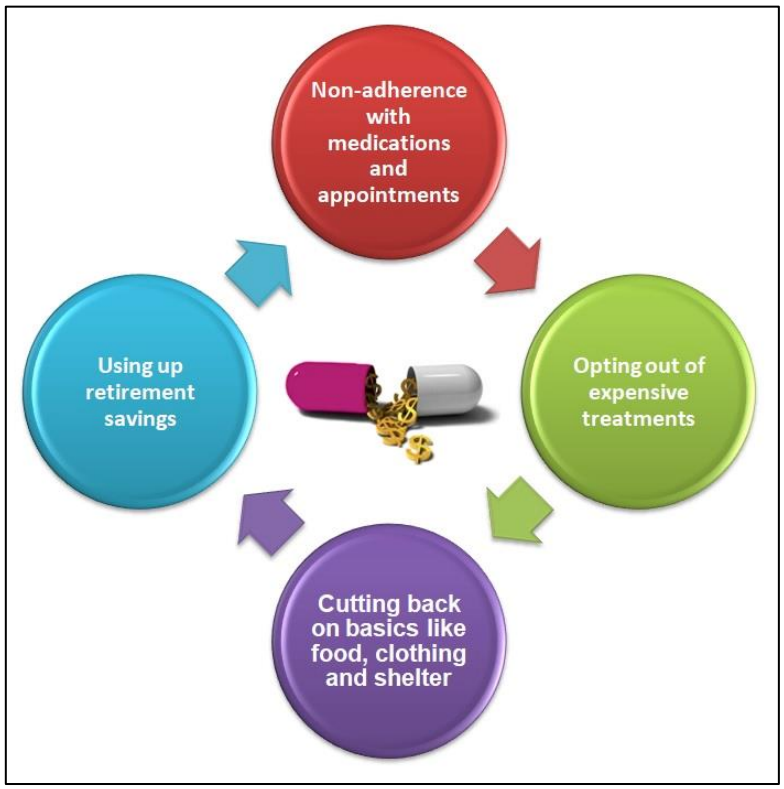

Figure 4. *Financial toxicity and its impact on patients' Quality of Life*

1.2 Aim and Structure

The aim of this study is the cost assessment in the field of oncology through the adoption of complex models, such as cluster analysis and artificial neural network, for the prediction of future costs in this area. This is more necessary day by day due to the rapidly changing therapeutic scenario of cancer patients, which corresponds to a crucial change in the cost of management in this field.

To achieve this goal, we performed a multistep analysis focused on the clinical and financial toxicity of new generation oncology drugs in order to evaluate the sustainability

of the health system in future years.

To assess the cost-effectiveness and predict the economic future tumor burden, we structured our study in four different sections:

- In the first section we studied the existence or not of a relationship between the costs of new generation cancer drugs and their relative toxicity through the application of a Voronoi model.
- The second section concerns the creation of a model to predict the number of new cases of cancer patients up to 2050 in the United States through the use of an artificial neural network algorithm (ANN). This step results absolutely fundamental in order to foresee the future expense associated with novel agents in different tumor types.
- The third section concerns the analysis of the costs of breast cancer, the most common tumor type among women, In particular, we compared the costs associated with the use of new targeted agents for the treatment of the two main types of breast cancer (HER2-positive and negative) in the United States with a forecast of costs up to 2035.
- The fourth section concerns the comparison of the costs of immunotherapeutic drugs (pembrolizumab and nivolumab) used in three of the most developed types of cancer, namely melanoma, lung cancer and kidney cancer by a cost-effectiveness analysis and a prediction of the expense related to the use of immunotherapy in cancer patients.

CHAPTER 2

USE OF VORONOI MODEL TO EVALUATE THE CORRELATION BETWEEN FINANCIAL AND CLINICAL TOXICITY

2.1 Cluster analysis and health economic evaluation

In the oncological therapeutic scenario of the last two decades, new targeted drugs have been introduced, being characterized by recognizing particular molecular targets of tumor disease. Precisely for this aspect, they generally have a lower toxicity compared to traditional chemotherapeutic drugs, thus becoming a standard of care in clinical practice for the majority of tumor types. Alongside this benefit, however, the introduction of targeted drugs has greatly increased international cancer spending [10] augmenting the pharmaceutical costs by 43% in the last ten years [11].

Although new generation therapies are generally better tolerated, their toxicity can not be considered negligible. Indeed, the list of related serious adverse events includes cardiovascular, respiratory and neurological adverse events that may vary among different molecularly targeted drugs. The main challenge of researchers will be to minimize the degree of toxicity related to the use of cancer drugs to improve patients' quality of life. This fundamental element from a medical point of view is also very important from an economic point of view. In fact, by reducing the toxicity and improving the quality of life of cancer patients, the costs related to the medical interventions necessary to manage toxicity and increase the patient's economic productivity, for example by reducing the days of absence from work, will also decrease. [12-16].

In this section, a cluster analysis has been carried out on the costs of targeted drugs and their relative toxicity profile to evaluate a possible correlation between these two variables.

This type of study is a set of multivariate analyzes of data whose purpose is to divide the elements into a set of data based on the similarity among them [*Figure 5*] [17].

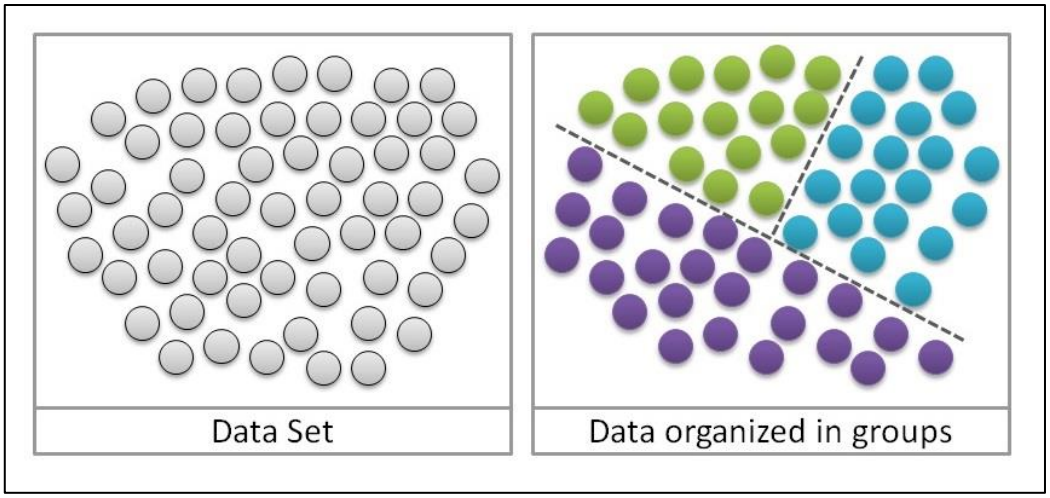

Figure 5. *Data distributed in cluster*

Clustering is one of the techniques used in evaluating the cost-effectiveness and economic sustainability of emerging drugs [18]. In this regard, Perrier *et al.* in 2014 compared the costs of oncology in Italy and France, using cluster analysis and dividing data referring to diagnosis, surgery, chemotherapy, and follow-up. In this study, the authors showed a wide heterogeneity between costs between Italian and French health care [19].

On the other hand, in 2016 Liao and his group performed a non-interventional study of more than 18,000 terminal patients with kidney cancer. The research underlined, through the identification of 4 clusters, the increasing costs associated with the presence of different pathologies in the same patient [20].

In addition to the medical field, this type of statistical analysis has been applied in different areas of scientific research given its versatility such as, for example, the epidemiological, economic or engineering fields [21,22].

In our study, we created a toxicity dataset by collecting data on serious adverse events and the rate of treatment interruption of all targeted cancer drugs that were registered through

the approval of phase II and III studies by the United States Food and Drug Administration. The creation of the dataset was a rather complex phase and it was possible to collect the values present in the PubMed portal and represents a basic step in the research for the analysis of clinical studies. Through the cluster analysis application we have selected groups of homogeneous data that have led to the choice of suitable variables for their comparison. For the visualization of the subgroups chosen by the cluster study we used the Voronoi diagram [23] named after Georgij Voronoj, a Russian mathematician of the second half of the 1800s [*Figure 6*].

This type of model divides a given metric space on the basis of different types of mathematical distances from well-defined points called centroids [23].

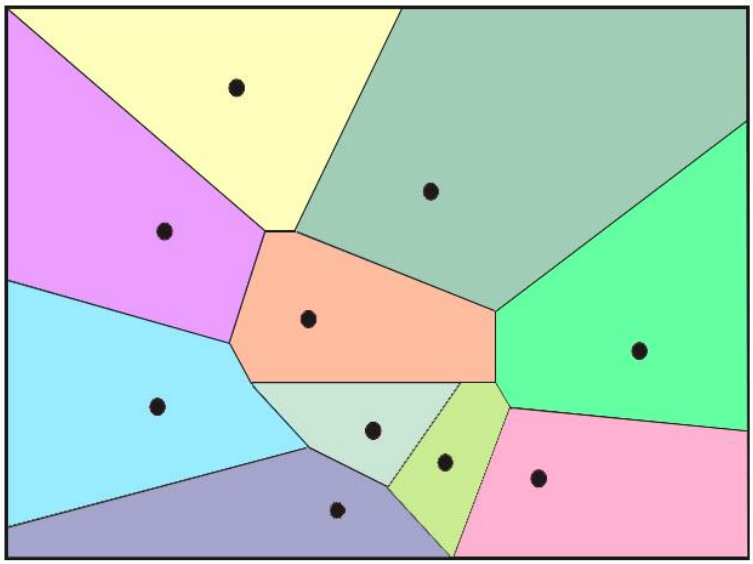

Figure 6. *Example of a Voronoi diagram [23]*

Specifically these points, considering the type of distance chosen, have the ability to collect close to them the most similar data compared to those more distant. With the application of the Voronoi diagram, we investigated the way in which the data related to the toxicity behave with respect to those related to the cost, thus succeeding in giving a useful information concerning the type of relationship existing between them. In this

regard, Liu and his group in 2009, using the Voronoi diagram, studied the rural subdivision of a territory demonstrating that the distance between the motorways and the rivers of some land parcels was the element that mostly influenced the distribution of settlements rural [24]. Five years later, Vaz *et al*, showed using the same method a significant difference between the various regions of Portugal that had different models of institutional innovations [25].

Therefore, in this chapter, we evaluated the existence or not of a correlation between the cost of targeted drugs and their relative toxicity translated in terms of adverse events related to treatment and the interruption rates of therapy due to serious side effects. This study was carried out through the creation of the dataset, description of the methodological tools used in particular an explanation of the cluster analysis used and discussion of the results obtained. A peculiar element of the work is the creation of the dataset, as it has been created through a revision of the literary and represents a novelty in the oncological studies.

2.2 Material and Methods

The search and selection of a large number of clinical trials has made possible to create the database necessary for our work. Initially, through the indications contained in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (*Figure 7*) [26] we selected the appropriate studies to perform the analysis through the search for key words such as "cancer", "neoplasia" and "clinical trial" on the scientific research engine PubMed since 1990 (year of development of first studies on the efficacy of these drugs) to 2018.

The second step was constituted by the choice of phase III clinical trials. These studies, if the final data reach the endpoints in terms of effectiveness predetermined a priori result,

lead to the approval of the experimental drugs by government agencies such as AIFA (Italian Drug Agency [27]), FDA (U.S. Food and Drug Administration [11]) and EMA (European Medicines Agency [28]).

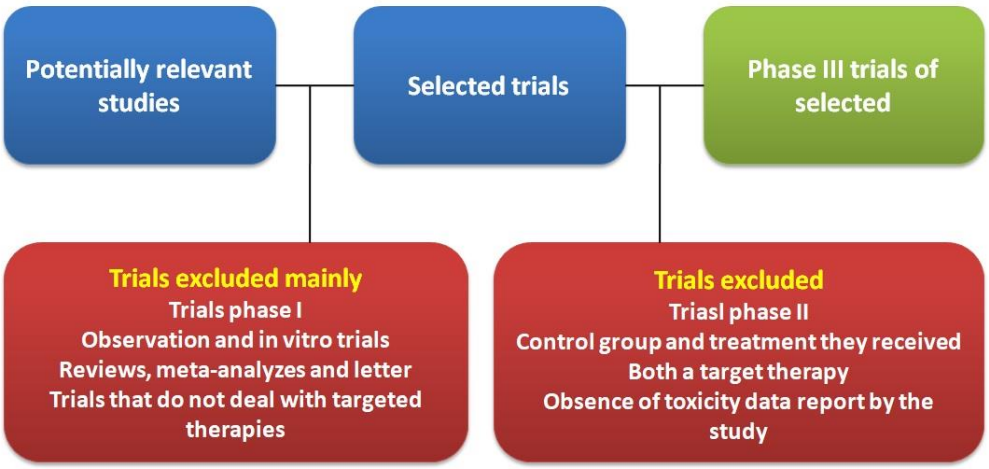

Figure 7. *Diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [26]*

For each clinical study, we collected all the fundamental information related to its drafting (authors, year of publication, reference pages etc.) and data on the efficacy and tolerability of targeted agents. Among the reported measures, we chose the time without disease progression, indicated in the studies as "Progression-Free Survival (PFS)", the rate of severe side effects (SAE) and the rate of interruption of treatment related to toxicity (D). The currency chosen for the study analysis was the US dollar.

Regarding the clustering of data and the Voronoi diagram, we used the R 3.5.1 software for Windows (62 megabytes, 32/64 bits).

The key data for our study were those related to the toxicity of drugs, considering as important variables the SAE and D rates, included together in the Toxicity Index (TI) and their relative cost.

In our analysis, we have chosen five centroids that most characterize the most significant groups by combining SAE and D rates such as:

$$\phi_1 = (10; 5);\ \phi_2 = (30; 15);\ \phi_3 = (45; 10);\ \phi_4 = (60; 20);\ \phi_5 = (75; 25)$$

The SAE rate is represented by the first value of each centroid, while the second value indicates the D rate. Specifically, the five centroids have been chosen on the basis of the different levels of SAE and D that lead to different levels of toxicity (TI): low (ϕ_1), medium-low (ϕ_2), intermediate (ϕ_3), medium-high (ϕ_4), high (ϕ_5).

The cluster ϕ_h is defined by C_h, for each h = 1,2,3,4,5 and express the SAE and D rates through the variables x and y, which are defined by the elements of the centroid ($\varphi_{(h,\,x)}$, $\varphi_{(h,\,y)}$)), for each h = 1, 2,3,4,5.

We consider the Euclidean distance, that is the original one of the Voronoi diagram, because the data groups of our analysis are characterized by the distance of the drug toxicity with the centroids. At the formal level, we can state that for each targeted agent j = 1,2,...,37 with the rate SAE_{xj} and the rate D_{yj}, we define:

$$d_E(j, \phi_h) = \sqrt{\left(x_j - \phi_{h,x}\right)^2 + \left(y_j - \phi_{h,y}\right)^2}$$

And we calculated the clusters related to targeted drugs as established by

$$C_h^K = \left\{j = 1, \dots, 37 | d_K(j, \phi_h) < d_K(j, \phi_{\bar{h}}), \forall \bar{h} \neq h\right\},\ \ \forall\, K = E, M, m,$$

$$\forall\, h = 1,2,3,4,5.$$

With regard to the costs of drugs we have created two clusters considering two variables,

the cost of one month of treatment and the costs related to each patient related to the median duration of PFS. Considering the first, we divided the data into three groups: group A (cost less than $7,000), group B (cost between $7,000 and $11,000) and group C (cost over $11,000). Regarding the cost of each treated patient for the median PFS, we have grouped the costs into 3 groups: group D with a value of less than $40,000, group E with a value between $40,000 and $80,000 and group F with a value over $80,000.

2.3 Results

At the end of PRISMA process, we have found more than 4,800 trials regarding the application of targeted agents in patients with solid tumor (Table 1) [29-65].

Target Agent	*Study Characteristics*		*Drug Efficacy*	*Drug Toxiciy*		*Drug Cost*		Ref
	Tumor Type	N. of Patients	Median PFS (Months)	SAE (%)	D Rate (%)	For 1 month	For median PFS	
Abiraterone acetate (first line therapy)	Prostate	546	16.5	48	10	8,627	142,346	24
Abiraterone acetate (successive line-therapy)	Prostate	797	5.6	7	19	8,627	48,311	25
Afatinib	NSCLC	230	11.1	49	8	6,970	77,367	26
Bevacizumab	GBL	82	5.6	65.8	17.7	4,400	24,640	27
Bevacizumab	RCC	327	10.2	29	28	4,400	44,880	28
Bevacizumab (first line therapy)	Colorectal	411	10.6	84,9	8.4	2,680	28,408	29
Bevacizumab (successive line-therapy)	Colorectal	409	5.7	64	16	2,680	15,276	30
Cabozantinib	Thyroid	219	11.2	69	16	14,300	160,160	31
Cetuximab	Head &Neck	222	5.5	82	20	7,000	38,500	32
Cobimetinib+Vemurafenib	Melanoma	247	9.9	62	12	26,300	260,370	33
Crizotinib	NSCLC	173	7.7	33	6	11,500	88,550	34
Enzalutamide (first line therapy)	Prostate	800	8.3	28	8	7,450	61,835	35
Enzalutamide (successive line-therapy)	Prostate	872	5.7	43	6	7,450	42,465	36
Erlotinib	Pancreas	282	3.8	61	10	2,450	9,310	37
Erlotinib (first line therapy)	NSCLC	86	9.7	45	13	3,000	29,100	38
Erlotinib (maintainance therapy)	NSCLC	438	2.9	11	16	3,000	8,700	39
Everolimus	Breast	482	7.8	23	19	7,000	54,600	40

Lenvatinib	Thyroid	261	14.7	75.9	14.2	13,945	204,992	41
Nivolumab	Squamous NSCLC	135	3.5	7	3	12,600	44,100	42
Nivolumab	Non-Squamous NSCLC	292	2.3	10	5	12,600	28,980	43
Nivolumab	Melanoma	210	5.1	11.7	2.4	12,600	64,260	44
Nivolumab	RCC	410	4.6	19	8	6,984	32,126	45
Palbociclib (+letrozole)	Breast	84	20.2	76	33	9,850	198,970	46
Palbociclib (+fulvestrant)	Breast	347	9.2	69,3	2.6	9,850	90,620	47
Pembrolizumab	Melanoma	277	4.1	75	6.9	23,017	94,370	48
Ramucirumab	Gastric	238	2.1	57	11	13,000	27,300	49
Ramucirumab	NSCLC	628	4.5	79	15	11,000	49,500	50
Ramucirumab	Colorectal	536	5.7	36	11	13,000	74,100	51
Regorafenib	Colorectal	505	1.9	54	44.8	7,600	14,440	52
Sonidegib	BCC	79	13.1	31	22	12,000	157,200	53
Sorafenib	RCC	451	5.5	34	10	6,600	36,200	54
Sunitinib	RCC	375	11	7	38	7,000	77,000	55
Sunitinib	GIST	207	6.4	20	9	7,000	44,800	56
T-DM1	Breast	495	9.6	15,5	5	9,800	94,080	57
Temsirolimus	RCC	209	3.8	11	7	2,960	11,248	58
Trametinib+Dabrafenib	Melanoma	211	9.3	32	9	16,300	151,590	59
Ziv-Aflibercept	Colorectal	612	6.9	83,5	26.8	11,000	75,900	60

Table 1. *Characteristics of targeted agents: Efficacy, Toxicity and Cost.*
The different colors in the columns related to cost refer to the different cost groups described below in Figure 10.
BCC = Basal-cell Carcinoma; GBL = Glioblastoma; GIST = Gastrointestinal Stromal Tumor; NSCLC = Non Small Cell Lung Cancer; PFS = Progression-Free Survival; RCC = Renal Cell Carcinoma.

Of them, 2,914 were excluded due to several reasons (i.e. phase I or in vitro studies, reviews), while 1,852 were phase II trials or studies without available data on toxicity and drug interruptions. At the and of the process, 37 studies resulted candidate to be included in this cost analysis.

The mean SAE and D rates were 44% and 14%, respectively while their mean/standard deviation were 1.68 and 1.42. Minimum and maximum SAE rate were 7% and 84.9%, while minimum and maximum D rate were 2.4% and 45%. Skewness was 0.10 for SAE and 1.48 for D rate. Kurtosis was -1.38 and 2.19, respectively.

This data, suggested that an extreme variability in terms of toxicity characterize the

targeted agents selected for this analysis.

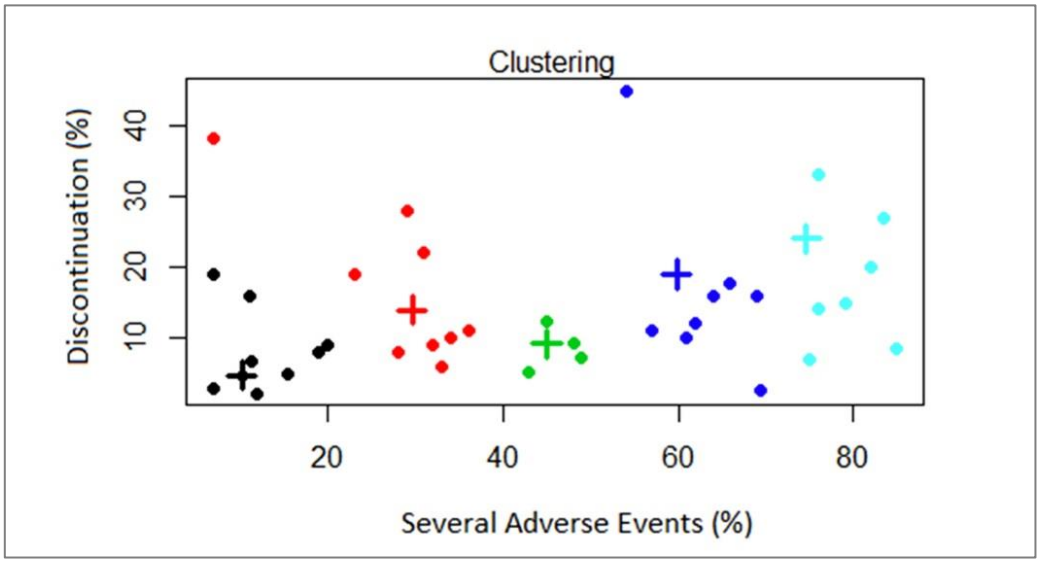

Figure 8. *Cluster analysis based on SAE and D rates*

The results of the cluster analysis based on Euclidean distance are illustrated in Figure 8. These findings show clearly that five different clusters based on SAE and D rates can be identified as demonstrated by the lack of overlap between the colored areas in Figure 8.

In order to represent the spatial dynamicity of the cluster analysis based on Euclidean distance we constructed a Voronoi diagram, as reported in Figure 9. This method will allow to easily collocate the future targeted agents that will be approved in next years into one of the five spatial areas only basing on their SAE and D rates.

Considering that all the drugs in each area of Voronoi diagram have resulted similar in terms of toxicity, we decided to assess if the cost of these agents is proportional to their cost. This notion results crucial to quantify the impact of oncological therapies on patients' quality of life, which is a crucial component of the concept of "Financial Toxicity".

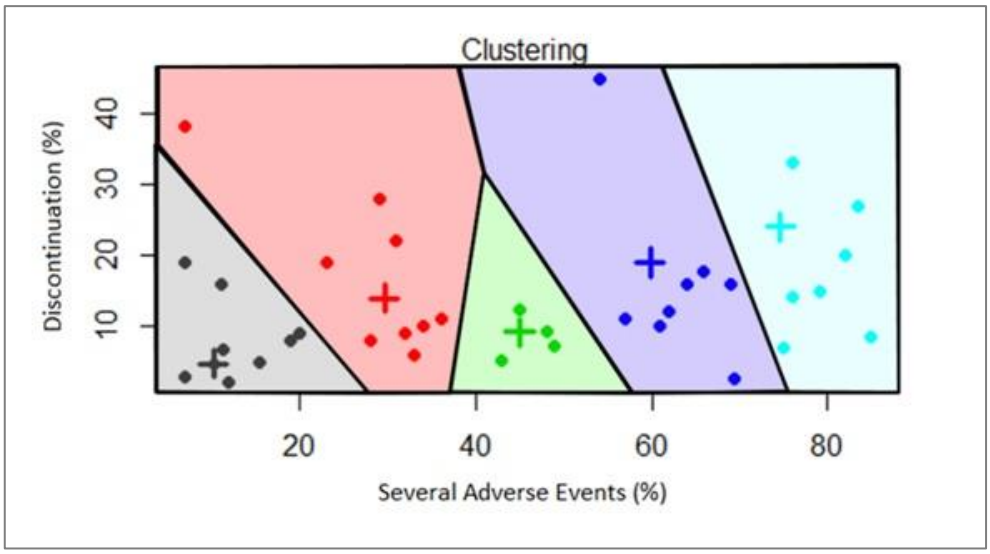

Figure 9. *Voronoi diagram based on Euclidean distance*

The first step of cost analysis has been constituted by the division of drug costs into three different groups considering both the cost for one month of therapy (*Figure 10A*) and the cost for the entire median duration of therapy based on median PFS reported in the clinical trials (*Figure 10B*).

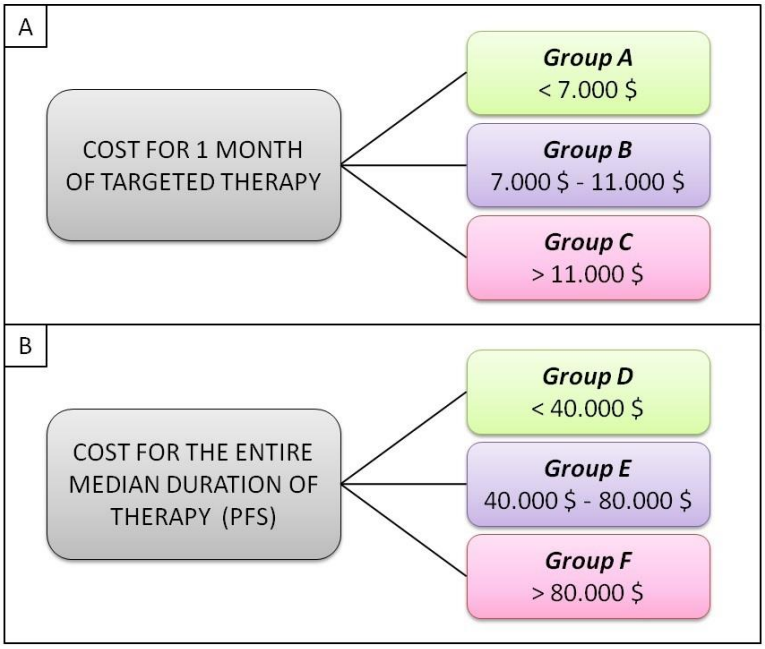

Figure 10. *Identification of different of cost groups*

In the second step, we analyzed the cost of each drug in the five clusters, observing that every cluster is characterized by the presents of low, medium and high cost agents, differently distributed if we consider the cost for one month or for the entire therapy of each patient (*Figure 11,12*).

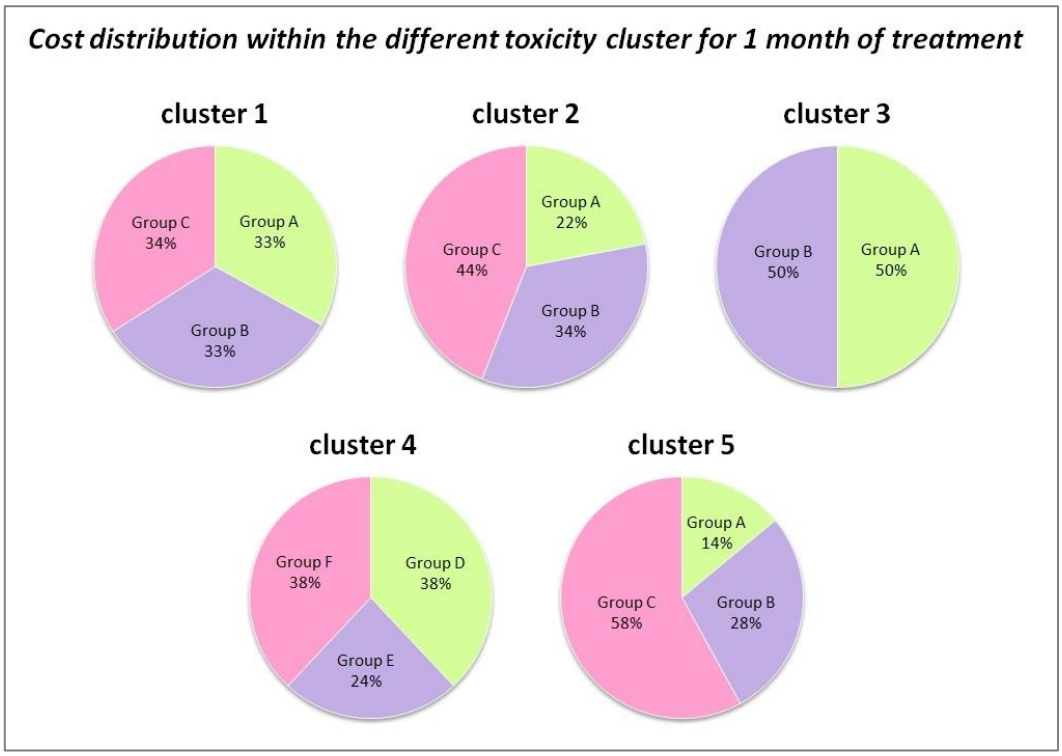

Figure 11. *The distribution of the cost for 1 month of therapy in the five clusters: low toxicity (cluster 1), medium-low toxicity (cluster 2), intermediate toxicity (cluster 3), medium-high toxicity (cluster 4), high toxicity (cluster 5)*

Considering the cost of one month, the major percentage of low cost drugs is reported in cluster 3, while cluster 5, characterized by the maximum SAE and D rates, shows the lower rate of low cost agents (14%) and the highest rate of the most expensive drugs (58%, *Figure 11*). As for the cost for median PFS cluster 4 was characterized by the major percentage of low cost drugs (63%), while cluster 5 presented the highest rate (42%) of expensive drugs even in this setting (*Figure 12)*.

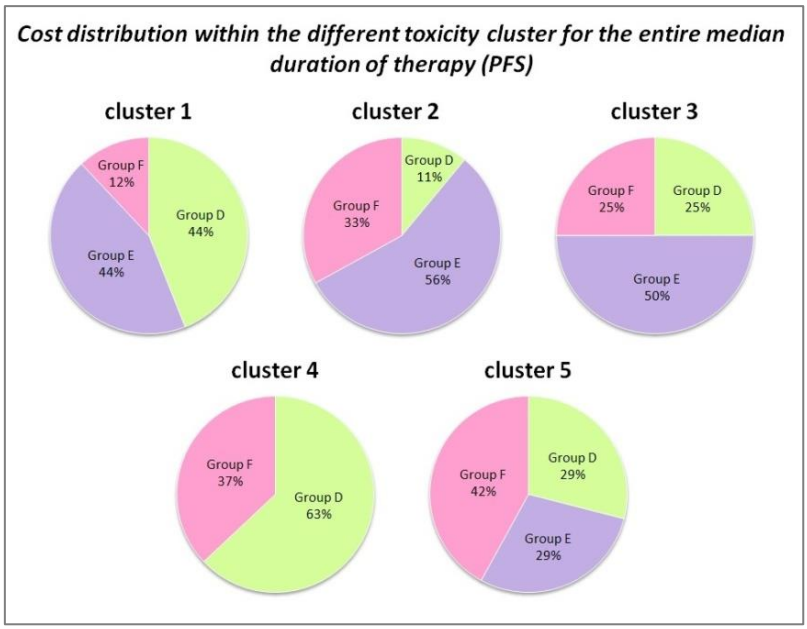

Figure 12. *The distribution of the cost for entire treatment of therapy in the five clusters low toxicity (cluster 1), medium-low toxicity (cluster 2), intermediate toxicity (cluster 3), medium-high toxicity (cluster 4), high toxicity (cluster 5)*

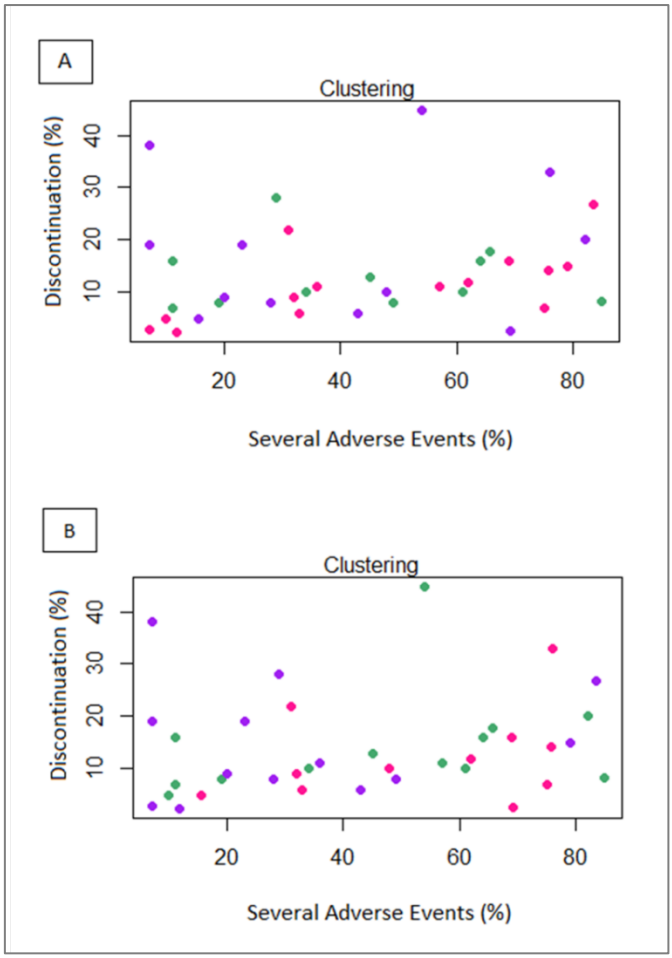

Figure 13. *Clustering analyses based on the cost for 1 month (A) or median PFS (B)*

Through the application of the cluster analysis we observed that a three clusters based on drug cost are almost completely overlapped in both the one month *(Figure 13A)* and PFS *(Figure 13B)* cost analysis.

2.4 Result Interpretation

In our paper, to assess the relationship between the toxicity and cost of all the oncological targeted agents approve by FDA, we considered the results coming from both the cluster analyses based on the Euclidean distance and the Voronoi Tessellation model. Our findings clearly demonstrated the lack of a relationship between the variables related to drug toxicity and the cost.

The evidence that the majority of high cost agents belong to cluster 5 (high toxicity) underlines that the price evaluation is completely independent from assessing the impact on patients quality of life. The consequences of the lack of this relationship are even more dramatic if we consider that agents with a high rate of SAE (cluster 5) are not only the most expensive but also require additional costs for the management of adverse events. At this regard, Roncato and his group [66] have tried to quantify the cost of this management. In particular, they investigated the economic amount of the adverse events associated with irinotecan, a chemotherapeutic agent commonly used in patients with colorectal or pancreatic cancer and glioblastoma. They estimated that, for each patients, over 4,800 € are required to treat the adverse event.

In the same view, Arondekar *et al.* [67] reported by using multivariate generalized linear models with a log-link function and gamma distribution a cost of $9,000 for the management of metabolic adverse events, $8,450 for hematologic toxicity, $6,476 for cardiovascular and $6,638 for gastrointestinal adverse events for each patients affected by metastatic melanoma. Furthermore, Bilir and his colleagues [68] classified the cost for the

treatment of SAE in patients with advanced melanoma, estimating that the most expensive management is associated with myocardial infarction, sepsis and coma (from $31,000 to $47,000). In their study, they also estimated a mean amount for hospitalization related to adverse events ranging from $19,000 to about $26,000) [68].

Among the limitation presented by our study, the major bias is related to the nature of this analysis, based on data of clinical studies and not from individual patients. In addition every study focused on drug toxicity may be affected by a variety of factors, including patients' comorbidities or interactions with concomitant treatments. Moreover, patients who result eligible for clinical trials represent only a selection characterized by usually normal organ function, thus probably underestimating the real rate of adverse events in daily clinical practice. Finally, we are aware that the various adverse events differently influence patients' quality of life, with absolutely distinct clinical, social and economic consequences.

Beyond these limitations, our study based on the construction of a dataset on toxicity and economic data on targeted agents shows the absence of a regular path, suggesting the need for a more strict connection between drug costs and their impact on patients' quality of life.

CHAPTER 3

CREATION OF AN ARTIFICIAL NEURAL NETWORK TO PREDICT THE NUMBER OF FUTURE CANCER CASES

3.1 Predictions of future tumor burden

In the United States, cancer is still considered the second leading cause of death (*Figure 14*) [69], with around 1,600 victims every day and an estimated total of over 600,000 in 2018 [70].

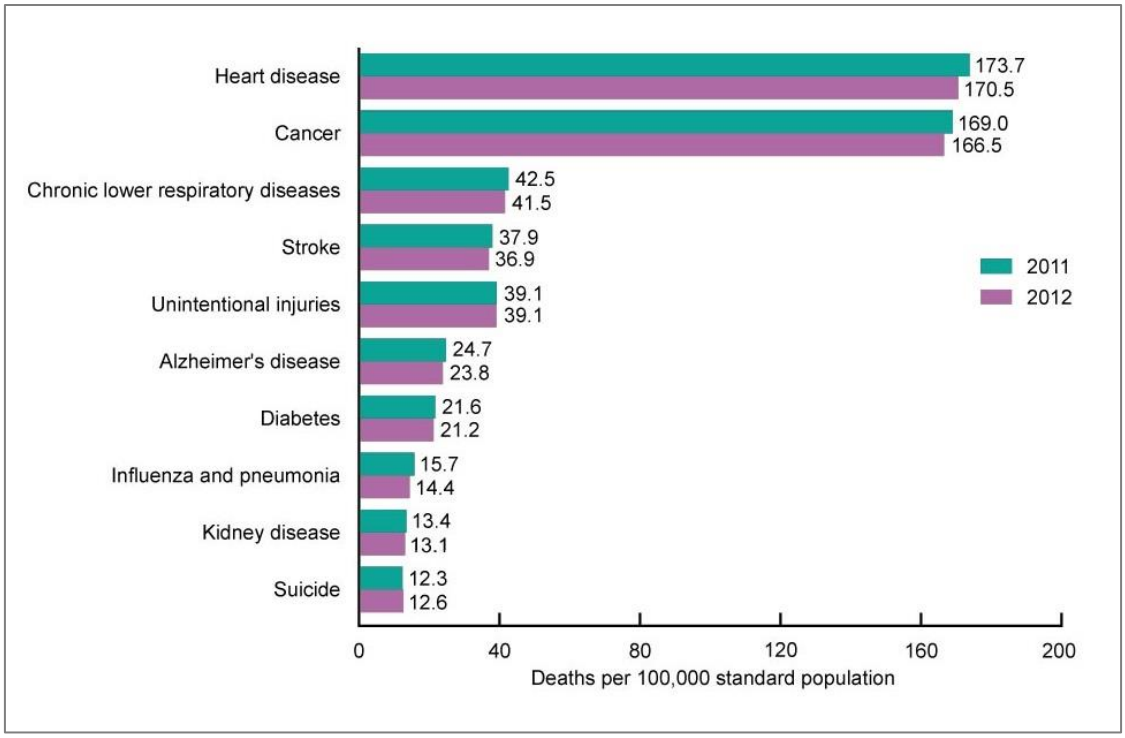

Figure 14. *Leading causes of death in the United States (2011-2012) [69]*

Despite this, over the past 25 years, there has been a real improvement of the mortality rates in cancer patients. In fact, since 1991, mortality has fallen by 25% in relation to the four most common cancers, including breast, colorectal, lung and prostate tumors [71].

In fact, as studied by de Santis and his group in their paper published in 2014, in the

coming years there will be more and more patients who will survive from cancer, estimated at about 18 million survivors in 2020 [72] (*Figure 15*).

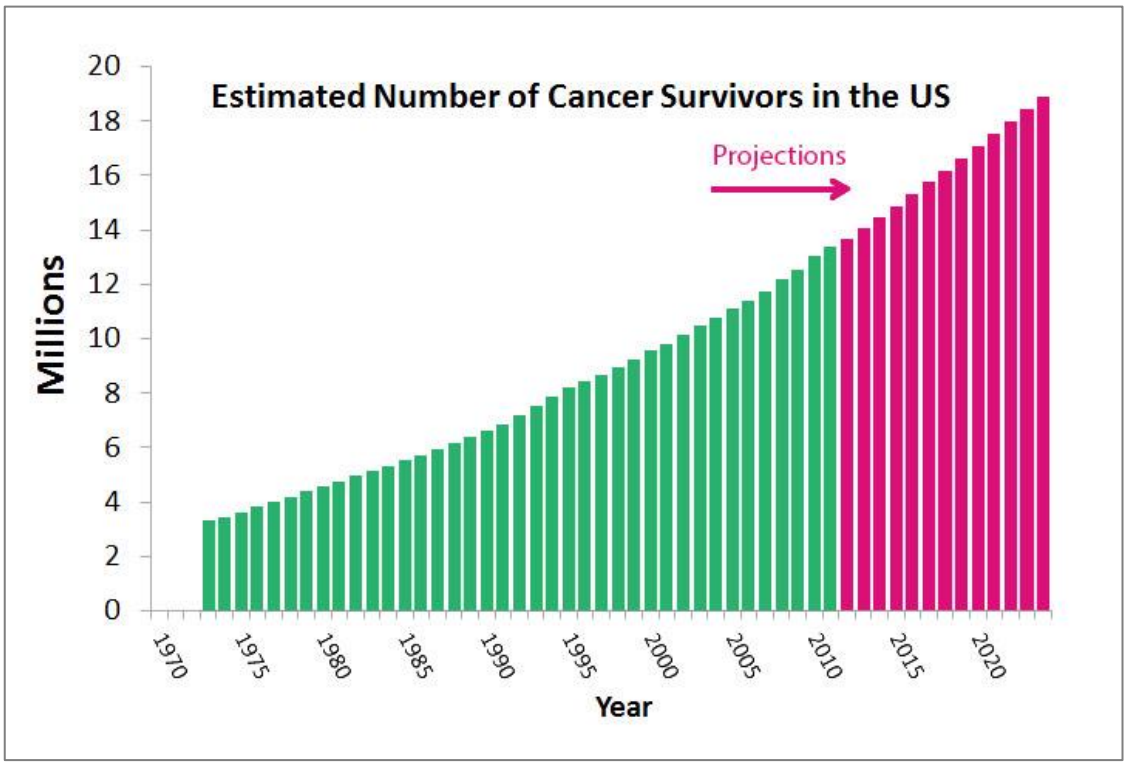

Figure 15. *Increasing rate of cancer survivors in the United States [72]*

This success is related to several factors in the oncological field, such as scientific research and health choices that have had a direct effect on patients' lives and on the choice of the best available treatments. Specifically, the elements that are reducing the mortality rate include all the awareness and prevention campaigns aimed to reduce the incidence of cancer (i.e. the campaign against smoking and obesity). Moreover, research and development of new effective diagnostic techniques and the introduction of new molecular and immunotherapeutic drugs have also played a crucial role in this setting. On this scenario, a very important element for a more efficient distribution of the available economic resources and for a more detailed planning of the costs necessary for treatment, is represented by the prediction of cancer incidence rates.

Important elements that most influence the increase in health costs are represented both by the introduction of high expensive treatments and by the increasing demographic trend and life duration, considering that the incidence of cancer diseases are related to the age of patients [73].

The future estimate of new cases of tumors can be made by referring to different forecasting techniques. For example, the most common models in this field are the classical models based on available national registers [74-78], the Poisson linear regression model that uses contingent tables to model data [79,80] and the Bayesian age-period-cohort models [81]. Although analytical techniques are widely used to make predictions, they nevertheless have limitations that have led researchers to investigate new models of more precise future predictions.

*3.2 Artificial Neural Network algorithms (***ANN)**

In this work, we decided to use an Artificial Neural Network (ANN) algorithm that allowed us to investigate the links between input and output variables to create predictions of future tumor incidences. This analytic technique takes into account neural networks, which are models based on the mechanisms used by the human brain for problem solving and are able to extract important information from raw data.

The first real contribution to the birth of neural networks was in 1943 when the neurophysiologist Warren Sturgis McCulloch and the mathematician Walter Pitts tried to create a first artificial neuron called "linear combinator of threshold" in their publication "A logical calculus of the ideas immanent in nervous activity". The creation of the network, in this model, was given by the combination of an appropriate number of data that were able to create simple Boolean functions, i.e. binary mathematical functions with two values (0 and 1) [82]. A new attempt was made in 1949, when the Canadian

psychologist Donald Olding Hebb tried to explain the complex mechanisms of the brain. It is thanks to his intuitions that "the Hebbian learning" was created, an algorithm based on the weight of the connections, that is the fact that the simultaneous activation of two neurons entails their strengthening. [83].

But the real definition of the first neural network model is found in 1958 when the psychologist Frank Rosenblatt designed the network called "Perceptron" composed of input and output variables, interconnected through an algorithm for minimizing errors (error back-propagation). Specifically, this mathematical formula modifies the weights of the connections (called synapses) based on the input and output values, creating a variation between the actual input and desired output [84].

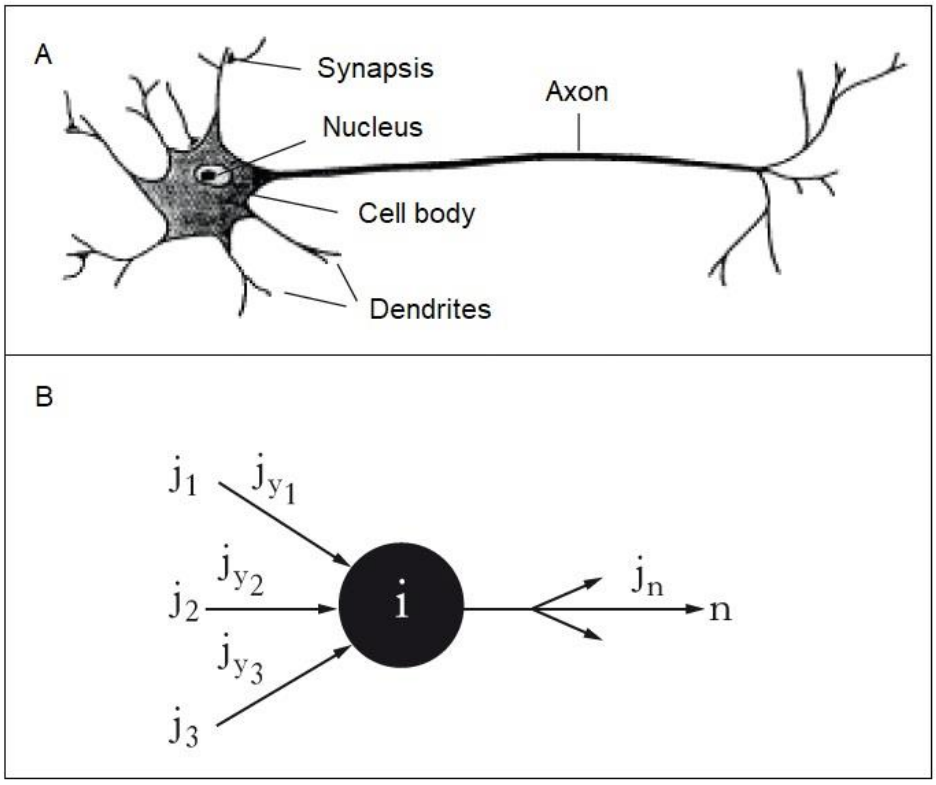

Figure 16. *Similarity between biological (A) and Artificial Neural Networks (B)*

During this period, up until the 1970s, the first programming languages related to artificial intelligence were introduced. The real step forward is in the 80s with the introduction of new and powerful processors on the market that have been able to run more intensive applications for analysis and simulations. From those years to today the process of technological advancement has grown so much new software programs able to really simulate the functioning of the human brain are continuously developed.

David Rumelhart (1986) defined the third layer of neural networks called the Hidden layer (H) that serves to identify learning patterns for multi-layer perceptron networks. The scholar introduced the error backpropagation that varies the weights of the edges between the nodes, bringing the real response closer to the desired one more and more.

The ANN is not an algorithm but rather a framework for parallel learning algorithms that cooperate to analyze and process complex data inputs [85]. An ANN is structured by a series of connected units called “nodes” or “artificial neurons”, with each connection, called “edge”, that can be activated according to the input and transmit a signal from a node to another. In this way, the information can be processed and transmitted by other connections (*Figure 16*).

In particular, each connection can transfer the output of a node *i* to the input of a node *j* [86]. The constant w_i is the weight of input node *i*.

Mathematically, an ANN is composed by a series of functions $g_i(x)$ that can be further divided into different functions dependent on each other (*Figure 16B)*. A commonly used form of composition is the non linear weighted sum:

$$f(x) = K\left(\sum_i w_i g_i(x)\right)$$

where K (tansig) is defined as the activating function (i.e. hyperbolic tangent or sigmoid function). K refers to a vector of functions gi, say:

$$g = (g_1, g_2, \dots \dots , g_n)$$

The model arising from this series of edges can analyze the short-term or long-term behavior of single neurons or networks, leading to the two main activities of ANNs: “learning” and “memory”. Learning constitutes the main function of ANN and has attracted great attention to this method. Learning is based on the ability to perform tasks by considering examples, generally with a programming not based on task-specific rules. Starting from a specific task, “learning” means to find among the set of observations the function $f^* \in F$, where F represents the class of functions, that optimally solve the task.

Specifically, the optimal solution have to minimize the cost (C) according to the function:

$$\hat{C} = \frac{1}{N} \sum_{i=1}^{N} (f(x_i) - y_i)^2$$

To the nodes of our ANN we have associated two activation functions: “tansing” and “purelin”. The first one in the Matlab language corresponds to the function of hyperbolic tangent "tanh(X)".

In Matlab the function “tansing” is not implemented as tanh(N) but as:

$$K(X) = \text{tansig}(X) = 2/(1+\exp(-2*X))-1$$

in order to calculate the results in a faster way.

The function “purelin” corresponds to the linear function Y=X (*Figure 17*), which transforms the output in a set of quantities spanning in desired ranges.

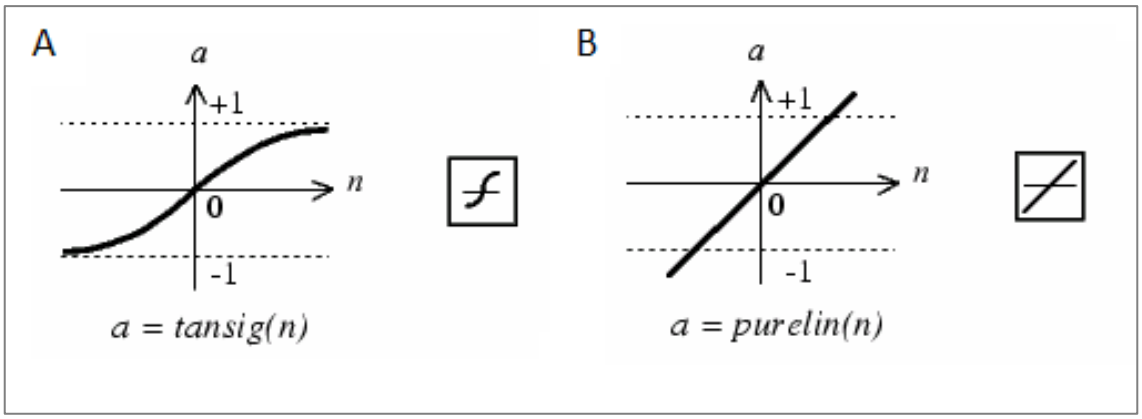

Figure 17. *Tan-Sigmoid Transfer Function (A) Linear Transfer Function*

Otherwise, Matlab uses the function "TrainBR" as the training function.

Due to its flexibility of training, these types of modeling algorithms are used in different fields, including Health care, Finance and Economy [87-90]. The application of ANNs includes a series of functions:

1) System control (i.e. trajectory prediction, management of natural resources)
2) Structure or sequence identification (face, object or text recognition, radars)
3) Decision making (i.e. chess, poker)
4) Automated trading systems (i.e. Finance)
5) Filtering activity (i.e. Social Networks and e-mail spam)

Specifically, in this work, we made a prediction of the amount of new cancer cases for the most widespread neoplasms, such as prostate, breast, colon and lung cancers, through the study and development of an ANN algorithm aimed to predict the future incidence of these tumors in the United States until 2050.

3.3 Materials and Methods

3.3.1 Construction of the data sets

Data on the number of habitants and life expectancy in the United States were collected

from Gapminder [91]. On the other hand, data on number of new cancer cases in the United States from 1975 to 2013 were extracted from the online public archives of National Cancer Institute [92]. As for risk factors, data on tobacco consumption were extracted from the paper published by Ng *et al.* [93], taking into account that the best fitting polynomial for predicting and interpolating missing data (X = year and Y = tobacco consumption) was *Y = -0.3737 * X^2 – 3.7956 * X + 2363*. Otherwise, the incidence of obesity were obtained from the data published by Wang *et al.* [94].

3.3.2 Implementation of ANNs

For each tumor type, we constructed an ANN based on the main risk factors internationally recognized. For the prediction of the future incidence of prostate cancer in the United States, we included in our ANN algorithm the three main risk factors identified by the WHO: (1) the demographic trend, (2) the life expectancy data and (3) race/ethnicity [95−97]. Due to the absence of historical series dedicated the family history of prostate cancer in the United States, we decided to not consider this as a risk factor for our analysis. We trained our ANN by using data from 1992 to 2013 on the number of new cancer cases to predict the incidence till 2050.

Breast cancer incidence grows with age [98], reaching a risk of developing this tumor in 11% of females older than 85 years [98]. In the same view, obesity correlates with an augmented risk of breast cancer [99,100] and has been associated with a worse survival in all breast tumor subtypes. In order to optimize the prediction of breast cancer new cases in the United States, we constructed an ANN based on the three risk major risk factors associated, according to WHO, to the development of this tumor: (1) the demographic trend, (2) the life expectancy and (3) the incidence of obesity. Data from 1992 to 2013 were employed for the training phase and allowed the prediction of new prostate cancer

cases till 2050. Concerning prostate cancer, we took into account the total population as an input variable.

Colorectal cancer can be classified as an age-dependent disease due to the notion that over 90% of these tumors occur in patients older than 50 years [101]. It has been reported that over 29% of colorectal tumors can be correlated to a Body Mass Index (BMI)>22.5 [102], with significant differences related to gender [103]. For the prediction of the incidence of colorectal cancer in the United States, we considered three main input variables in the ANN algorithm: (1) the demographic trend, (2) the life expectancy data and (3) obesity. As for prostate cancer, we used data from 1975 to 2013 for the training phase in order to validate and predict data from 2014 to 2050.

Tobacco consumption represents, as well known, the leading cause of the majority of lung cancer cases [104]. Based on the variety of pulmonary carcinogens (i.e. ionizing radiation, radon gas, etc), age can be considered as an indirect measure of exposure in both smokers and never-smokers patients [105]. In fact, several studies have evidenced the correlation between age and lung cancer incidence in non-smokers [106-108]. For the prediction of the number of new cases of lung cancer in the United States, we constructed our ANN including three input variables: (1) the demographic trend, (2) the life expectancy data and (3) the rate of tobacco consumption. The training phase was based on data from 1975 to 2013 and lung cancer incidence was predicted till 2050.

We choose as a forecasting model a layered feed forward network named “multilayered perceptrons (MLP)”, which are trained by back propagation algorithm that can adjust the connection strength between adjacent nodes. In particular, a perceptron presents distinct inputs and one output connected by a nonlinear function. This method is generally easy to use but requires a large amount of data for the thaining phase. The structure of our algorithm is illustrated in Figure 18.

The Learning Rate (LR) and Learning Momentum (LM) have been calculated by many trials based on the trial-and-error method. The performance of each typology was investigated by the Mean Square Error. We tried to improve the quality of our results by choosing the minimum number of nodes in order to avoid the memorization of data by the ANN and optimize their learning for generalization. The structure of our ANNs was based on three layers that have as many neurons as input variables, while the output layer has one neuron. The ANNs for colorectal, lung, breast and prostate tumors are constituted by 10, 25, 20 and 20 neurons, respectively, to implement the "tansig" function in the hidden layer.

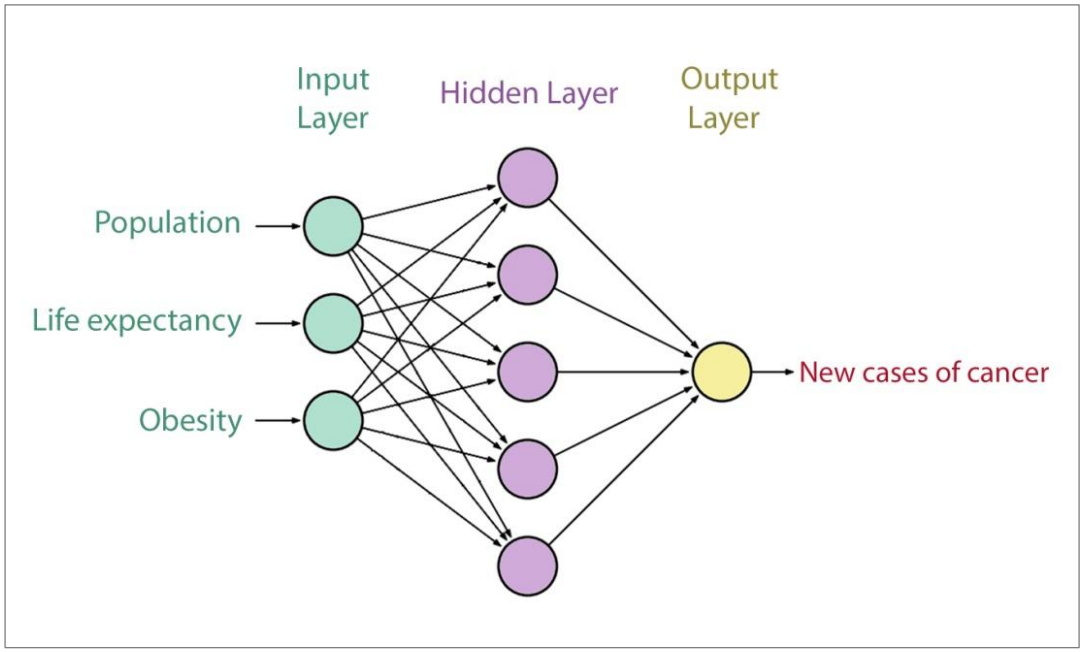

Figure 18. *The structure of our artificial neural network algorithm (ANN)*

Our analysis was performed by using the Software package Matlab R2014b (Mathworks Inc.). Inputs were classified by "mapminmax" function of Matlab, to be inserted between -1 and +1 for accounting the differences and degrees of magnitude of these variables. Taken together, about 70% of data for used to train our model and 30% to validate our predictions.

3.4 Results

3.4.1 Prostate cancer

The incidence of this tumor has decreased from 200cases/100,000 habitants observed in the 1990s in the United States to less than 150/100,000 in 2010. Based on our predictions, the incidence will go down till 50/100,000 from 2025 (*Figure 19A*).

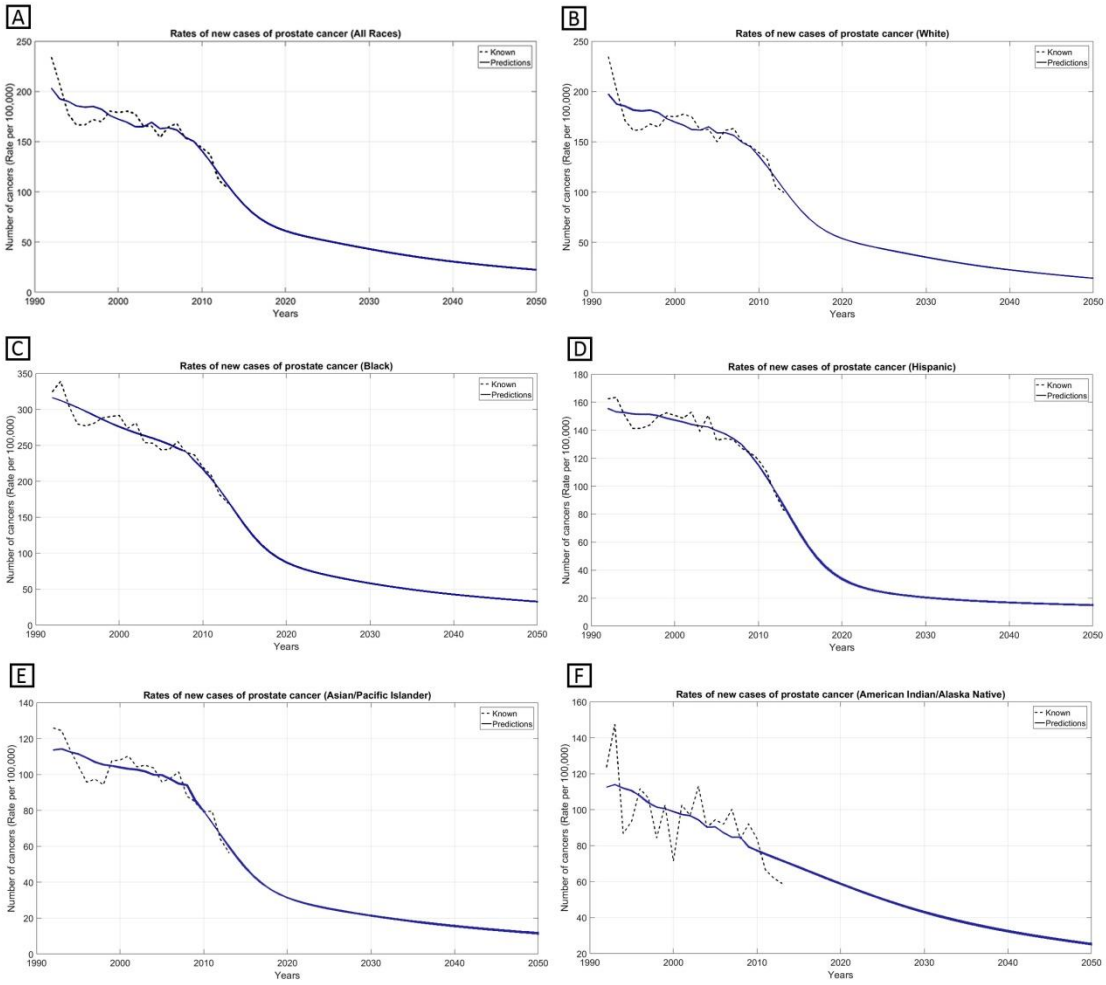

Figure 19. *Trend and predicted new cases of prostate cancer overall (A) and by Ethnicity (B=White; C=Black; D=Hispanic; E=Asian/Pacific Islander; F=American Indian/Alaska Native)*

Based on the evidence that the output also depends on races, we retrained this ANN with prostate cancer cases of White, Black, Hispanic, Asian/Pacific Islander and American

Indian/Alaska Native ethnicities. Regarding all the different races, our predictions show a fast decrease starting from 2010 to 2018, becoming slower from 2020 till the plateau obtained in 2050 (*Figure 19A*). The trend reported in the overall population is similar to that observed in White patients, which shows an incidence of less than 200/100,000 cases in the 1990s, further decreasing under 50/100,000 in 2020s (*Figure 19B*). The incidence is higher in Black patients (*Figure 19C*), who register an incidence lower that 200/100,000 only since 2012 and will fall down under 50/100,000 only after 2020 (*Figure 19C*). On the other hand, Asian/Pacific and American Indian/Alaska native patients are associated with a lower incidence (*Figure 19E, 19F*), with only American Indian/Alaska Native Races showing a decreasing trend almost steady (*Figure 19F*).

The fading in prostate cancer reduction from 2018 could be a consequence of the fading in life expectancy and population increase. The racial differences are related to behavioral distinctions and unequal access to high-quality health systems, although this difference is quickly diminishing.

3.4.2 Breast cancer

The incidence of this tumor can be considered almost constant in the last 25 years, considering that from 1990s has gone from 133 cases/100,000 to 124/100,000 habitants in 2015 (*Figure 20*).

According to our predictions, the incidence of breast cancer will fall to 123/100,000 in 2020, with a plateau in 2030 (*Figure 20*). Performance of Train and Validation phases showed that the ANN algorithm gained worst results (Performance of Train = 0.641; Validation phases = 0.577) in comparison with prostate, colorectal and lung cancer, may be due to the huge variety of cancer-related risk factors associated with the development of breast cancer.

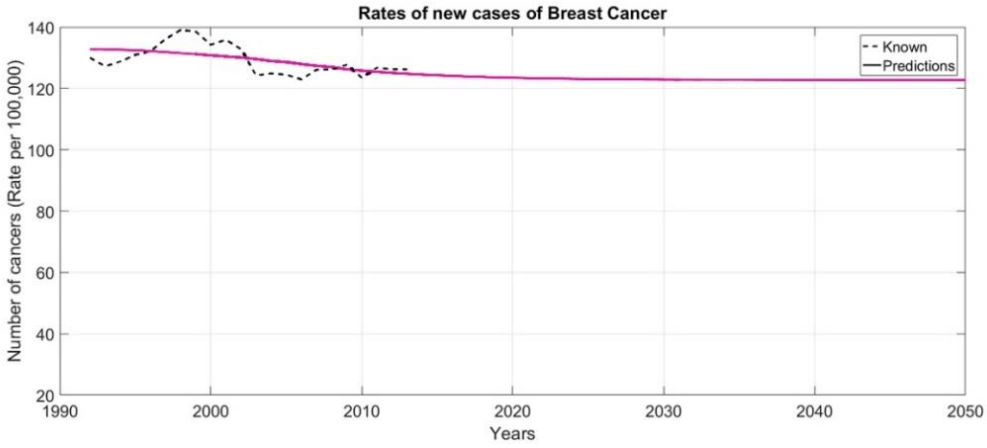

Figure 20. *Trend and predicted new cases of breast cancer. Our calculations are based on population, life expectancy and obesity data for female*

3.4.3 Colorectal cancer

The incidence of this tumor has progressively augmented from 1970s (60 cases/100,000 habitants), reaching a maximum in 1985 (66/100,000, *Figure 21A*). Since late 1980s, the decreasing trend led to an incidence of 55/100,000 in 2000 and to 35/100,000 in 2015 (*Figure 21A*). According to our predictions, the incidence will account for a minimum of 30/100,000 in 2025, reaching a plateau till 2050 (*Figure 21A*).

Based on the role of gender in this tumor [109], we successively predicted the incidence in men (*Figure 21B*) and women (*Figure 21C*). We observed that the incidence reached its maximum in both males (79/100,000) and females (57/100,000) in 1985 (*Figure 21B, 20C*). Notably, our predictions show that the decrease of the incidence will reach a plateau in 2030 in men (30/100,000), whilst the incidence will drop under 20/100,000 in 2050 in women (*Figure 21B, 21C*).

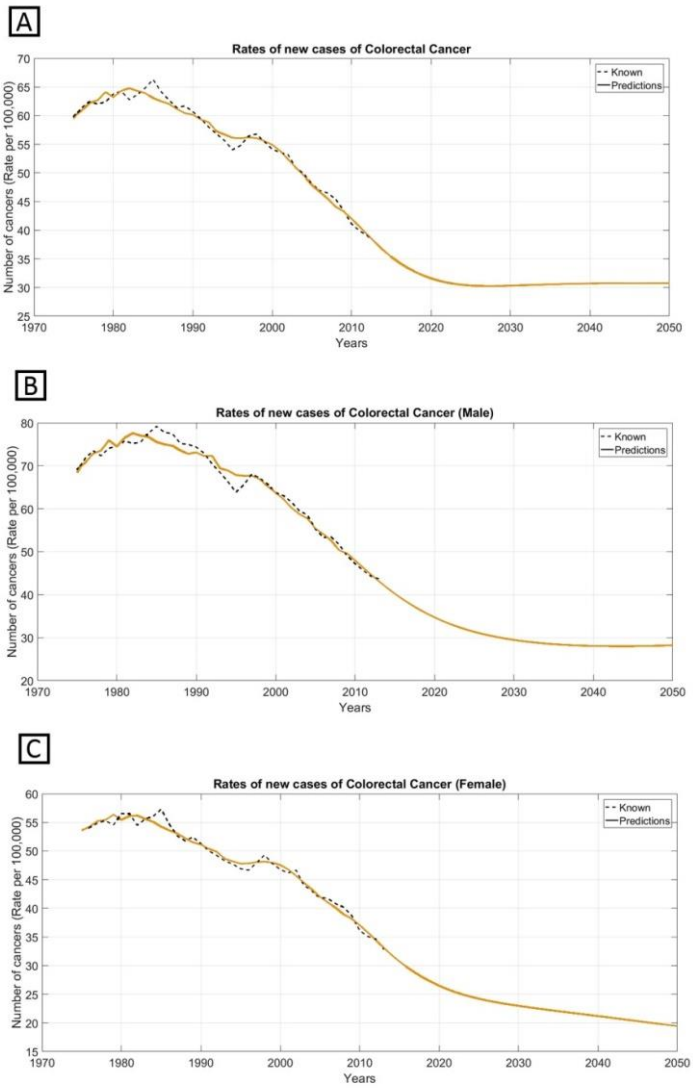

Figure 21. *Trend and predicted new cases of colon cancer overall (A) and by gender (B=males; C=females). Our calculations are based on population, life expectancy and obesity for males and females*

3.4.4 Lung cancer

Since 1970s, the incidence of lung cancer has augmented from 53 cases/100,000 habitants, to a maximum of 69/100,000 in 1992 (*Figure 22A*). After this year, the gradually reduction in tobacco consumption has caused a decrease in the incidence of lung cancer, as evidenced in *Figure 22A*.

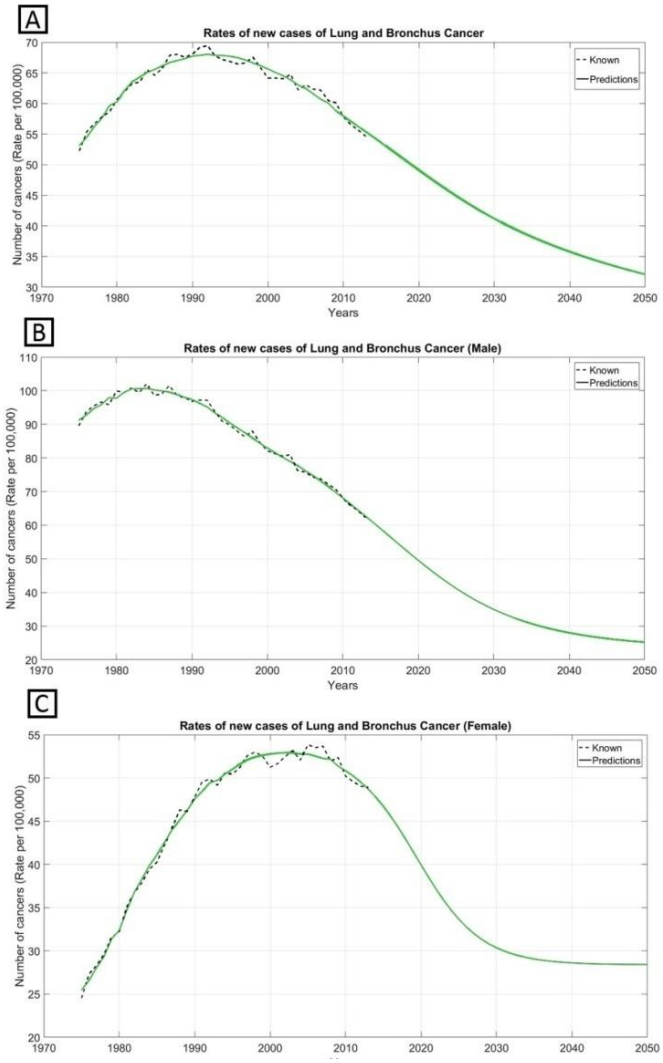

Figure 22. *Trend and predicted new cases of lung cancer overall (A) and by gender (B=males; C=females).*

This positive trend, according to our predictions, will lead to a reduction till 42/100.000 in 2030 and till 32/100,000 in 2050 (*Figure 22A*).

After this step, we decided to focus on the different incidence of lung cancer registered in males (*Figure 22B*) and females (*Figure 22C*), mainly due to the distinct time changes in the smoking attitude in the last 40 years.

While the maximum incidence was observed in 1984 in men (102/100,000), the highest value (54/100,000) in women was registered in 2005,may be related to the fast augment of tobacco consumption among females about 20 years later than men (*Figure 22B, 22C*). Of

note, the fall of the incidence seems to be slower in males than in females, with a plateau from 2050 (25/100,000), differently from the plateau predicted for females from 2035 (28/100,000, *Figure 22B, 22C*).

3.5 Result Interpretation

The variety of factors that influence the risk of developing cancer has led to the necessity of developing novel predicting tools with the ability of training from historical series of data. On this scenario, ANNs seem to represent the best candidate due to the possibility of continuously implementing the accuracy of this model by increasing the series of included input variables. Moreover, ANNs take into account the time changes of included variables, which represent a typical feature of cancer-related risk factors, such as smoking attitude, obesity or racial migrations, and can be an indirect tool to measure the impact of prevention campaigns, screening programs and innovation technologies.

Among the four tumors with the highest incidence, we observed a general decrease of tumor burden in the United States. The incidence trend of prostate cancer registered in the 1980s and early 1990s (*Figure 19A*) were probably associated with the introduction of prostate-specific antigen (PSA) screening, which allowed the detection of asymptomatic diseases [110]. The reduction in tumor incidence from 2010 to 2013 can be correlated with the limitations in PSA testing. Indeed, the US Preventive Services Task Force (USPSTF) published a recommendation on the use of PSA as a screening tool for prostate cancer. The task force, basing on data from Prostate, Lung, Colorectal and Ovary cancer screening study (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, recommended that the potential harms of testing (erectile dysfunction, incontinence and serious surgical complications) were major than the benefits (PSA screening reduced cancer-related mortality by 4 men for every 1000 men, after 14 years of

follow-up) [111].

In breast cancer, the ANN did not reach good performances. The low data variability since 1990 till 2050, together with the huge series of risk factors associated with the development of this disease, ,can partially give a reason to the worst performance of our algorithm in this disease. This evidence indicates that the number of new cases does not parallel with the trends observed for age and obesity in the United States (i.e. the peak from 1995 to 2002 in cancer incidence in a time-interval characterized by the reduction of both risk factors) and support the need for identifying more effective input variables beyond the risk factors recognized by the WHO.

Regarding colorectal cancer, the reduction of the incidence rates before 2000 should be correlated with the changes in risk factors and the diffusion of screening (fecal occult blood testing (FOBT) and endoscopy) [112]. The prevalence results distinct between males and females due to a series of variables including estrogen exposure, menopausal status, insulin resistance, chronic inflammation and steroid hormones [113, 114].

As for lung cancer, it is the leading cause of cancer-related death in both men and women [115]. Decreasing its incidence constitutes a major objective for cancer researchers worldwide, and both the results of these enforces and the global prevention campaigns aimed to reduce smoking attitude are represented in Figure 22A, which show a drop in the incidence of lung cancer. This progressive decrease would be even faster as an effect of the global policy towards the 2040 tobacco-free world goal [116]. Concerning the gender differences (*Figure 22B, 22C*), they parallel with the historical attitudes in tobacco consumption, with females starting to smoke in large number later and at older ages than men.

However, our study has a series of limitations, including: (1) biases related to data selection, although partially decreased by performance analysis and validation phase; (2)

the variety of cancer-associated risk factors, which may be only partially represented by the three major risk factors reported by WHO for the four most frequent tumours.

In conclusion, our model based on ANN algorithm to predict tumor burden in US could represent a crucial resource to plan and evaluate cancer-control programs. Urgent worldwide policies towards a dramatic decrease of cancer-related risk factors are absolutely needed and will contribute to the drop of incidences and the route to cancer eradication in future decades.

CHAPTER 4

ESTIMATION OF PRESENT AND FUTURE COSTS OF BREAST CANCER

4.1 Therapeutic and socio-economic landscape of breast cancer

Breast cancer is the most common cancer among women in the world and is the leading cause of death in developing countries with an estimated increase of 6 million new cases in the next 20 years [117]. It has been estimated that 266,120 new cases of invasive breast cancer and 63,960 of non-invasive tumors in 2018 in the United States [118] (*Figure 23*).

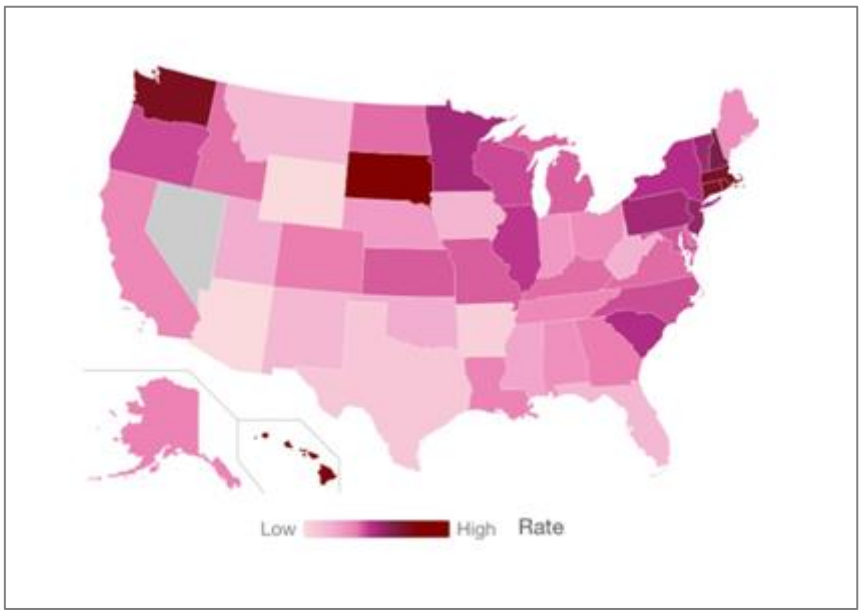

Figure 23. *Annual breast cancer incidence rate per 100,000 people [118]*

In Italy, the Italian Association of Tumor Registry (AIRTUM) together with the Italian Association of Medical Oncology (AIOM) estimated in 2018 52,800 new cases of breast cancer, with an increase of about 8,000 new cases compared to 2011 [119].

In 2017, Stefano Capri and his group, using the data from the cancer register of the Agency of Health Protection of the Province of Milan, estimated how the costs of cancer are distributed in the different stages of the disease with the aim of evaluating the variables

that influence the average cost of treatment of breast cancer. Through a generalized linear model they studied the costs related to 12,580 cases of breast cancer with a total cost of € 22,515 per patient inclusive of average costs for diagnosis, treatment, follow-up and for medical dedicated to the treatment of patients [120] (*Figure 24)*.

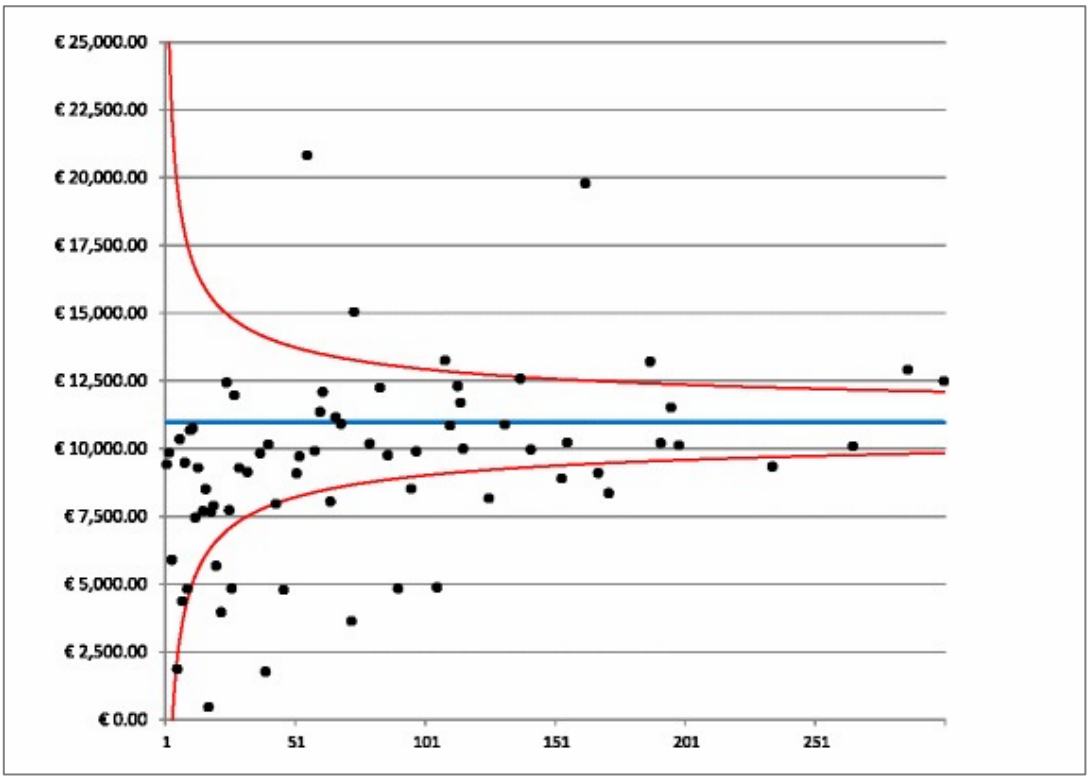

Figure 24. *Distribution of costs related to the volume of hospital in Italy [120]*

An important element in breast cancer treatment has been the introduction, even in this type of disease, of "molecular target" drugs, which are directed towards specific targets expressed in cancer cells, increasing patients' life expectancy. Alongside this success, however, these new drugs have a much higher cost than previous agents. This can be explained by the higher costs related to the research and development of these drugs, leading to both an increase of the investment in the development of new drugs from $10,000 (1960) to $70,000 (2010) and a reduction of the death rate from 1,300/100,000 to 800/100.000 patients [121].

In recent years, the study and research of molecular targets associated with a better prognosis for cancer patients and fewer side effects of therapies is becoming more and more important. Specifically, it was discovered that a part of breast tumors express the oncogene called HER2. This allowed to identify two well-defined disease classes, HER2-positive and HER2-negative tumors. The progress in understanding the role of presents of HER2 has allowed, in this type of disease, to develop drugs such as Trastuzumab, Pertuzumab and Lapatinib that are targeted towards this genetic alteration. In contrast, in the HER2 negative patients, drugs such as Bevacizumab, Everolimus and Palbociclib have been developed, leading to an advantage in terms of overall survival and quality of life.
The purpose of the following work is to identify and estimate the different costs of the use of these drugs by making a prediction on the costs incurred for their employment.

4.2 Materials and Methods

We estimated a cost for each patient basing on an ideal height 1.60 m and an ideal weight of 60 kg and considering every patient as a candidate to receive all the drugs approved for the specific type of breast cancer (for HER2 positive: Pertuzumab + Trastuzumab, T-DM1 and Lapatinib; for HER2 negative: Bevacizumab, Everolimus and Palbociclib). The doses of Lapatinib, Everolimus and Palbociclib are fixed and orally administered for all patients, independently from their height and weight. The dose of Bevacizumab is calculated considering 5 mg of drug for each kg of patient weight. As for Pertuzumab plus Trastuzumab and T-DM1, the doses are calculated based on the body surface obtained by Mosteller formule:

$$\text{Body Surface } (\text{m}^2) = \sqrt{\text{Height (cm)} \times \text{Weight (kg)} \div 3600}$$

To estimate the cost of the entire treatment for each patient, we considered the median duration of treatment expressed in the clinical trials as Progression-Free Survival (PFS), defined as the time from the start of targeted therapy to tumor progression or death.

We used to estimate the total number of patients treated in the United States from 2015 to 2050 the results obtained by ANN reported in Chapter 3. To quantify the number of patients who will receive a treatment through targeted approaches, we have to consider that only the 20% of the total number of patients with a diagnosis of breast cancer will develop metastases during their life [122]. Of them, 20% will result affected by breast cancer tumors harboring HER-2 positivity, while the 80% will be affected by HER2 negative tumors [123].

4.3 Results

4.3.1 Estimated per patient cost with HER2 positive tumours

As previously reported, patients affected by HER2 positive breast tumors can receive three different target therapies: (1) the combination of Pertuzumab and Trastuzumab, (2) T-DM1 and (3) Lapatinib. The first combination is characterized by a median duration of treatment of 18.5 months in the 808 patient enrolled in the clinical trial [124]. Otherwise, the administration of T-DM1 was associated with a median disease control of 9.6 months in the clinical trial that has led to its approval by FDA [125], while Lapatinib registered a median PFS of 8.4 months [126].

Taking into account the ideal height and weight reported in the Materials and Methods, we calculated the cost for one month of therapy and for the median duration of treatment expressed by median PFS for each agent. The highest cost is registered by the combination of Pertuzumab and Trastuzumab. Indeed, the monthly cost of this therapeutic approach can be estimated in $9,390 ($4,890 + $4,500), with a cost for the median entire treatment

of $173,715 (*Figure 25*).

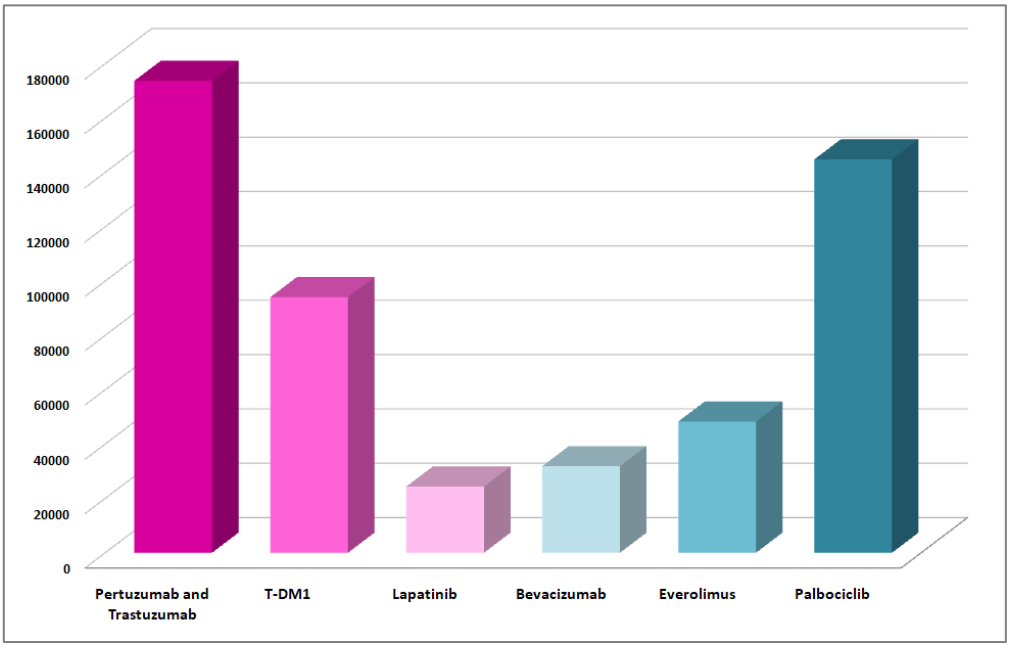

Figure 25. *Estimated per patient cost with different drugs ($)*

On the other hand, the costs for the median duration of target therapy with T-DM1 and Lapatinib result lower and can be estimated in $94,080 and $24,360, respectively (*Figure 25*).

4.3.2 Estimated per patient cost with HER2 negative tumours

As previously in the Materials and Methods, patients affected by HER2 negative tumors can receive three different therapeutic approaches: (1) Bevacizumab, (2) Everolimus (3) Palbociclib. The first drug registered a median duration of treatment of 11.8 months in the clinical trial that led to its approval by FDA [127]. On the other hand, treatment with Everolimus reported a median time of disease control of 6.9 months [128]. As for Palbociclib, two different studies [129,130] showed a median duration of treatment of 20.2 and 9.2 months, respectively.

The highest per patient cost is registered by Palbociclib, which amounted in $198,970 and

$90,620 considering both the clinical trials focused on this agent [129,130], with an average per patient cost of $144,795 (*Figure 25*). On the other hand, the costs for the median duration of target therapy with Bevacizumab and Everolimus result lower and can be estimated in $31,860 and $48,300, respectively (*Figure 25*).

4.3.3 Estimated total cost for HER2 positive and negative tumours (2015-2050)

Firstly, we compared the per patient cost of the two subpopulations given by the addiction of the cost of each drug, which was $292,155 for HER2 positive and $224,955 for negative tumours, respectively. As for the number of metastatic patients estimated by our ANN algorithm and reported in Table 2, it is evident that the incidence will decrease till 2030 and successively slowly increase from 2035 to 2050 (*Table 2*).

YEAR	Estimated N. of patients	Pertuzumab and Trastuzumab	T-DM1	Lapatinib	Bevacizumab	Everolimus	Palbociclib
2015	**24856**	863,572,008	467,690,496	121,098,432	633,529,728	960,435,840	2,879,219,616
2020	**24704**	858,291,072	464,830,464	120,357,888	629,655,552	954,562,560	2,861,612,544
2025	**24622**	855,442,146	463,287,552	119,958,384	627,565,536	951,394,080	2,852,113,992
2030	**24511**	851,585,673	461,198,976	119,417,592	624,736,368	947,105,040	2,839,256,196
2035	**24551**	852,975,393	461,951,616	119,612,472	625,755,888	948,650,640	2,843,889,636
2040	**24560**	853,288,080	462,120,960	119,656,320	625,985,280	948,998,400	2,844,932,160
2045	**24567**	853,531,281	462,252,672	119,690,424	626,163,696	949,268,880	2,845,743,012
2050	**24568**	853,566,024	462,271,488	119,695,296	626,189,184	949,307,520	2,845,858,848

Table 2. *Estimated total cost with different drugs ($)*

Starting from HER2 positive tumors, treatment with Pertuzumab and Trastuzumab is associated with the highest cost in 2015, accounting for $863,572,008, which is

approximately two folds and seven folds the estimated cost of treatment with T-DM1 ($467,690,496) and Lapatinib ($121,098,432), respectively (*Table 2, Figure 26)*. Based on these results, the estimated total cost for the treatment of patients with HER2 positive breast tumours in 2015 is $1,452,360,936 (*Table 3, Figure 27*), with Pertuzumab and Trastuzumab representing the 59.5% of the total amount. Concerning the predictions for 2050, the total cost for patients with HER2 positive tumours is estimated at $1,435,532,808 (*Table 3, Figure 27*), registering a reduction of about 1% compared to 2015.

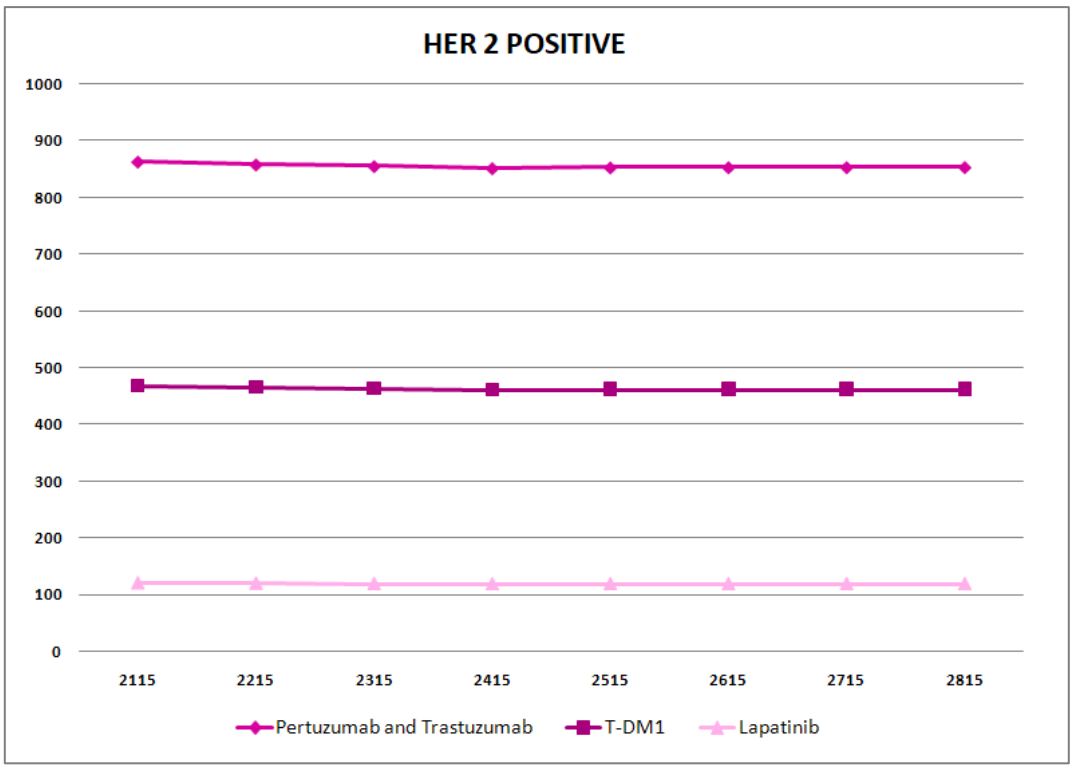

Figure 26. *Estimated total cost with different agents (expressed in one hundred million $)*

Regarding the expense for patients with HER2 negative breast tumours, the highest estimated cost in 2015 is associated with the use of Palbociclib ($2,879,219,616, *Table 2, Figure 28*), while the lowest is registered by Bevacizumab ($633,529,728, *Table 2, Figure 28*).

YEAR	Estimated N. of patients	HER 2 POSITIVE	HER 2 NEGATIVE
2015	**24856**	1,452,360,936	4,473,185,184
2020	**24704**	1,443,479,424	4,445,830,656
2025	**24622**	1,438,688,082	4,431,073,608
2030	**24511**	1,432,202,241	4,411,097,604
2035	**24551**	1,434,539,481	4,418,296164
2040	**24560**	1,435,065,360	4,419,915,840
2045	**24567**	1,435,474,377	4,421,175,588
2050	**24568**	1,435,532,808	4,421,355,552

Table 3. *Estimated total year cost for HER2 positive and HER2 negative breast tumors ($)*

The total cost for HER2 negative tumours in 2015 is estimated in $4,473,185,184, with Palbociclib, Everolimus and Bevacizumab accounting for the 64.4%, 21.5% and 14.1%, respectively (*Table 3*, *Figure 27*).

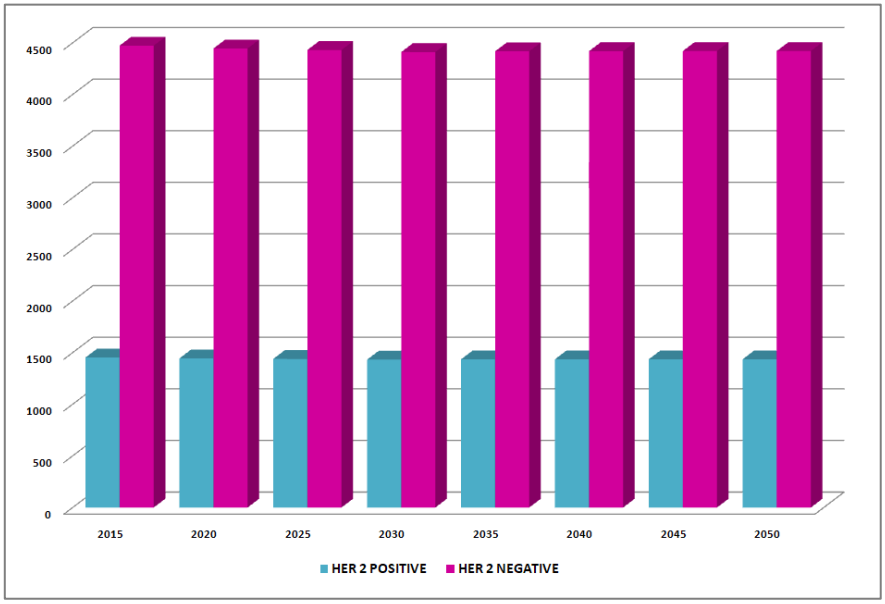

Figure 27. *Estimated total year cost for HER2 positive and HER2 negative breast tumors (expressed in one hundred million $)*

As for HER2 positive tumours, we estimate that the total cost will decrease by about 1% in 2050 (*Table 3, Figure 27*).

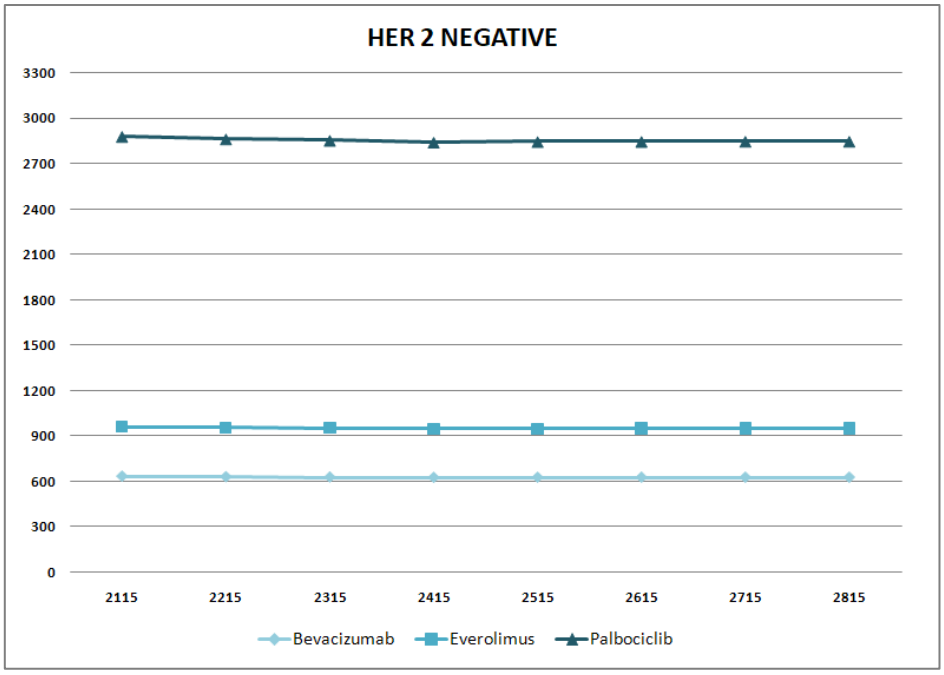

Figure 28. *Estimated total cost with different agents (expressed in one hundred million $)*

Taken together, these data show that the cost for the HER2-negative patients was $3,0208,24,248 higher that for HER2-positive tumors in 2015, and this difference will decrease to $2,985,822,744 in 2050 (*Table 3, Figure 27*).

4.3 Result Interpretation

In recent years the therapeutic scenario in the field of cancer is completely changing. In particular, therapeutic treatments for breast cancer are evolving towards specific therapies no longer generalized, for example through the use of targeted drugs. In our study, we estimated the increasing costs of breast cancer treatment in the United States. This is mainly due to the entry into clinical practice of combinations of drugs such as Pertuzumab and Trastuzumab together with Palbociblib for the treatment of HER2 positive and

negative tumors, representing the two main subtypes of this disease. These high costs can be explained on one hand by the increase in the per mg cost of drugs used and, on the other hand, by the extreme and exciting results that lead patients with this type of disease to a diagnosis much more encouraging and positive than in the past. Treatment of the HER2 negative tumors results more expensive than HER2 positive and this is mainly due to the smaller number of patients experiencing this type of disease.

There are many elements that explain the progress of the incidence of this disease [131]. The International Agency for Research on Cancer (IARC), the WHO Cancer Research Agency, has published a new report which estimates the growth in breast cancer incidence due to various factors such as increase in the average age and population. From 2000 to 2010, in the United States, Americans aged 65 or over were over 5 million, an increase of about 15% compared to the total growth of 9.7% [132,133].

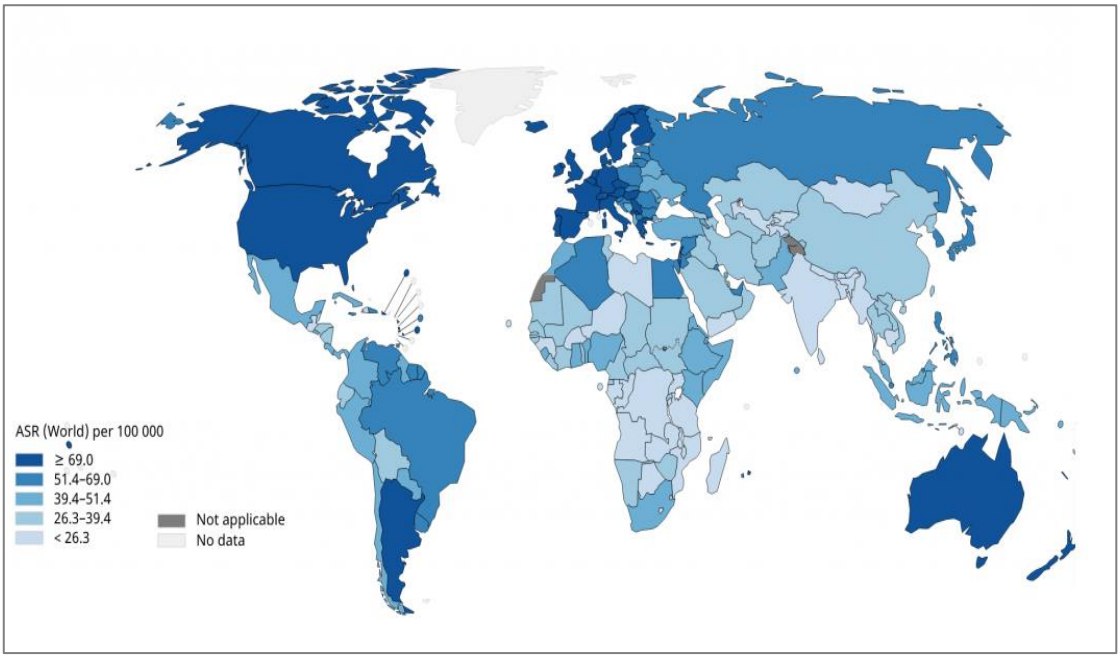

Figure 29. *Estimated age-standardized incidence rates (World) in 2018, breast, female all ages [136]*

The greatest number of people over 65 will lead to an increase in chronic diseases that will

affect the growth of the elderly population, which will be about 90 million by 2050 [134,135].

Furthermore, there is a gender difference between male and female diseases. In fact, male tumors are extremely heterogeneous depending on the socio-economic status of the countries and on the type of disease, having a three times higher incidence in the economically more developed countries, such as Europe and North America compared to economically disadvantaged countries. This situation does not occur in female tumors, where we do not find much difference between developed and developing countries (*Figure 29*) [136].

The non-heterogeneity of the incidence of female tumors explains why in many countries the companions of prevention managed to reduce cancer incidence, such as for lung cancer where we can notice a notable reduction of future incidences. In breast cancer this does not occur incisively. In fact, even in our predictive ANN model we can see a growing trend in estimates of breast cancer incidences in the coming decades.

However, our study is subject to various limitations, due first to having taken as reference that the total number of patients can be subjected to all the best therapies available. This element can lead to a higher estimate of costs especially considering the elderly patients who may not all be able to receive all these treatments. In addition, our estimates have taken into account parameters such as obesity, aging and population growth not considering variables such as the hereditary of this type of disease, which became a major topic following the case of Angelina Jolie. Nevertheless, like other factors could lead to a more accurate estimate of the number of future cases, however the absence of a historical archive on the temporal trend of this as of other variables does not allow their inclusion in artificial intelligence algorithms such as ANN. A further limitation of our analysis is represented by the non inclusion of the variation of the costs of treatments. Indeed, we

considered the cost of each drug as fixed, not taking into account future inflation and the expiration of the various patents in the coming years, being difficult to estimate the trend given the vast time interval (2015-2050) in our study.

Despite these limits, our estimates indicate the importance of assessing the future costs of breast cancer treatments for the coming years in order to improve future economic sustainability, ensuring the best treatment for all patients who will be able to take advantage from the new target drugs, which will lead to better clinical efficacy and less adverse effects. This is extremely necessary given the probable and imminent arrival of immunotherapeutic drugs even in patients affected by breast cancer, whose cost, if not adequately monitored, could further jeopard the economic balance of the health system in future years.

CHAPTER 5

ASSESSING THE ECONOMIC IMPACT OF IMMUNOTHERAPY IN CANCER CARE

5.1 The clinical and economic impact of immunotherapy in cancer scenario

In the last five years, the advances in our knowledge of the role of immune cells in tumor development and progression have led to a therapeutic revolution in this field. The immune system acts as a sensor of tissue homeostasis and control tissue changes during neoplastic transformation. Each stage in the development and progression of cancer is the result of a cross-talk the tumor and host-immune system, which undergo to a series of changes that led from an initial phase in which immune cells are able to eliminate tumor cells to a phase in which they lost this ability and promote tumor growth and invasion (a phenomenon called "Immunoediting", *Figure 30*) [137].

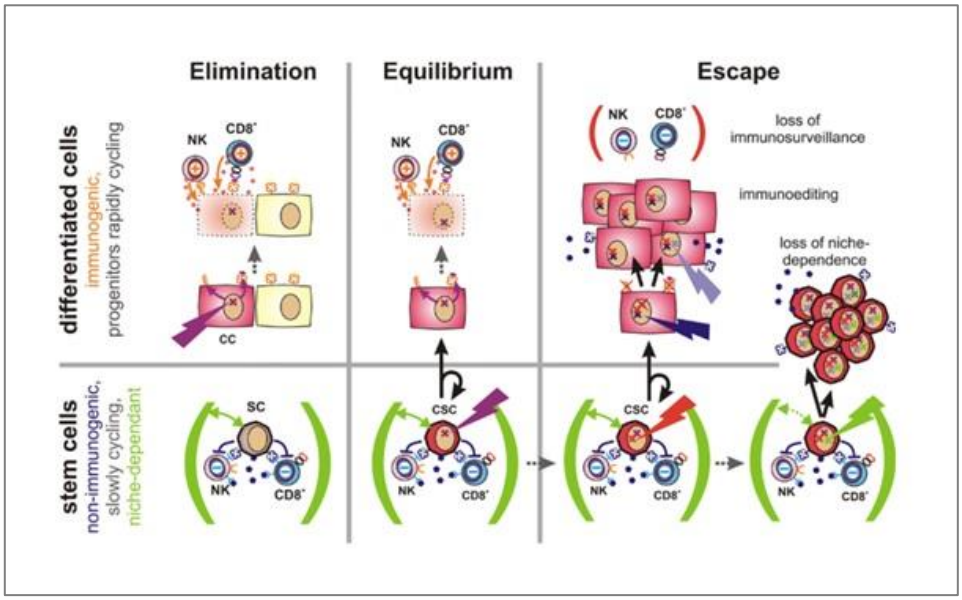

***Figure 30**. Lost of functions by immune cells due to the cross-talk with tumor cells [137]*

Starting from the end of 19th century, the growing awareness of the fundamental role of immune cells has led to the development of a series of immunotherapeutic agents, till the final consecration as a practice changing strategy after 2010 (*Figure 31*).

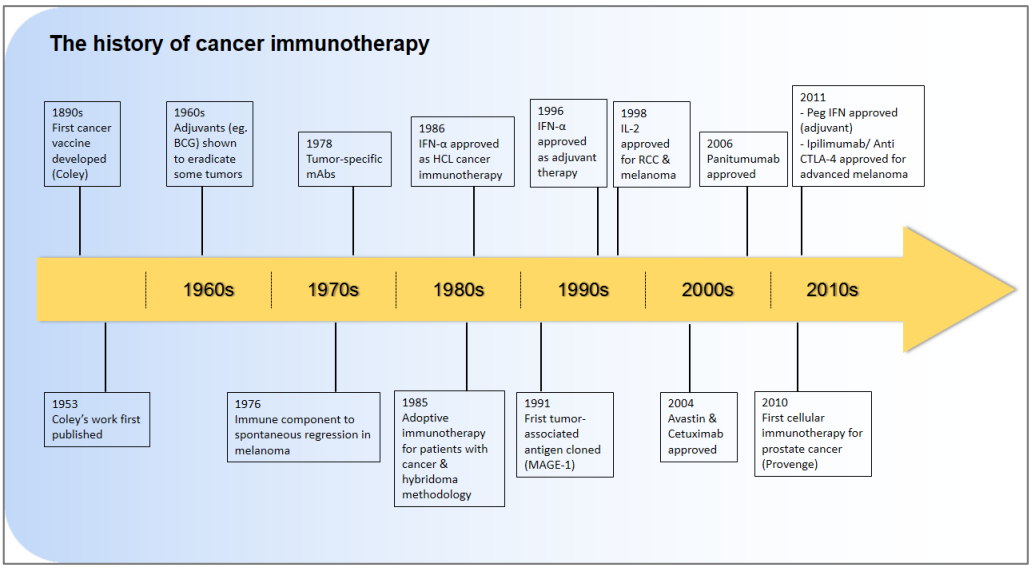

Figure 31. *Development of immunotherapeutic agents from 19th century till now [137]*

On October 2018, Professor James Allison and Professor Tasuku Honjo have won the Nobel prize in Physiology or Medicine for their discoveries on the mechanisms by which tumor cells are able to defuse the killing ability of immune cells (*Figure 32*).

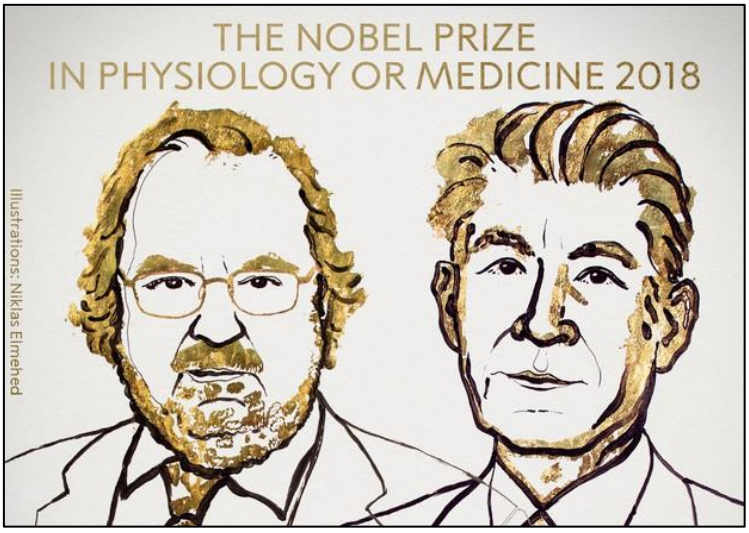

Figure 32. *Nobel price 2018 winners for their discoveries on immunotherapy of cancer*

These advances have led to the development of a series of agents targeting Programmed-Death (PD)-1 and its ligand (PD-L1), including Nivolumab, Pembrolizumab, Avelumab, Atezolizumab and Durvalumab. These agents are currently approved for the treatment of patients with melanoma, lung, renal, bladder and head and neck tumor and have completely changed the quality of life and outcome of cancer patients.

In 2012, the WHO estimated about 1.8 million of lung cancer new cases in the United States (*Figure 33*). Of them, Non-Small Cell Lung Cancer (NSCLC) constitutes the 85% [138], with about 70% of patients with metastatic and 30% with limited disease and 1.5 million of lung cancer-related deaths [139].

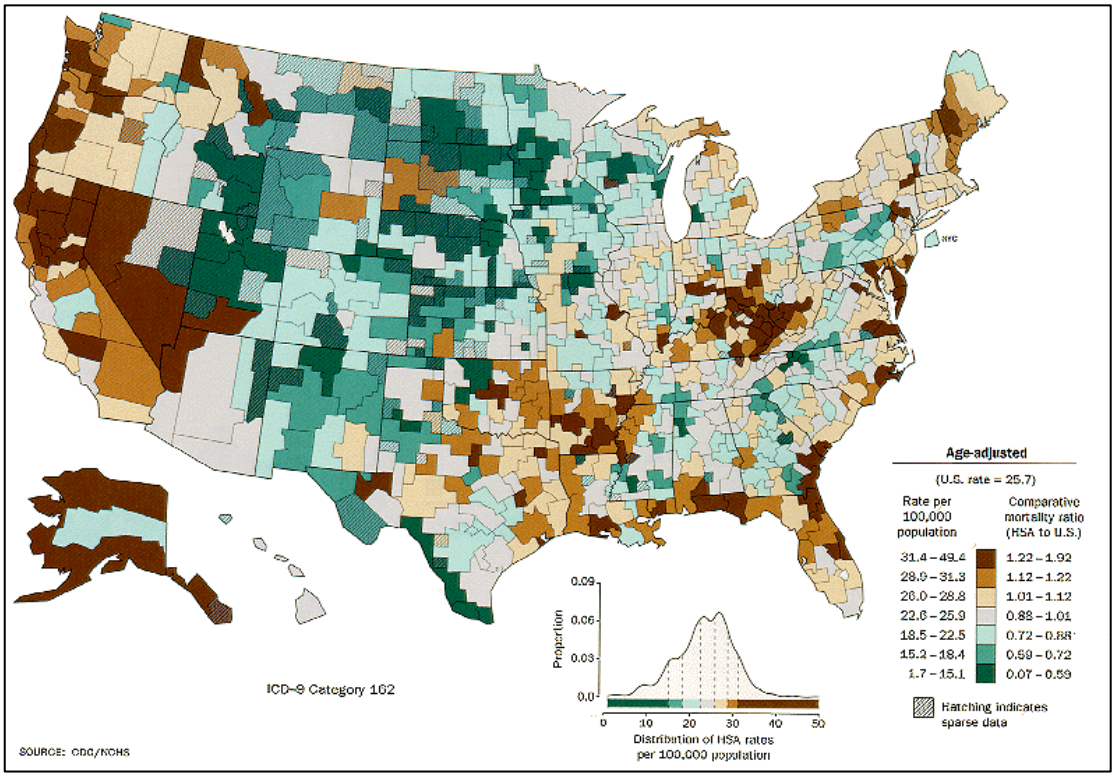

Figure 33. *Incidence of lung cancer in the United States [138]*

In chapter 3, we showed a reduction of the incidence of lung cancer in future years. This can be mainly explained by the progressively decreasing smoking attitude in the United

States, which can be considered the result of effective government anti-smoking advertising campaigns that have increased the awareness about tobacco-induced damages and diseases (*Figure 34*).

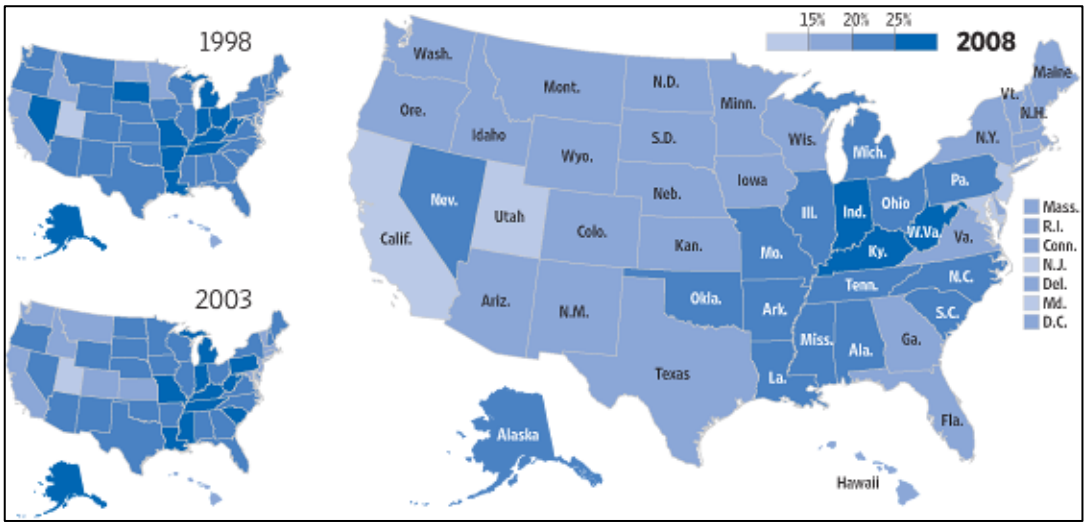

Figure 34. *Smoking prevalence in adults in the United States [138]*

The advent of immunotherapy agents, such as nivolumab and pembrolizumab, has completely changed the therapeutic approach to this disease. Nivolumab was approved in 2015 for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy [140]. This was related to the results of a phase III study comparing Nivolumab compared to chemotherapy showed an advantage in terms of median overall survival (9.2 vs 6.0 months) and rate of serious adverse events (7% vs 55%) [141].

Otherwise, on 2nd October 2015 the FDA approved pembrolizumab for pre-treated patients with metastaticPD-L1 positive [140], basing on the results of the KEYNOTE-001 study [142]. In this study, patients with PD-L1 positive tumours presented a median Progression-Free Survival of 6.3 mouths, with a median OS that was not reached at time of analysis [142]. More recently, Pembrolizumab has demonstrated to be effective and safe in

combination with chemotherapy as first line therapy in patients with metastatic NSCLC [143]. Indeed, this combination, compared to chemotherapy alone, showed a rate of overall survival at 12 months of 69% vs 49% (hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001), and this was independent from PD-L1 status [143], opening to the possibility of using immunotherapy in all NSCLC patients.

Although these drugs have dramatically improved the outcome of patients with lung cancer, their economic impact on the Health System has been absolutely not negligible and merits careful consideration in order to guarantee the economic sustainability of health system and the access to care for all cancer patients. On this scenario, we aimed to calculate in this section the economic burden of immunotherapy in lung cancer patients.

5.2 Materials and Methods

We estimated a cost for each patient basing on an ideal weight of 70 kg and considering every patient as a candidate to receive all the drugs approved for the specific type of lung cancer. To estimate the cost of the entire treatment for each patient, we considered the median duration of treatment expressed in the clinical trials as Progression-Free Survival (PFS), defined as the time from the start of targeted therapy to tumor progression or death.

We used to estimate the total number of lung cancer patients treated in the United States from 2015 to 2050 the results obtained by ANN reported in Chapter 3. To quantify the number of patients who will receive a treatment through immunotherapies, we have to consider that 85% of lung cancer cases are Non-Small Cell Lung Cancer [138] and 70% of patients will present metastases during their life [139]. When requested according to FDA approval, the rate of PD-L1 positivity has been taken from the specific clinical trials, quantified as the 60.8% of NSCLC patients.

5.2.1 Improved survival with immunotherapy in NSCLC

The high percentage (70%) of patients with metastatic tumors explains, together with the not enthusiastic results obtained by chemotherapy [144,145], the low rate of patients (5%) still alive at 5 years from the diagnosis [139]. In the last decade, the therapeutic approach to NSCLC has been fully changed by the introduction of immunotherapy, such as Nivolumab, Pembrolizumab and Atezolizumab. Nivolumab was approved on March 2015 for patients with metastatic squamous NSCLC progressed on chemotherapy [140]. This was based on the results of a clinical study that compared nivolumab vs chemotherapy and showed an advantage in terms of survival (9.2 vs 6.0 months), median duration of disease control (3.5 vs 2.8 months) and incidence of serious toxicities (7% vs 55%) [141].

Successively, the FDA extended its approval also to pre-treated patients with non-squamous NSCLC [140]. In fact, nivolumab showed better results in terms of survival (12.2 vs 9.4 mouths) and rate of serious toxicities (10% vs 54%) compared to chemotherapy [146].

Otherwise, on October 2015 Pembrolizumab was approved by the FDA for previously treated patients with advanced NSCLC expressing PD-L1 protein [140], based on the findings from the KEYNOTE-001 study [142], which showed a median duration of disease control of 6.3 mouths [142].

Finally, Atezolizumab was approved based on the results of a phase III trials that showed a median duration of therapy of 5.6 months [147].

5.3 Results

5.3.1 The cost of Immunotherapy in NSCLC

First we calculated the per patient cost of treatment with Nivolumab, Pembrolizumab and Atezolizumab in NSCLC patients. In Table 4 we summarized the main data on median

treatment duration expressed in number of cycles, dose, price for a single cycle and total price for each patient (*Table 4*).

Drug	Flat	Drug	Price/cycle	Median	Total
Nivolumab	240 mg	$26.064/mg	$6,088	14 cycles	$87,575
Pembrolizumab	200 mg	$46.495/mg	$9,139	9 cycles	$83,691
Atezolizumab	1200 mg	$7.183/mg	$8,620	8 cycles	$68,960

Table 4. *Main characteristics of Immunotherapy*

The highest cost is registered by Nivolumab ($87,575 *Figure 35),* while Pembrolizumab was associated with the lower cost ($68,960, *Figure 35*).

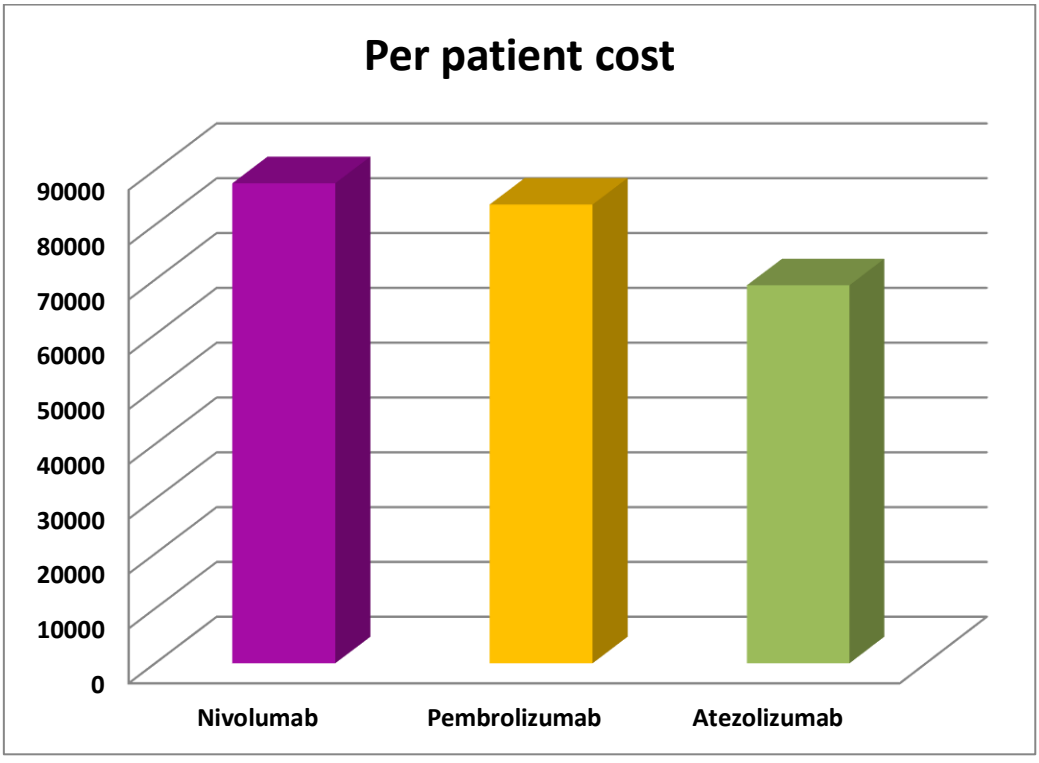

Figure 35*. Per patient cost with different immunotherapies for the median duration of treatment ($)*

Year	Metastatic NSCLC (total)	Metastatic NSCLC (males)	Metastatic NSCLC (females)	Metastatic NSCLC (total PDL1+)	Metastatic NSCLC (males PDL1+)	Metastatic NSCLC (females PDL1+)
2015	62,792	35,112	27,680	38,178	21,348	16,829
2020	53,293	29,603	23,690	32,402	17,999	14,403
2025	44,831	24,596	20,235	27,258	14,954	12,303
2030	38,956	20,977	17,979	23,685	12,754	10,931
2035	35,228	18,099	17,129	21,419	11,004	10,414
2040	33,543	16,602	16,941	20,394	10,094	10,300
2045	32,692	15,801	16,891	19,877	9,607	10,270
2050	31,769	14,937	16,832	19,315	9,082	10,234

Table 5. *Predictions of the number of patients*

As a second step, we calculated the number or patients who result candidate to receive the three drugs, considering that all patients treated with chemotherapy are potentially candidate to receive immunotherapy (*Table 5*).

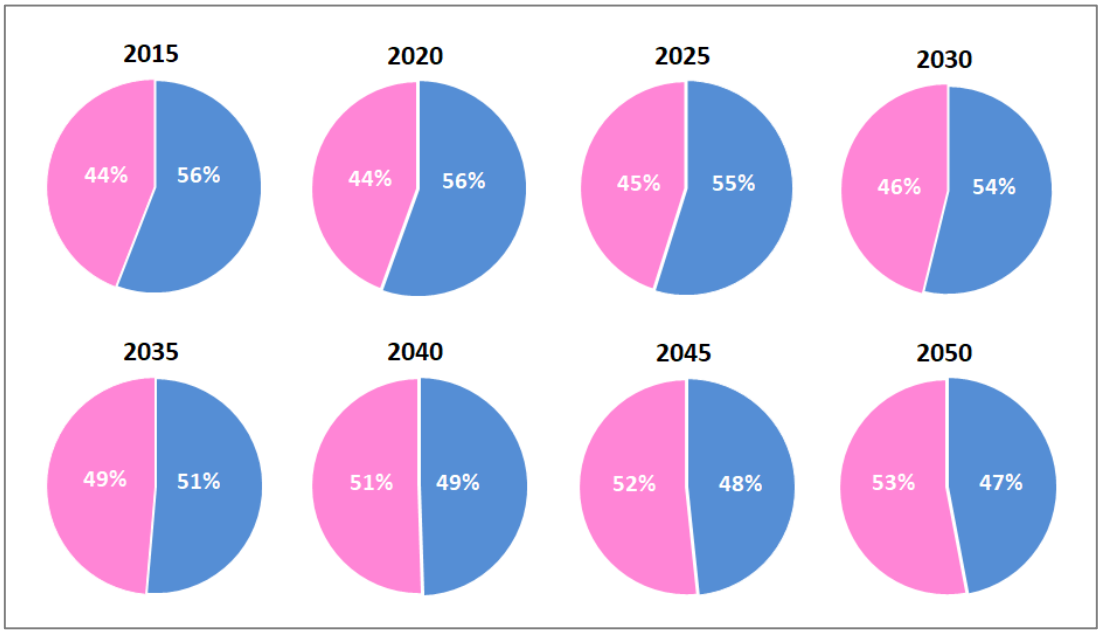

Figure 36*. Distribution of patients based on gender (2015-2050)*

The only exception is represented by Pembrolizumab, which can be administered only in

patients with PD-L1 positive tumors. The distribution of patients from 2015 to 2050 between the two genders are reported in *Figure 36*. Otherwise, Figure 37 shows the number of patients based on gender who present PD-L1 positive tumors are result thus candidate to receive Pembrolizumab.

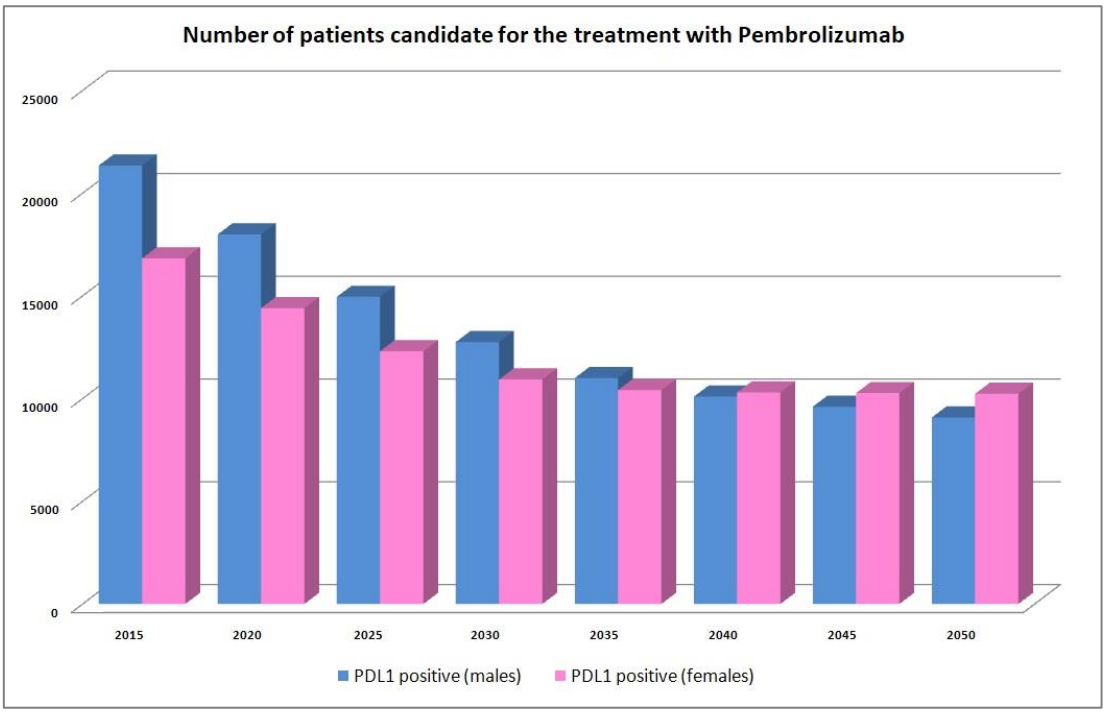

***Figure 37**. Number of patient with PDL1 positive tumors*

NIVOLUMAB						
Year	N. of patients			Cost		
	All	Males	Females	All	Males	Females
2015	62,792	35,112	27,680	5,499,021,223	3,074,945,661	2,424,075,562
2020	53,293	29,603	23,690	4,667,130,972	2,592,485,790	2,074,645,182
2025	44,831	24,596	20,235	3,926,115,547	2,154,004,333	1,772,111,214
2030	38,956	20,977	17,979	3,411,557,688	1,837,036,692	1,574,520,996
2035	35,228	18,099	17,129	3,085,106,550	1,585,046,635	1,500,059,915
2040	33,543	16,602	16,941	2,937,487,065	1,453,893,002	1,483,594,063
2045	32,692	15,801	16,891	2,863,025,983	1,383,808,919	1,479,217,065
2050	31,769	14,937	16,832	2,782,155,725	1,308,097,266	1,474,058,459

***Table 6.** Cost for the treatment with Nivolumab*

PEMBROLIZUMAB						
Year	N. of patients			Cost		
	All	Males	Females	All	Males	Females
2015	38,178	21,348	16,829	3,195,123,035	1,786,650,626	1,408,472,409
2020	32,402	17,999	14,403	2,711,765,798	1,506,324,622	1,205,441,176
2025	27,258	14,954	12,303	2,281,210,003	1,251,551,610	1,029,658,394
2030	23,685	12,754	10,931	1,982,233,949	1,067,382,360	914,851,589
2035	21,419	11,004	10,414	1,792,554,457	920,967,352	871,587,105
2040	20,394	10,094	10,300	1,706,782,390	844,762,519	862,019,871
2045	19,877	9,607	10,270	1,663,517,906	804,041,223	859,476,682
2050	19,315	9,082	10,234	1,616,529,467	760,050,114	856,479,353

Table 7. *Cost for the treatment with Pembrolizumab*

ATEZOLIZUMAB						
Year	N. of patients			Cost		
	All	Males	Females	All	Males	Females
2015	62,792	35,112	27,680	4,330,145,630	2,421,333,174	1,908,812,455
2020	53,293	29,603	23,690	3,675,082,522	2,041,425,294	1,633,657,228
2025	44,831	24,596	20,235	3,091,577,826	1,696,147,746	1,395,430,081
2030	38,956	20,977	17,979	2,686,394,726	1,446,554,956	1,239,839,770
2035	35,228	18,099	17,129	2,429,334,258	1,248,128,073	1,181,206,186
2040	33,543	16,602	16,941	2,313,092,869	1,144,852,542	1,168,240,326
2045	32,692	15,801	16,891	2,254,459,284	1,089,665,578	1,164,793,706
2050	31,769	14,937	16,832	2,190,778,862	1,030,047,245	1,160,731,617

Table 8. *Cost for the treatment with Atezolizumab*

By multiplying this number for per patient cost we obtained the total expense reported in Table 6-8 and Figure 38. Based on the differences between males and females, we divided the total expense based on gender (*Figures 39-40*).

From these Figures it is evident that the total expense will gradually decrease till 2050. This tendency is much more clear in males, characterized by a progressively reduced

incidence associated to the decreasing smoking attitude. This cost reduction results higher from 2015 to 2020, characterized by a decrease of 17.8%, while the lowest difference is registered from 2040 to 2045 (2.6%).

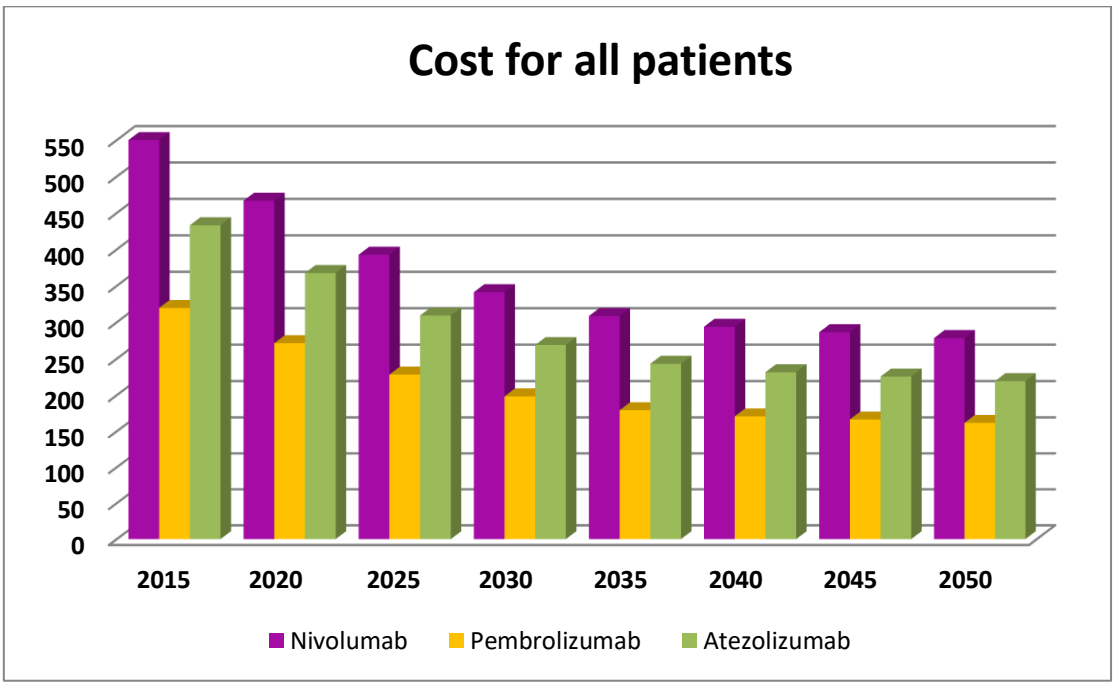

***Figure 38**. Cost with different immunotherapies (expressed in $10,000,000)*

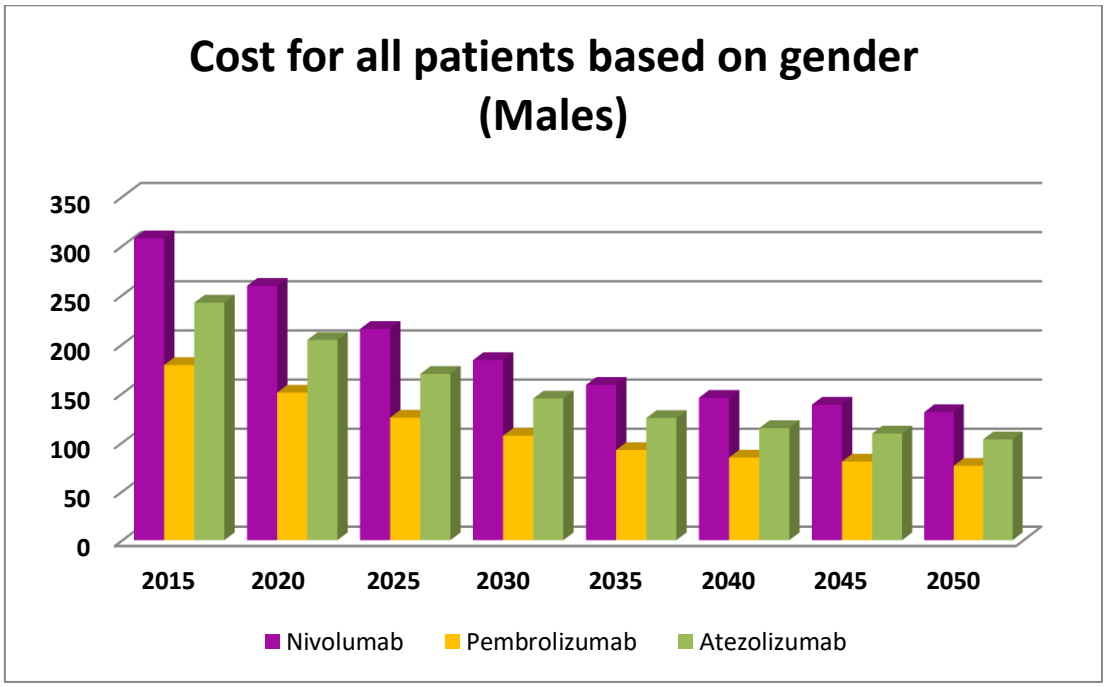

***Figure 39**. Cost with different immunotherapies in males (expressed in $10,000,000)*

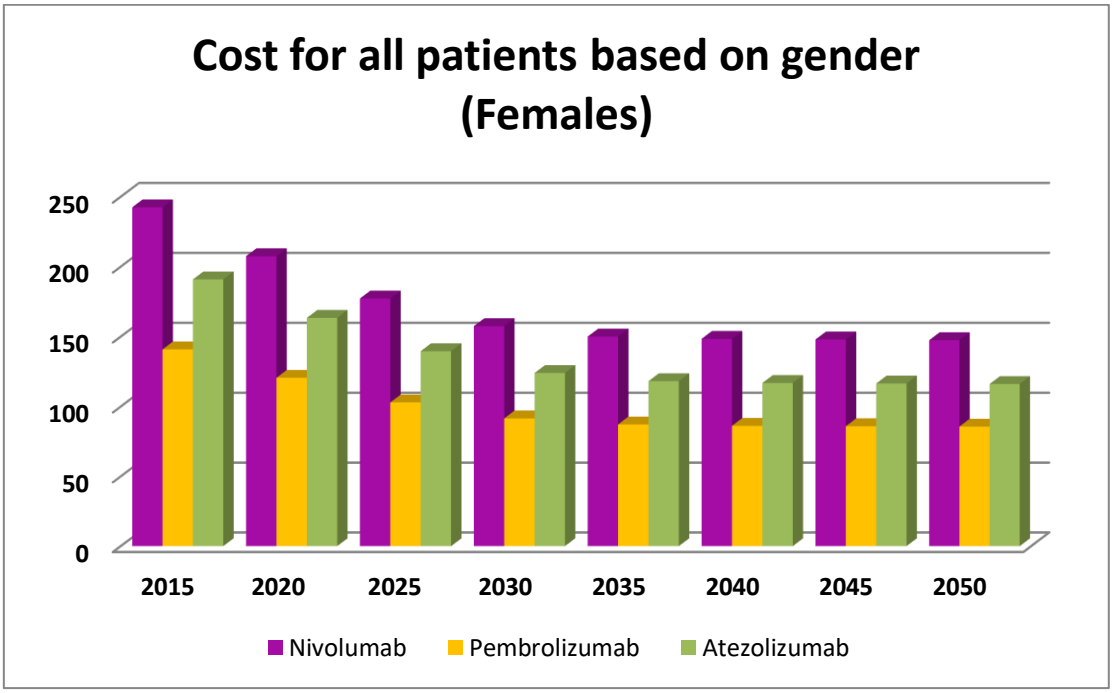

***Figure 40**. Cost with different immunotherapies in males (expressed in $10,000,000)*

Furthermore, these results also suggest that Pembrolizumab results less expensive than the other two agents. In particular, the expense associated with the use of Pembrolizumab for the total number of NSCLC PD-L1 positive metastatic patients results $3,195,123,035 in 2015 and will decrease to $1,616,529,467 in 2050. On the other hand, the use of Nivolumab is correlated with the highest cost, which will pass from $5,499,021,223 in 2015 to $2,782,155,725 in 2050 (*Table 6-8*).

5.4 Result Interpretation

The economic sustainability of health care represents a fundamental topic for current worldwide economies. The necessity of increasing the control on the cost-effectiveness of emerging drugs in the oncology field is mainly due to the development of targeted agents and immunotherapeutic approaches that have led to a crucial increase in patients' life

expectancy, although associated with a rapid increase of the cost of management in this setting.

In this Chapter, we estimated the per patient and total costs related to the administration of anti-PD-1 agents Nivolumab, Pembrolizumab and Atezolizumab in patients with metastatic lung cancer. Based on our results, Nivolumab registered the highest per patient and total cost (*Figure 35*), while Pembrolizumab resulted the less expensive agent.

Our analysis presents several limitations. Indeed it is based on predictions, which are not limited by biases related to, for example, data collection and analysis. Nevertheless, our data clearly support the necessity of a straight collaboration between cancer and economy researchers to design the tools necessary to guarantee the sustainability of Health System in future years. This relationship will lead to a series of consequences: (1) the design of new tools to evaluate the correlation between drug cost and clinical benefit (i.e. the expense for the management of toxicities, the cost related to medical personnel, the socio-economic impact of disease status, etc); (2) the creation of novel measures of drug reimbursement, which will mainly consider the percentage of patients who do not respond to therapies; (3) the development of new clinical and molecular factors for the identification of patients who will respond to highly expensive targeted agents and immunotherapies.

In conclusion, the enthusiastic endpoints reached by immunotherapy in patients with metastatic lung cancer are opening the way to a huge and fast diffusion of these agents into daily clinical practice. However, these results should carefully take into account the economic burden of immunotherapy in order to guarantee the access to cure for all cancer patients in future years.

CHAPTER 6

DISCUSSION

Health spending represents an important percentage of the budgets of worldwide countries, also influencing the management and choices of economic subjects. In this regard, for example, 73% of Americans in 2013 (about 57 million) have found difficulties in paying medical expenses due to reduced spending on food, clothes and other necessities and more than 40% have done an extra job for health insurance payment [148].

In 2016, US health care costs were $3.3 trillion. This makes health care one of the largest industries in the country. It is equal to 17.9% of the Gross Domestic Product (GDP), unlike the average expenditure of 11 high-income countries, namely Canada, Germany, Australia, United Kingdom, Japan, Sweden, France, the Netherlands, Switzerland, Denmark, which was estimated at 11.5% in a study published in the Journal of the American Medical Association [149].

In comparison, the cost for health care was $27.2 billion in 1960, just 5% of GDP. This translates into an annual health cost of $10,348 per person in 2016, which is almost double that in other countries and much more than that spent in the 1960s ($146) [149].

Healthcare costs have risen faster than average annual income, which is around $59,019, creating an inability to pay health care costs for people. In fact, more than 17% of Americans spent more than a year on payment while more than 8% could not pay [148].

This American health situation can be explained at various levels. Researchers at Harvard Chan School described why the costs are so high. One of the main aspects are the other costs of drugs, health services and diagnosis in America. In addition, many health-related costs are related to planning, regulation and the managerial level of the American health care system [149].

Moreover, in a report published in the Journal of the American Medical Association (JAMA) it is highlighted that America in 2016 spent about 18% of the GDP in health care compared to other countries that are associated to a value that varies between 1% and 3% [150].

This study states that an important element of the high cost of health care in the United States is spending on health care workers. In fact, nurses, doctors and specialists earn much more in America than other countries, making an average amount of about $219,000, in 2016, two folds the average of the other countries (about $87,000 in Sweden and about $155,000 in Germany) [150].

As for drug-related spending, the US cost per capita is about $1,500 compared to other countries where spending is around $750 per capita. This scenario is similarly projected also regarding health services. In fact, even the surgical interventions cost more having an average cost, in 2013, of about $75,000 compared to the average costs of the Netherlands of about $15,000 and $36,000 of Switzerland. Moreover, the average cost for a Magnetic Risonance is more than $1,000, compared to about $400 in Australia and almost $500 in the Netherlands [150].

According to a study by the Organization for Economic Cooperation and Development (OECD), Asia records an annual growth of around 15% in healthcare spending, recording an almost 4-fold increase in inflation (around 4%) [151]. This scenario is mainly caused by the aging of the population and the gradual abandonment of family ties, i.e. the choice of families not to care for the elderly by transferring them to specialized facilities but also by the increase of diseases such as tumors, cardiovascular diseases, diabetes caused by changes foodstuffs following the economic development and which, according to estimates, will exceed 39% in 2030 [152].

Also England is in line with the other States with regard to the increase in health expenditure of about 4% between 2001 and the following 9 years, resulting in a growth rate of about 0.5% from 2010 to 2014 [153].

The industrialized countries have to fight against two opposing phenomena: on one hand, the increasing growth in the "health demand" of the population due above all to the augment of elderly people that Eurostat has estimated will reach about 13% in 2080 [154]. On the other hand, the continued restriction of state budget, which will progressively reduce the funds dedicated to health market. In this regard, a recent study by a group of British researchers published in the British Medical Journal (BMJ) shows that the cuts in health care costs negatively affect substantially the health status of the population. [155]. The researchers estimated a 1% reduction in health expenditure between 2010 and 2014, compared to the period between 2001 and 2009 where there was an increase in spending of just under 4% and this change was also found compared to mortality rates which increased by about 1% in the period in which health expenditure decreased (2011-2014) unlike the period between 2001 and 2010 where the rate was about 0.75% [155].

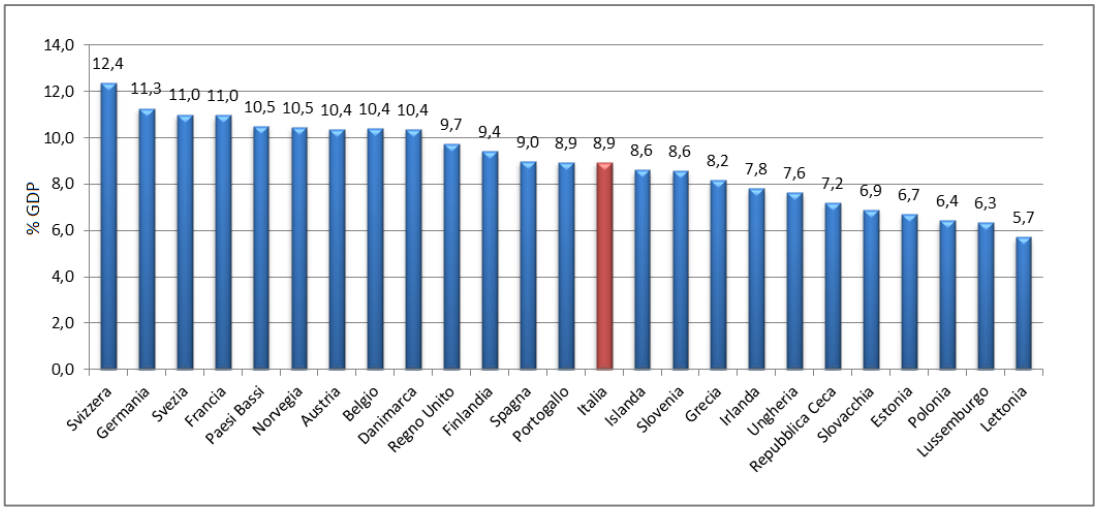

***Figure 41**. Percentage of GDP related to health spending [157]*

Italy is also in a similar situation. From 2010 to today, healthcare spending is just over 0.6% annually in nominal terms, compared to a higher annual average inflation rate of around 1.1% [156]. Next to these little reassuring data, we can see how the percentage of spending of the national health system (NHS) compared to total spending has increased from about 14.5% to almost 14% in the four years from 2010 to 2014 [156] using 8.9% of GDP in 2016 (*Figure 41*) [157].

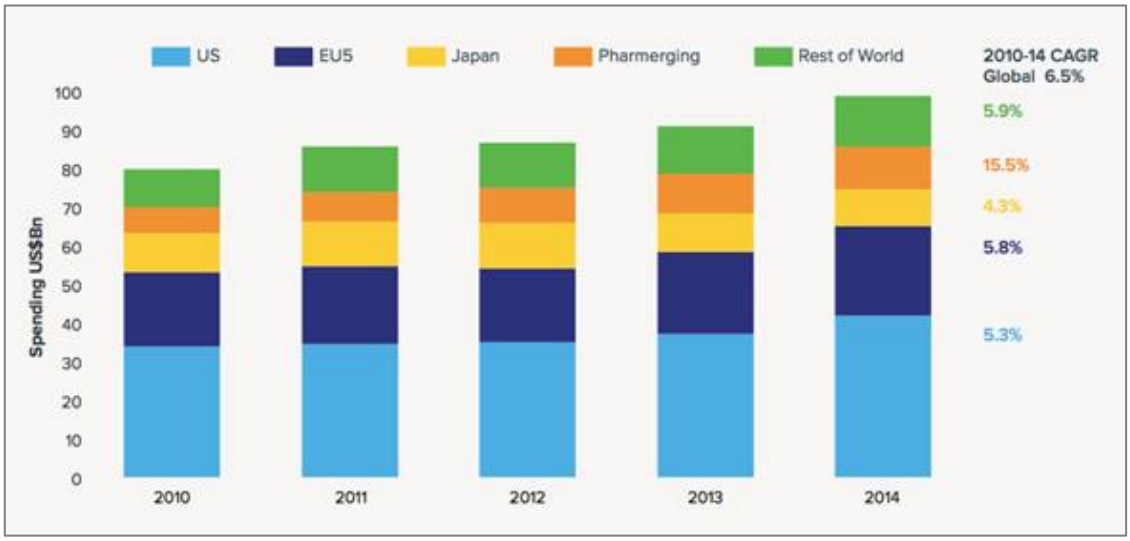

Figure 42. *Global Oncology drug spending [159]*

The approach to cancer patients has globally changed in the last few years. A cluster of innovative drugs with promising new mechanisms of action has led to enthusiastic results for a large variety of tumors. The wide number of clinical trials currently ongoing or under regulatory review suggests that this revolution from the "chemotherapy era" is just the beginning of a new phase characterized by more personalized (but even more expensive) medicines in the oncological field. With just a few molecules approved against each tumor target, the cost competition has been very reduced till now but will represent a measure to

rationalize the management of economic resources in future years. Furthermore, the longer median duration of therapies has also increased the cost of these therapeutic approaches.

Global spending for oncology treatments and supportive cares increased by 10% in 2014, reaching $100 billion compared to the $75 billion registered in 2009 (*Figure 42*) [158,159].

Based on this time trend, it is possible to foresee a total spending in 2018 ranging from 117 to $147 billion. These predictions take into account the low rate of patent expiries and biosimilar competition, which we will be counteracted by the rising rate of diagnosis and available therapies.

Targeted therapies account for almost half of total spending and have grown by over 14% in the last five years [158]. In the major developed markets, the cost increase is related to the augmenting number of protecting brands and new products (*Figure 43*), which have led from a per patient expense of $71 reported in the United States in 2010 to $99 in 2014 (*Figure 44*) [158,159].

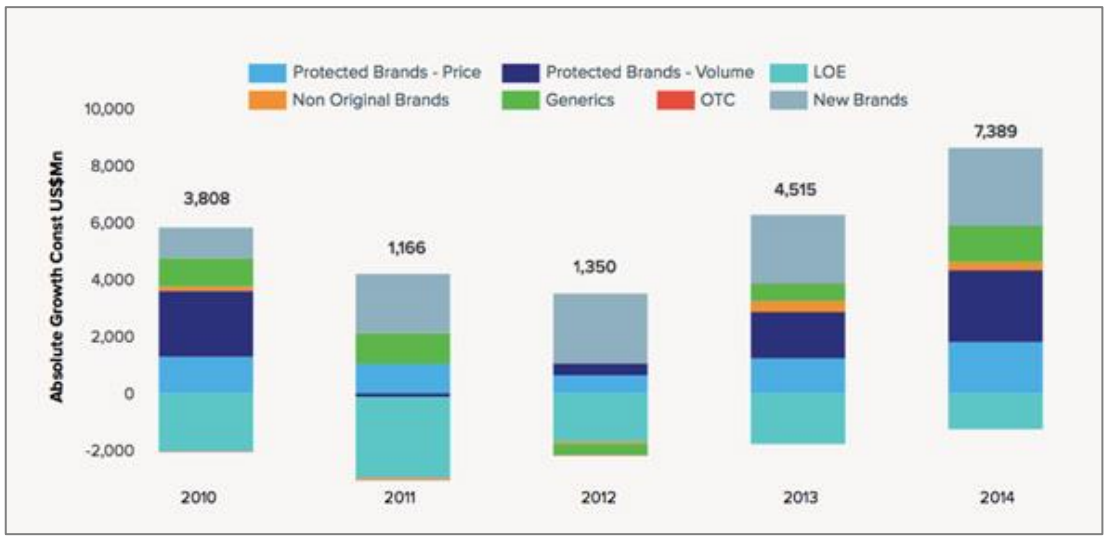

***Figure 43**. Oncology spending growth dynamics in developed markets (2010-2014) [159]*

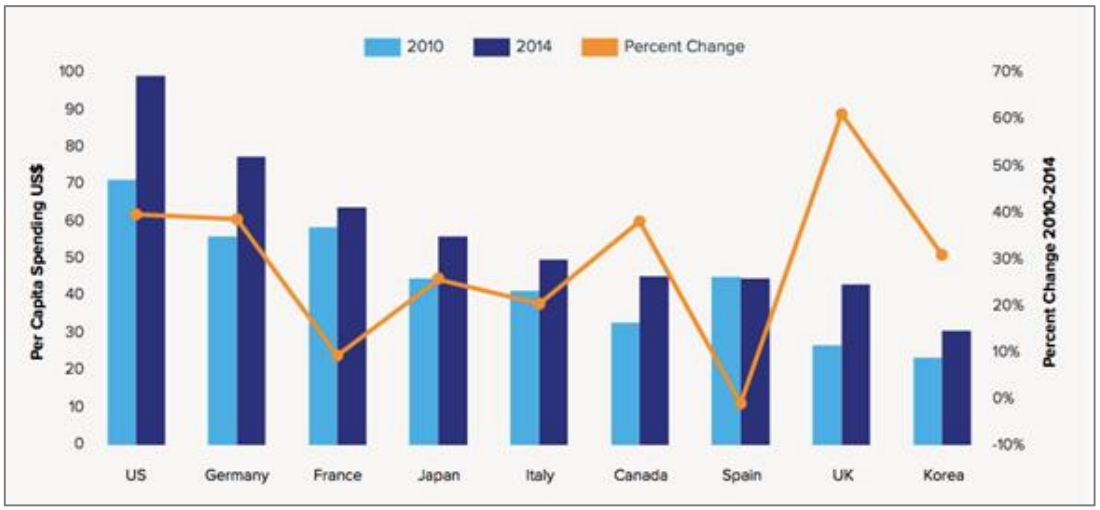

Figure 44. *Per patient spending for oncological drugs (2010-2014) [159]*

This corresponds to an increase in inflation-adjusted terms of about 40% of treatment costs over the past ten years, thus registering an augment of the rate of oncology drug spending, raised from 10% to 11.3% in the last five years in US and from 13% to 14.7% in Europe (*Figure 45*) [158,159].

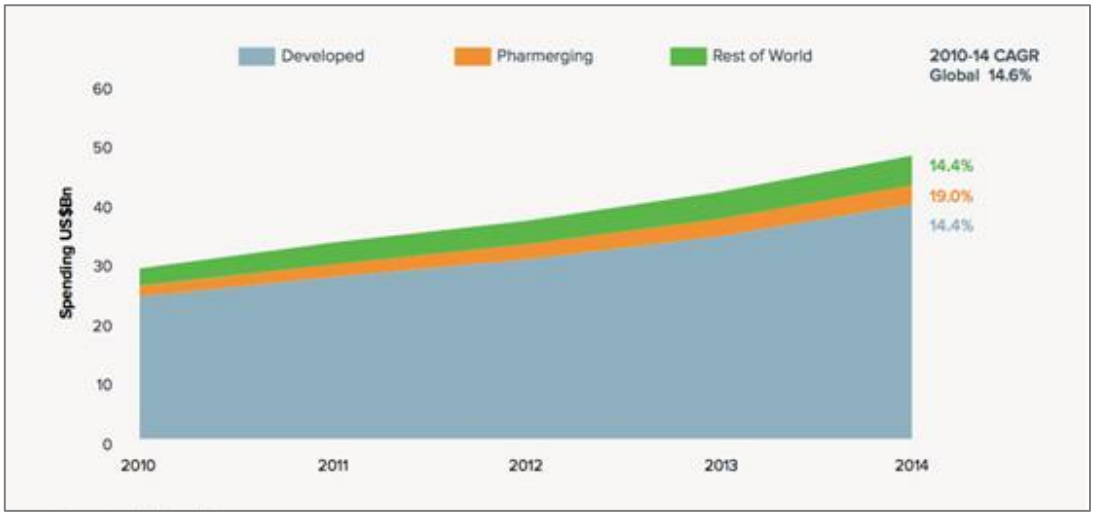

Figure 45. *Target therapy growth (2010-2014) [159]*

This fact will become even more complicated based on the prediction that is expected that each single target agent will receive three or more indications in future years (*Figure 46*) [158,159].

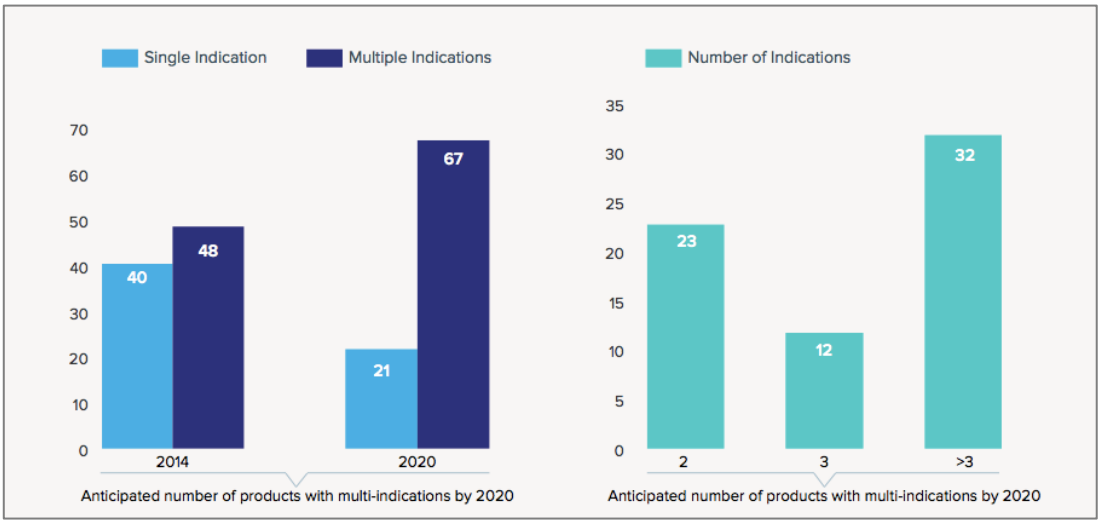

Figure 46. *Number of indication for target therapies [159]*

This will complicate the assessment of an appropriate pricing by payers since, in the majority of cases, drug's clinical value may be higher in areas with small patient subpopulations while most of its use is for indications with relatively less value. For example, Japan and South Korea have had access to almost half of globally launched new oncology drugs in the last five years (*Figure 47*) [158,159].

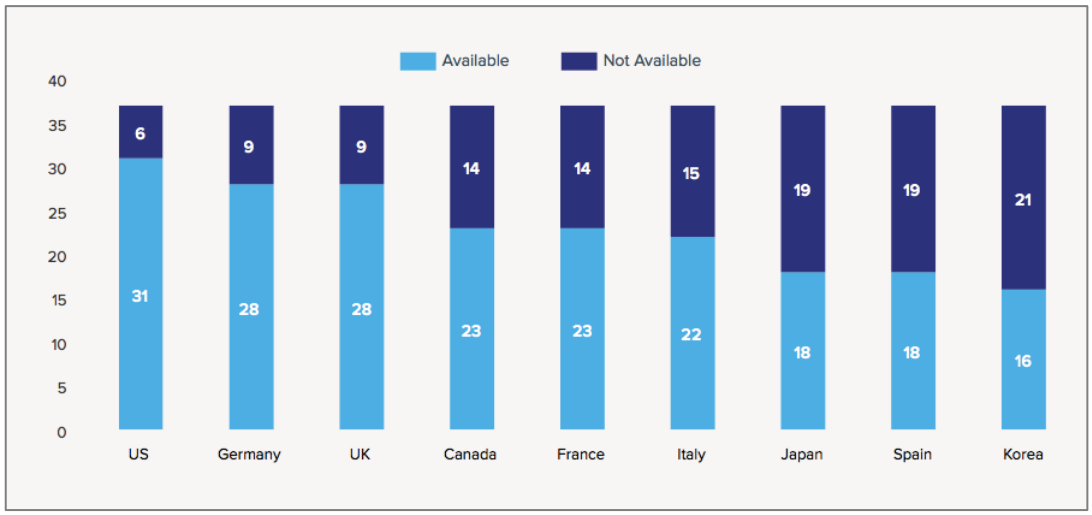

***Figure 47**. Availability of new oncology molecules (2010-2014) [159]*

The rate of available new molecular entities varies among the different therapeutic approaches, with a prevalence of available hormonal therapies based on their low cost (*Figure 48*). This phenomenon will reach a minimum in future years based on the high cost of immunotherapies.

***Figure 48**. Availability of new oncology molecules based on drug typology (2010-2014) [159]*

Within the nine developed markets, growth has increased from 1.4 (2012) to $7.4 billion (2014). The access to best available cures varies among different countries and reflects the difficulties in assessing the right value for emerging therapeutic interventions. Even when available, the lack of drug reimbursement tools not based on formal cost-effectiveness basing on spending per quality life year gained (cost per QALY, or CPQ) constrains the access for patients. Indeed, the differences among drug reimbursement in different countries are significant (*Figure 49*) [160].

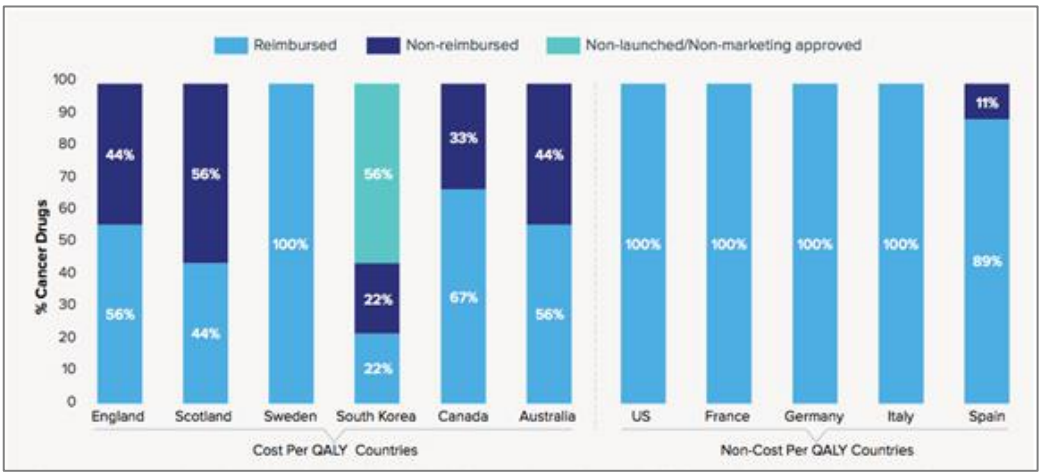

Figure 49. *Reimbursement status among different countries [160]*

In our manuscript we have taken into account several aspects implicated in predicting the economic burden of novel targeted therapies and immunotherapies in cancer patients. In particular, in Chapter 2 we explored the relationship between drug cost and toxicity, aimed to assess if there is a correspondence between the high cost and the reduction of drugs' impact on patients' quality of life. Based on our analysis, the cost of targeted agents seems to be not correlated with their toxicity profile. Indeed, several drugs registered both the highest costs and rate of severe adverse events and drug interruptions, thus suggesting the

necessity to include variables related not only to the cost-effectiveness but also to the cost/toxicity of emerging oncological drugs. This results extremely important also considering the cost due to the management of adverse events (i.e. costs for patient hospitalization, personnel involved, supportive care), which are absolutely not negligible but usually not considered among the costs taken into account for the economic evaluation.

In Chapter 3, we decided to realize a personalized model to predict the incidence of the four most frequent tumors in the United States. This was mainly due to the evidence that the majority of already existing models are based only on mathematical trends elaborated from already registered data. Differently, our model based on ANN algorithm takes into account not only the number of previous cases but also the historical trends of the risk factors associated with the development of these diseases. Thus, with our model it is possible to quantify the effect of activities aimed to reduce the tumor-related risk factors, such as anti-smoking policies, or to calculate the effect of ethnicity migrations on the incidence of different tumors. Under an economic point of view, our model does result more accurate and can reduce the biases associated with predictions, thus allowing to calculate the economic burden of cancer patients in future years with a reduced rate of errors, estimated <2%. Based on our predictions, we calculated in Chapter 4 the expense related to the use of molecularly targeted agents in patients with breast cancer. The necessity of dividing patients based on their biological profile into due categories (HER2 positive and negative tumors) results absolutely needed due to the evidence that a progressively lower rate of patients are treated with traditional chemotherapy due to the worst clinical results and drug tolerability compared to emerging agents. Nevertheless, our analysis does not consider the cost related to the pathological assessment of the biological subtypes, which may require from hundreds to thousands dollars for a single patient depending on the complexity of the diagnosis.

On the other hand, Chapter 5 was focused on the cost of immunotherapy, which includes the most expensive (but also more effective) emerging drugs. The amount of the expense related to the use of immunotherapy in lung cancer patients in future years underlines the need of optimizing the selection of patients who can really benefit from this therapeutic approach. Moreover, it promotes the investment of economic resources for the research of predictive biomarkers of tumor response in order to reduce the rate of ineffective and clinically/economically "toxic" agents in cancer patients.

In conclusion, our data taken together suggest that a careful evaluation of drug costs is absolutely fundamental and will affect the possibility of accessing to best available cures in future years. This cannot forget the straight necessity to design more effective tools for price assessment and reimbursement, which should be diffused globally to avoid disparities among countries. The collaboration between the different entities involved in this process represents the basis for future economic strategies, which should be aimed to equilibrate the rate between sustainability and quality of cures worldwide. Although several step forward have been done, the route to an ideal use of economic resources in Health System seems still long and full of pitfalls.

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FIGURE LEGENDS

TABLE LEGENDS

Table 1. Characteristics of targeted agents: Efficacy, Toxicity and Cost.

The different colors in the columns related to cost refer to the different cost groups described below in Figure 10.

BCC = Basal-cell Carcinoma; GBL = Glioblastoma; GIST = Gastrointestinal Stromal Tumor; NSCLC = Non Small Cell Lung Cancer; PFS = Progression-Free Survival; RCC = Renal Cell Carcinoma.

Table 2. Estimated total cost with different drugs ($)

Table 3. Estimated total year cost for HER2 positive and HER2 negative breast tumors ($)

Table 4. Main characteristics of Immunotherapy

Table 5. Predictions of the number of patients

Table 6. Cost for the treatment with Nivolumab

Table 8. Cost for the treatment with Atezolizumab