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«ΟΙΚΟΝΟΜΙΚΑ και ΔΙΟΙΚΗΣΗ της ΥΓΕΙΑΣ»

"Real World Data of Nivolumab as Second-Line Treatment in Advanced Non-Small Cell Lung Cancer in Greece: Effectiveness Analysis and Cost Estimation of the Treatment"

Μάμαλη Ελένη

Διπλωματική Εργασία υποβληθείσα στο Τμήμα Οικονομικής Επιστήμης
του Πανεπιστημίου Πειραιώς για την απόκτηση
Μεταπτυχιακού Διπλώματος Ειδίκευσης στα Οικονομικά και Διοίκηση της Υγείας.

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UNIVERSITY of PIRAEUS

DEPARTMENT of ECONOMICS

M.Sc. in Health Economics and Management

"Real World Data of Nivolumab as Second-Line Treatment in Advanced Non-Small Cell Lung Cancer in Greece: Effectiveness Analysis and Cost Estimation of the Treatment"

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To my brother, Dimitrios Mamalis,MD

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Ανάλυση Αποτελεσματικότητας και Εκτίμηση Κόστους του Nivolumab ως Δεύτερης Γραμμής Θεραπεία για τον Προχωρημένο Μη-Μικροκυτταρικό Καρκίνο του Πνεύμονα βασισμένη σε Πραγματικά Δεδομένα Ασθενών

Περίληψη

Υπόβαθρο: Τα τελευταία δύο χρόνια το nivolumab καθιερώθηκε ως η νέα θεραπεία δεύτερης γραμμής για τον προχωρημένο μη-μικροκυτταρικό καρκίνο του πνεύμονα. Η παρούσα μελέτη αποτελεί μια πολυκεντρική αναδρομική μελέτη που βασίζεται σε δεδομένα πραγματικών ασθενών που έλαβαν θεραπεία με nivolumab ως δεύτερη γραμμή ύστερα από επιδείνωση με χημειοθεραπεία.

Μέθοδος: Σε 14 κέντρα υγειονομικής περίθαλψης στην Ελλάδα ασθενείς με στάδιο III-IV μη-μικροκυτταρικού καρκίνου του πνεύμονα, με όλους τους ιστολογικούς τύπους, που είχαν εξέλιξη της νόσου μετά από χημειοθεραπεία με βάση την πλατίνα, υποβλήθηκαν σε θεραπεία με nivolumab ως θεραπεία δεύτερης γραμμής. Σκοπός της μελέτης αυτής ήταν να αξιολογήσει την αποτελεσματικότητα και το προφίλ ασφάλειας του nivolumab σε αυτούς τους ασθενείς, να πραγματοποιήσει ανάλυση υποομάδων και τέλος να εκτιμήσει το συνολικό κόστος που σχετίζεται με τη θεραπεία με nivolumab.

Αποτελέσματα: Συνολικά 141 ασθενείς συμπεριλήφθηκαν στη μελέτη. Η μέση ηλικία των ασθενών ήταν 67,2 έτη, 104 ήταν άνδρες και 107 ήταν καπνιστές, 54,8% είχαν αδενοκαρκίνωμα, 38,7% πλακώδες καρκίνωμα, 64,8% διαγνώστηκαν με στάδιο IV, 13,9% με IIIB και 65% με στάδιο IIIA. Από τους 141 ασθενείς, 19 ασθενείς (13,48%) δεν αξιολογήθηκαν. Από τους 122 ασθενείς που υποβλήθηκαν σε αξιολόγηση το 29% είχε πλήρη/μερική ανταπόκριση, το 34% είχε πρόοδο της νόσου και το 37% είχε σταθερή νόσο. Ο μέσος χρόνος συνολική επιβίωση (OS) ήταν 19,7 μήνες (95% CI, 12,7-NE) ενώ ο μέσος χρόνος χωρίς πρόοδο της νόσου (PFS) ήταν 7,4 μήνες (95% CI, 5,9-11,6). Στην ανάλυση των υποομάδων δεν υπήρξαν στατιστικά σημαντικές διαφορές όσον αφορά την ηλικία και το φύλο. Αξιολογήθηκαν τοξικότητες βαθμού 3-4, αλλά οι τοξικότητες αυτές δεν είχαν επίπτωση ≥5. Μόνο τα άμεσα υγειονομικά κόστη, σε ασφαλιστικές τιμές, που σχετίζονται με τη θεραπεία συμπεριλήφθηκαν στην ανάλυση. Το συνολικό μηνιαίο κόστος της θεραπείας με nivolumab για έναν ασθενή υπολογίστηκε σε 5.616,08€ ενώ το συνολικό ετήσιο κόστος σε 67.392,96€ ανά ασθενή.

Συμπεράσματα: Το Nivolumab απέδειξε το σημαντικό όφελος επιβίωσης στην κλινική πρακτική, καθώς η αποτελεσματικότητα φαίνεται να είναι υψηλότερη σε αυτόν τον πληθυσμό πραγματικών ασθενών σε σύγκριση με τα αποτελέσματα που προέκυψαν από τις κλινικές δοκιμές. Το προφίλ ασφάλειας που προέκυψε από τη μελέτη μας, επιβεβαιώνει εκείνο που αναφέρθηκε στις κλινικές δοκιμές. Το συνολικό κόστος της θεραπείας με nivolumab ως δεύτερης γραμμής για τον προχωρημένο μη-μικροκυτταρικό καρκίνο του πνεύμονα είναι υψηλό, αλλά η αυξημένη αποτελεσματικότητά του και η χαμηλή συχνότητα εμφάνισης ανεπιθύμητων ενεργειών, σε σχέση με προηγούμενες θεραπείες, ευνοούν την ένταξη και την αποζημίωση από τα ασφαλιστικά συστήματα υγείας.

Σημαντικοί όροι: Nivolumab, δεδομένα πραγματικών ασθενών, κλινική πρακτική αποτελεσματικότητα, συνολική επιβίωση, επιβίωση χωρίς εξέλιξη, προφίλ ασφάλειας, υγειονομικά κόστη.

Real World Data of Nivolumab as Second-Line Treatment in Advanced Non-Small Cell Lung Cancer in Greece: Effectiveness Analysis and Cost Estimation of the Treatment

Abstract

Background: For the last two years, nivolumab has become the new standard of care for second line treatment in advanced non-small cell lung cancer. This is a retrospective multicenter study using real world data of pretreated patients with advanced NSCL that received nivolumab as second line treatment.

Methods: In 14 health care centers in Greece patients with stage III-IV of NSCLC, with all histological types, who had disease progression after at least on platinum based chemotherapy, were treated with nivolumab as second-line treatment. The aim of this study was to evaluate the effectiveness and the safety profile of nivolumab in this patients, to perform a subgroup analysis and finally to estimate the total cost related to nivolumab treatment.

Results: A total of 141 patients were included in the study. The median age of the patients was 67.2 years, 104 were male and 107 were current or former smokers, 54.8% had adenocarcinoma, 38.7% squamous carcinoma, 64.8% were diagnosed with stage IV, 13.9% with IIIB and 65% with stage IIIA. Of the 141 patients, 19 patients (13.48%) were not evaluated. From the 122 evaluable patients 29% had CR/PR, 34% had PD and 37% had SD. The median OS was 19.7 months (95% CI, 12.7-NE) while the median PFS was 7.4 months (95% CI, 5.9-11.6). In the subgroup analysis there were no statistical significant differences regarding age and gender. Grade 3-4 toxicities were evaluated but non of these toxicities had an incidence ≥5. Only direct costs of the treatment were included in the analysis expressed in insurance prices. The total cost of nivolumab treatment per month was estimated at 5.616,08€ per patient and the total annual cost at 67.392,96€ per patient.

Conclusions: Nivolumab proved its meaningful survival benefit in clinical practice since the effectiveness appears to be higher in this unselected non-clinical trial population as compared to the results of the clinical trials. The safety profile reported in our study confirmed those reported in the clinical trials. The total cost of nivolumab treatment as second-line therapy in advanced NSCLC results high but its increased effectiveness and

the low incidence of adverse events, respect to previous treatments, favor its introduction as second-line treatment.

Keywords: Nivolumab, real-world data, clinical practice, effectiveness, overall survival, progression free survival, safety profile, healthcare costs.

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THEORITICAL FRAMEWORK

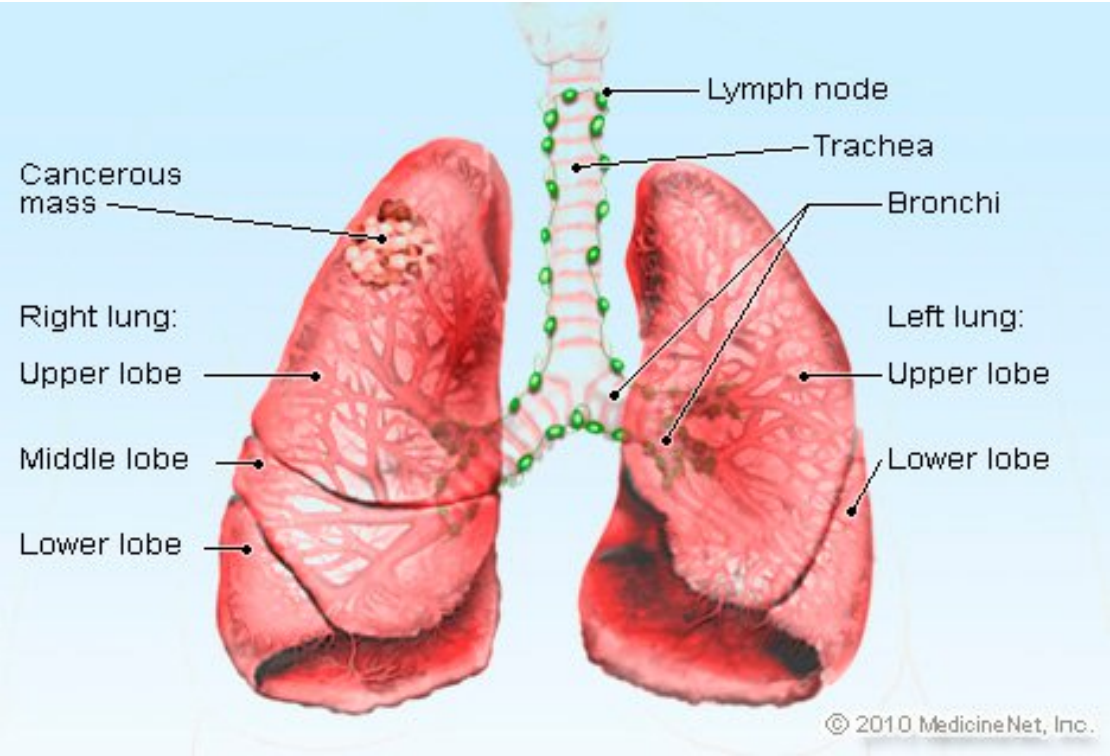
Chapter 1

Lung Cancer

1.1 Definition and Classification of Lung Cancer

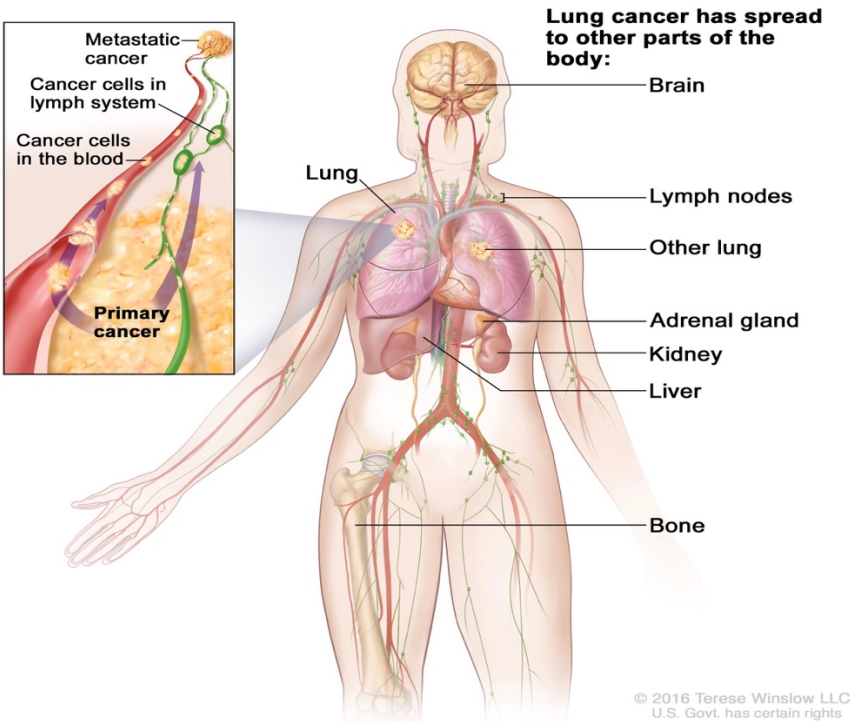
Lung cancer is the uncontrolled growth of abnormal cells arising from the respiratory epithelium (bronchi, bronchioles and alveoli). A variety of benign and malignant tumors may arise in the lung but the 90% to 95% are carcinomas. Carcinomas of the lung arise by an accumulation of genetic abnormalities that transform the bronchial epithelium to neoplastic tissue. Malignant tumors may develop from any of the cell types present in the lung that preserve the capacity to proliferate. Most lung cancers develop from the epithelial cell lining the airways. Lung cancer are also known as bronchogenic carcinomas because of their presume origin from first-order, second-order and third order bronchi while a small number of tumors arise in the periphery of the lung, from the alveoli and terminal bronchioles.

Figure 1.1
Anatomy of lungs



In an unknown interval of time cancer cells may acquire the ability to escape from the primary focus and follow a variety of paths. They may infiltrate in to adjacent regions of the carina or mediastinum, penetrate into the bronchial lumen or extend into the pleural surface and from the pleural cavity to the pericardium. More than 50% of lung cancers spread to the nodes, in particular, the nodes involved in most cases are the tracheal, bronchial and mediastinal nodes. Often malignant tumors spread in distance of the thoracic cavity. The metastasis occurs through the lymphatic and haematogenous pathways and may spread to any organ or tissue of the body. In more than half of the cases lung tumors metastasize into the adrenal, but also liver, brain and bones are frequent sites of metastasis. ((Contran and Robbins, 2007)

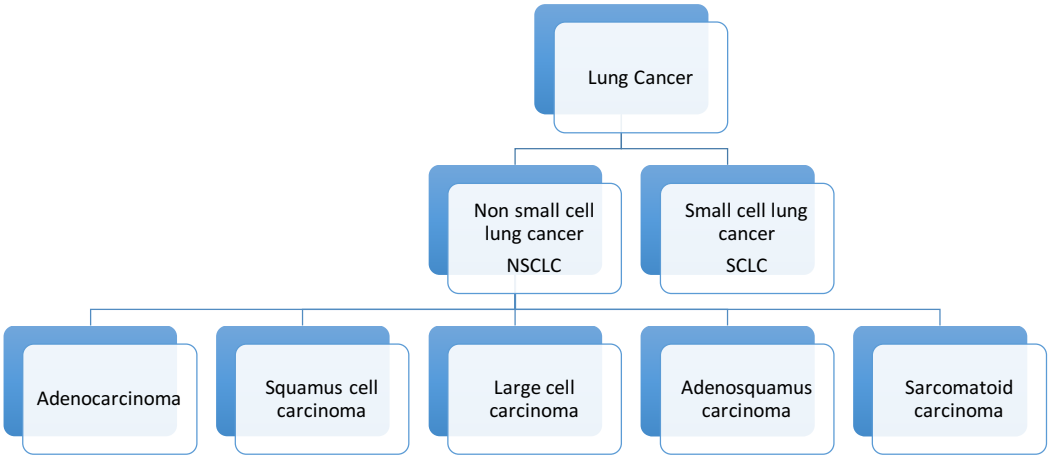
Figure 1.2
Lung cancer and possible metastasis



Lung tumors can be classified by their origin in **primary** tumors and **secondary** tumors. Primary tumors are the tumors that originates from the lungs while secondary tumors are those beginning in other parts of the body and metastasize into the lungs.

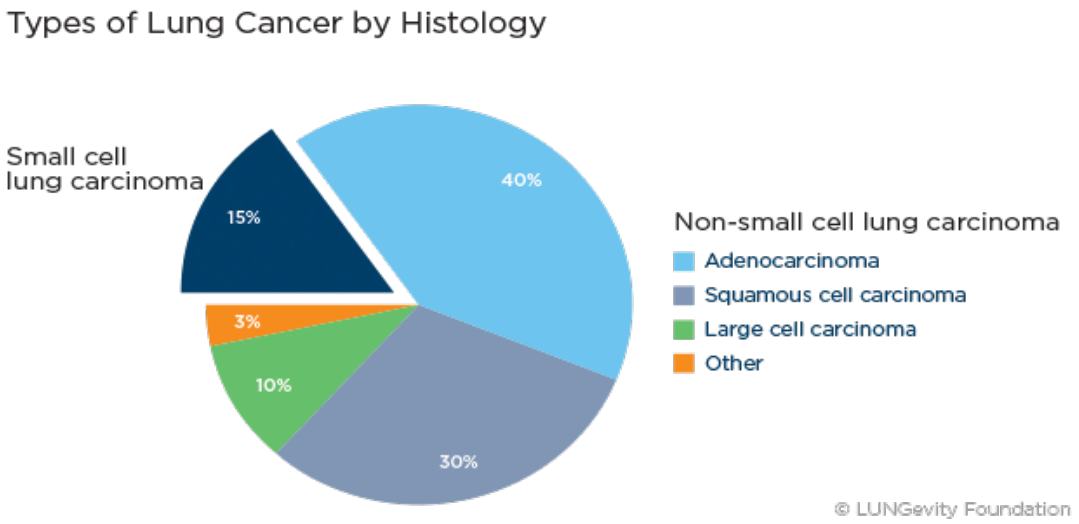
Lung cancers are a class of tumors that have several typical morphological patterns based on the microscopic examination. According to the world health organization classification the two main categories of primary lung neoplasms are **small cell lung cancer** (SCLC 10% to 15% of all cancers) and **non-small cell lung cancer** (NSCLC 80% to 85% of all cancers). Histologically non-small cell lung cancer is divided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma. There are also other subtypes of NSCLC like adenosquamus carcinoma and sarcomatoid carcinoma but these are less common types. Figure 1.3 shows the main lung cancer types.

Figure 1.3
Main Categories of Primary Lung Cancer



- **Adenocarcinomas** represents approximately 40% of all lung cancers and usually occurs in the periphery of the lungs. This type of cancer occurs mainly in former smokers but is also the most common type in non-smokers. It is most frequent in women and it is the type of lung cancer that occurs in younger people most respect to other types. This type of lung cancer is more likely to be diagnosed before it metastasize thanks to its trend to grow slower.
- **Squamous cell carcinoma** accounts for about 30% of all lung cancers and is correlated to a history of smoking. This type of NSCLC tend to grow in the central part of the lung, near to the bronchus.
- **Large cell carcinoma** accounts for about 10% of all lung cancers and tends to grow and spread very fast. A subtype of this cancer is known as large cell neuroendocrine carcinoma and it is similar to small cell lung cancer. (American Cancer of Society, 2018)

Figure 1.4
Types of lung cancer by histology



Source: Lungevity.org

Updated: January 3,2018

- **Small cell lung cancer** represents approximately the 15% of all lung cancers and is also known as oat cell lung cancer because of the small size of the cancer cells in the microscope. (American Cancer of Society, 2018). This type of lung cancer is associated with cigarette smoking and only 1% occur in non-smokers. It can originate from any part of the lung, bronchus and periphery, and is the most aggressive of the lung tumor subtypes with rapid metastasis. Surgical resection for SCLC in ineffective, but this type of lung cancer is particularly sensitive to radiation and chemotherapy. (Contran and Robbins, 2007)

The various types of lung cancer have different natural histories and responses to therapy, thus the histologic distinction between SCLC and NSCLC is essential for both prognostic and therapeutic reasons. Figure 1.4 presents the rates of the lung cancer histological subtypes.

1.2 Etiology

Lung cancer is believed to be caused by a combination of exposure to environmental exposures and an individual's susceptibility to those agents. Scientists

have developed the multiple hit theory which suggests that the exposure to carcinogens produces genetic lesions in the cells which transform into malignant carcinomas.

The main factors that can cause lung cancer are:

- Tobacco smoking
- Industrial hazards (radiation, asbestos)
- Air pollution (radon)
- Molecular genetics

Tobacco smoking has been established, by clinical studies, to be having a positive relationship with lung cancer since it induces histologic changes in the respiratory epithelium. These lesions are observed mostly in squamous cell carcinoma and small cell lung cancer. The appearance of epithelial changes begin with squamous metaplasia that progress to squamous dysplasia, carcinoma in situ and invasive carcinoma. Approximately 87% of lung cancers occur in current or former smokers. More than 1200 substances have been counted in cigarette smoke, many of which are potential carcinogens, such as polycyclic aromatic hydrocarbons that work as initiators and phenol derivatives working as promoters of lung cancer. The frequency of lung cancer increases linearly with the amount of daily smoking and exponentially with the years of smoking. That means that the risk of lung cancer is higher for a smoker smoking 20 cigarettes a day for 30 years respect to someone smoking 60 cigarettes each day for 10 years, although the amount of cigarettes is equal for both cases. (Contran and Robbins, 2007)

Approximately 25% of all lung cancers worldwide account in never smokers. The term never smokers refers to persons who have smoked less than 100 cigarettes in their lifetime. (Charles S. Dela Cruz MD PhD, 2011). In particular secondhand smoke, or environmental tobacco smoke is responsible for the death of 3000 non-smoking adults each year as a result of breathing the numerous carcinogens included into the smoke. (Contran and Robbins, 2007)

Industrial exposures increase the risk of lung cancer. High-dose ionizing radiation is carcinogenic and can lead to lung cancer. The risk although is higher with exposure to asbestos. Asbestos is a class of naturally occurring fibrous minerals that has been used since 1800 in construction and insulating materials. It is universally recognized as a carcinogen, particularly when combined with smoking. Among workers exposed to asbestos one in five deaths is due to lung cancer. The latent period before the development of lung cancer is 10 to 30 years. (Contran and Robbins, 2007)

The **air pollution** plays an important role in the increased incidence of lung cancer. Particularly, studies show a linear relationship between exposure to high concentrations of **radon** and lung cancer. Radon is a radioactive gas produced by radium, which is a product of uranium. Both uranium and radium are ubiquitous in soil and rock. Radon itself decays into a series of radioisotopes, known as radon decay products which emit alpha particles. a-Radiation damages the respiratory epithelium, inhalation of radon decay products and alpha particles emission in the lungs may cause genetic alterations to the cells.

Molecular genetic studies have shown an accumulation of genetic lesions in the lung cells that lead to lung cancer. This include activation of dominant oncogenes, such as RAS, EGFR, MYC family oncogenes, and inactivation of tumor-suppressor genes. A large number of inactivated tumor suppressor genes have been identified in the pathogenesis of lung cancer, the most commons are p53 and retinoblastoma tumor suppressor gene.

1.3 Pathogenesis

The transformation of a normal lung cell into a malignant carcinoma requires the accumulation of multiple genetic and epigenetic alterations. In fact lung cancer cells may have to accumulate a large number of such lesions. Early alterations are caused from DNA point mutations or chromosomal deletions that inactivate tumor-suppressor genes (**TSG**). A TSG loss that occurs in 80% of NSCLC is that of **p53** which is a transcription factor involved in cell progression, DNA repair and regulation of apoptosis. Mutations to p53 inactivate its normal tumor suppression capabilities, as a consequence DNA damage remains unchecked, the damaged cell proceed through the cell cycle and the apoptosis is evaded. This creates a genetic condition in which the cell is more susceptible to more mutations.

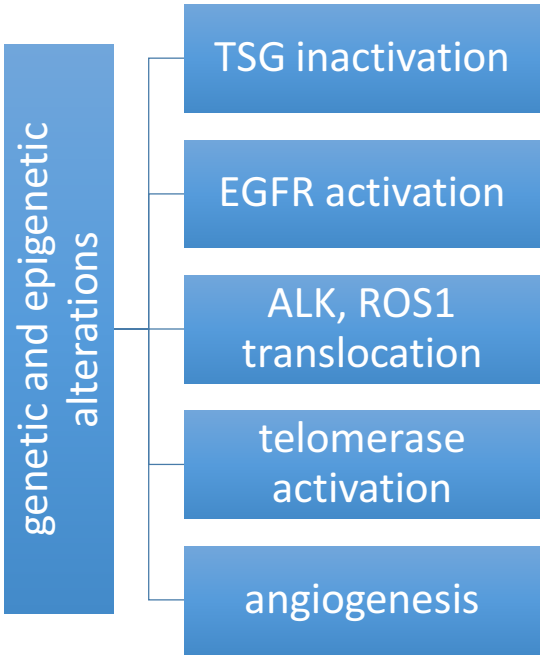
Another critical alteration that occurs in the development of NSCLC is the upregulation of oncogene **EGFR** (epidermal growth factor receptor). Overexpression of EGFR protein or amplification of the EGFR gene has been found in approximately 70% of NSCLC. The binding of a ligand to EGFR receptor activates a cascade of intracellular events leading to increased cell proliferation, angiogenesis and a decrease of apoptosis. (Fauci S. Anthony, 2008)

In the majority of lung cancers, activation of **telomerase** is detected. Telomerase is a ribonucleoprotein that adds a sequence to the 3' end of telomeres. A telomere is a repetitive sequence at the end of the chromosome that protects the chromosome from DNA damage. Telomeres shorten with each cell division limiting cell proliferation, by extending the telomere, telomerase contributes to prolonged cell survival.

Other genetic mutations that plays critical role in the development and progression of NSCLC is the translocation of anaplastic lymphoma kinase (**ALK**) identified in 2 to 7% of patients with NSCLC, and the translocation of **ROS1** gene identified in 2% of NSCLC patients. These translocations lead to novel fusion genes with transforming activity. (Martin Reck MD PhD, 2017)

Additionally, tumor cells in order to sustain, grow and metastasize require an adequate blood supply. Consequently they promote **angiogenesis** by their capability to produce vascular endothelial growth factor (VEGF), which binds to VEGF receptor on the endothelial cells inducing the creation of new blood vessels from the preexisting.

Figure 1.5
Main Genetic and Epigenetic alteration of Lung Cancer



In figure 1.5 are summarized the main genetic and epigenetic alterations that are responsible for lung cancer. A large number of studies are today in progress for the identification of other specific alterations involved in the pathogenesis of the disease in order to develop new drugs capable to target this specific alterations.

1.4 Disease diagnosis

1.4.1 Symptoms

The symptoms of lung cancer are caused by the growth of the local tumor, the spread to adjacent structures, growth in regional nodes and metastases in distant sites of the body. Frequently lung caser gets diagnosed in advanced stages, although 5-15% of patients get diagnosed accidentally, while they are asymptomatic, during a routine chest radiography. Most patients have distant metastasis on diagnosis, even after treatment the mean survival after diagnosis is approximately 1 year. The major presenting symptoms are: **cough** (75%), **weight loss** (40%), **chest pain** (40%), and **dyspnea (**20%). (Contran and Robbins, 2007)

The symptoms produced by the primary tumor depend on its location. Central tumors may cause cough, dyspnea, hemoptysis, wheeze, stridor, and postobstuctive pneumonitis. Peripheral tumors in addition to causing cough and dyspnea can lead to pleura effusion and severe pain as a result of pleural or chest wall involvement.

The cough, that is the main symptom of lung cancer, appears when the tumor irritates the cough receptors in the airway. Frequently as the tumor is growing, it may cause the obstruction of an airway, like a bronchus, causing the appearance of cough.

In some cases, patients appear with hemoptysis, this symptom occurs when the tumor is in a central airway. The angiogenesis induced by the tumor leads to the creation of new blood vessels which are leaky and tortuous, predisposing them to easy rupture causing the hemoptysis.

In addition, regional metastases of the tumor in the thoracic cavity may cause a variety of symptoms including obstruction of the trachea, esophageal compression that produce dysphagia, paralysis of the phrenic nerve with compression of the diaphragm and dyspnea.

In other cases, lung cancer gets diagnosed when it has already spread to distant organs of the body, in this case the first symptoms of the disease reflect this metastatic spread of the tumor. When the tumor spreads to the brain it could cause headache, nausea and neurologic deficits, while a bone metastasis can cause pain and pathologic fractures. Another frequent lung cancer metastasis is lever metastases that leads to liver dysfunction, biliary obstruction anorexia and pain.

Endocrine syndromes are seen in 12% of the patients. Ectopic production of parathyroid hormone, induced mainly by squamous cell carcinoma, can cause hypercalcemia and hypophosphatemia. The ectopic secretion of antidiuretic hormone, common in small cell lung cancer, can cause hyponatremia. (Fauci S. Anthony, 2008)

The presence of lung cancer disease may be suspected by physicians based on the symptoms presented in the patient. Nonspecific symptoms such as anorexia, weight loss, fever and more specific symptoms like cough, hemoptysis, dyspnea, chest pain could be related to the presence of primary lung tumor. Although, none of these symptoms appears only to patients with lung cancer, however the symptoms of the respiratory system that persist more than 15 days, although patient is under medication therapy, should be examined further by a chest x-ray and blood examination, especially in those patients that are current or former smokers.

1.4.2 Diagnosis

The diagnosis of lung cancer begins with the investigation of the symptoms appearing to the patients. A diagnosis cannot be based only in the symptoms appearing to the patient, a complete medical history, a history of weight loss, determination of performance status and a physical examination should be recorder. There are also required some standard laboratory tests, this include hematology test, renal and hepatic function test and bone biochemistry test.

Radiological examination is important to confirm the suspicion of lung tumor, to evaluate its size and to determine its extent. Usually the first examination is the chest radiography which can reveal the tumor. After that, for the determination of the exact extent of the primary tumor in the lung, its possible spread to the lymph nodes and pleura, and the metastasis in abdominal organs like liver and adrenals, a computed tomography (CT) of the chest and the upper abdomen is conducted. Imaging of the brain is recommended to all patients and it is necessary to those patients with headaches and other neurological symptoms that create the suspicion of brain metastasis. Imaging of the brain could be carried out with a CT brain or with an MRI (magnetic resonance imaging) in order to exclude the presence of brain metastases. Often the MRI is preferred instead of brain CT, as it is more sensitive. Another imaging examination conducted as a preoperative examination is the PET/CT scan. This examination allows the observation of the tumor and its metabolic activity. If bone metastases are suspected a bone scan is

conducted, but it is not necessary if a PET/CT has already been done, as it is more sensitive in detecting bone metastases.

After imaging examinations are conducted, a histopathological examination (biopsy) is necessary, as it is the only method that can confirm the diagnosis. Biopsies can be obtained by taking sample from the primary tumor with bronchoscopy or, when this is not possible, this can be done by transbronchial needle aspiration guided under CT. If imaging studies suggest mediastinal or hilar lymph node metastases, and the tumor is not visible on controversial bronchoscopy, endobronchial or/and esophageal ultrasonography with needle aspiration is carried out, in order to take a sample and confirm the involvement of the lymph nodes.

Cytologic examination can also be done in order to show clear morphologic features of the tumor. Unlike histopathologial examination, which is conducted to a tissue sample of the tumor, cytologic examination examines the cancer cells which are automatically detached from the tumor. Histological features of the tumor are important both for the establishment of the diagnosis but also for the selection of the correct treatment.

Despite the improvements in thoracic surgery, radiotherapy, chemotherapy and recently the use of immunotherapy, the survival rates of lung cancer remain low. This comes from the fact that most patients with lung cancer get diagnosed in advance stage of the disease. Consequently, early diagnosis and prevention are needed.

Prevention is not possible for all types of lung cancer. The best way to reduce the risk of lung cancer is to adopt a healthy lifestyle without smoking, avoid secondhand smoking, and encourage current smokers to quit since after a period of smoking cessation, lung tissue starts to regenerate reducing the risk of lung tumor. A healthy diet with lots of vegetables and fruits may also protect against lung cancer in both smokers and not smokers. The role of chemoprevention as an approach in the prevention of lung cancer is not yet established as no benefits have yet been demonstrated. Some studies have shown that two possible chemoprevention agents, vitamin E and β-carotene, appears to increase the rate of lung cancer in heavy smokers.

1.5 Staging

Lung cancer staging is necessary for the correct treatment decision. Staging is usually done initially with Computed tomography (CT) examination and other imaging methods including positron-emission tomography (PET-CT) and magnetic imaging resonance (MRI), but the tissue diagnosis remains the essential element for the correct staging and treatment decision. In those types of cancer that are removable by surgical procedure, staging after surgery is more accurate as it allows the laboratory examination of the entire removed tumor. Each type of lung cancer follows a specific and unique staging system.

Non-small cell lung cancer (NSCLC) uses the tumor-node-metastasis (TNM) international staging system, where T refers to the tumor size and spread to regional tissues, N refers to the involvement of the nodes, and M to the presentence or absence of distant metastases. Figure 1.6 shows the staging system of NSCLC according to the American Joint Committee of Cancer (AJCC) / Union for International Cancer Control (UICC)

Figure 1.6
Staging system of non-small cell lung cancer (NSCLC)

T – Primary Tumour		
Tx		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Tumour 3 cm or less in greatest diameter surrounded by lung or visceral pleura, without evidence of main bronchus
	T1a(mi)	Mininally invasive adenocarcinoma
	T1a	Tumour 1 cm or less in greatest diameter
	T1b	Tumour more than 1 cm but not more than 2 cm
	T1c	Tumour more than 2 cm but not more than 3 cm
T2		Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features: Involves main bronchus (without involving the carina), invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region
	T2a	Tumour more than 3 cm but not more than 4 cm
	T2b	Tumour more than 4 cm but not more than 5 cm
T3		Tumour more than 5 cm but not more than 7 cm or one tha directly invades any of the following: chest wall, phrenic nerve, parietal pericardium, or associated separate tumour nodule(s) in the same lobe as the primary
T4		Tumours more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

N – Regional Lymph Nodes		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

M – Distant Metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleaural or pericardial nodules or malignant pleural or pericardial effusion
	M1b	Single extrathoracic metastasis in a single organ
	M1c	Multiple extrathoracic metastases in one or several organs

International Association for the Study of Lung Cancer, 2015

Source: international association for the study of lung cancer (2015)

Using the TNM staging system the stages of **non-small cell lung cancer** are described with a Latin number from I to IV.

Stage IA: the tumor is 3cm or smaller and has not spread into the main area of the bronchi, the lymph nodes or other organs.

Stage IB: the tumors is between 3and 5cm and may have spread into the main bronchus, within 2cm of the carina, or may have spread into the pleura.

Stage IIA: tumor size is between 5 and 7cm and there is no involvement of the regional lymph nodes or the tumor is smaller or equal to 5cm but there is involvement of the regional lymph nodes.

Stage IIB: this stage has also two subcategories, in the first one the tumor is between 5 and 7cm and has spread to the regional lymph nodes, in the second case the tumor is bigger than 7cm has spread to the opposite lung and there is no involvement of the nearby lymph nodes.

Stage IIIA: in this stage the tumor is bigger than 7cm and has spread to the lymph nodes of the mediastinum, to the side where cancer is detected.

Stage IIIB: the tumor has a size bigger than 7cm, may have spread to the lymph nodes on the opposite side of the main tumor, may have spread to other organs of the thoracic cavity like heart or big vessels, or may be accompanied by pleural effusion.

Stage IV: in this stage the tumor may be any size and may or may not have spread into the nearby lymph nodes. In this stage cancer may have also spread to the opposite lung, and to distant tissues or organs of the body.

The stages of NSCLC are illustrated more detailed in Table 1.1.

Table 1.1

Non-small cell lung cancer stages

NSCLC stages according to TNM			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2 T3	N1 N0	M0 M0
Stage IIIA	T1 T2 T3 T3	N2 N2 N1 N2	M0 M0 M0 M0
Stage IIIB	Any T T4	N3 Any N	M0 M0
Stage IV	Any T	Any N	M1

Source: European Society of Medical Oncology (ESMO)

The staging of Small-cell lung cancer (SCLC) is mainly based in the location of the lesions and includes two main categories:

- **Limited disease**: in this stage cancer is found in the lung and may or may not have spread into the nearby lymph nodes.
- **Extensive disease**: in this stage cancer may have spread to the opposite lung, the pleura and in distant tissues or organs of the body.

1.6 Treatment

The field of cancer treatment has advanced faster than any other field in medicine, particularly the major progress has been made in lung cancer treatments. Treatment defer between the different types of lung cancer, non-small cell lung cancer and small-cell lung cancer. Specifically, treatment of lung cancer depends on the type of lung cancer (small or non-small cell lung cancer), the size and the position of the tumor, its stage, the biomarkers, if any, presented in the cancer, and the overall health of the patient. Some of the most common treatments include surgery, radiation, chemotherapy, targeted treatments and recently immunotherapy. This treatments could be applied alone or in combination, based on the type and how advanced the cancer is.

1.6.1 Surgery

In patients diagnosed with early stage, stage I and stage II of non-small cell lung cancer, resection with surgery is the primary treatment to remove the cancerous cells and the lymph nodes involved. In most patients with stage IIIA of NSCLC surgery can be used as first treatment or after chemotherapy, with or without radiation, in order to minimize the size of the tumor in order to be operable. Stage IV of NSCLC can't be treated with surgery because of the distant metastases of the lung tumor in other organs or tissues of the body. In this stage surgery could be used in order to relieve symptoms caused from me lung tumor or the bones metastasis.

In case of small cell lung cancer a very small percentage of patients, diagnosed in early stage and with no spread to the lymph nodes, could be submitted to surgery. Surgery is rarely used in this type of cancer because often the tumor has already spread in other

organs of the body at the moment it gets diagnosed. In case of early diagnosis, surgery followed by chemotherapy or radiotherapy may reduce the risk of cancer recurrence.

Depending on the size and the location of the tumor different types of surgery could be applied. Part of the lobe could by removed with a segmentectomy or a wedge resection, an entire lobe may be removed with a lobectomy, or an entire lung with a pneumonectomy. In some cases surgical removal could be done with thoracoscopy, this type of procedure has the advantages of smaller incisions and shorter recovery period.

1.6.2 Radiation

Radiation therapy uses high-energy X-rays in order to damage DNA of cancer cells. It can be used as a treatment in both small-cell lung cancer and non-small cell lung cancer and it can be given before surgery as a primary treatment, or after surgery.In patients who are not candidates for surgery, because of their general health that increases the risk of surgery complication, or in those patients that prefer a non-surgical approach, radiotherapy is usually recommended and may be given alone or combined in many cases with chemotherapy.

In those patients with small localized lung cancer, after surgery, radiation usually with a technique known as stereotactic body radiation therapy (SBRT) is highly preferred in order to sterilize the area from any residual cancer cells. For locally advanced stages, radiotherapy can be given either as a pre-surgery treatment, to reduce the size of the tumor so it can be surgically removable, or to replace surgery for those types of lung cancer not surgically removable in combination with chemotherapy. Stage IV is a metastatic stage not surgically treated. In this case radiation is given to reduce symptoms caused from the metastases in certain organs, such as pain from bone metastases and headaches caused from metastases to the brain.

For patients with small cell lung cancer radiation treatment may be used depending on the stage of cancer. For limited stage of SCLC radiation in combination with chemotherapy is the recommended treatment.

The customized to the patient, type, size and location of the tumor schedule of radiation is important as it can damage healthy tissues.

1.6.3 Chemotherapy

Chemotherapy is a therapy usually given intravenously, reaching this way rapidly the entire body. It is the basic treatment for small- cell lung cancer, particularly for patients with limited-stage chemotherapy is given in combination with radiotherapy, while in those patients with extensive-stage chemotherapy is given alone as standard treatment.

In patients with non-small cell lung cancer the chemotherapy may be used as neoadjuvant therapy, before surgery, in order to shrink the tumor and be surgically removed. As adjuvant therapy, after surgery, it is given to destroy any residual cancer cell. In case of locally advanced stage that can't be removed by surgery chemotherapy can be given combined with radiotherapy, while for more advances cancers that have metastasize in distant organs of the body, chemotherapy is given as the main treatment. The chemotherapy regimen usually uses a combination of two chemo drugs, a cisplatin or carboplatin plus one other drug. Chemotherapy is given into cycles that generally last about 3 to 4 weeks, but for advanced stages it could be given for 4 to 6 cycles.

In addition to first line chemotherapy, strategies, such as maintenance therapy and second line therapies have further improved outcomes in patients with non-small cell lung cancer. Some studies have shown that maintenance chemotherapy given after first line chemotherapy is intended to prevent the development of the disease and help patients live longer. However the role of maintenance treatment has not been yet defined and treatment decisions should be taken personalized for each patient. In case that patients do not respond in first-line treatment, second-line treatment is recommended with single chemo drug, or a chemo drug combined with a targeted therapy or immunotherapy drug.

1.6.4 Targeted therapies

Over the last decade, molecular research advances, have made an improvement in diagnosis and managing of lung cancer and in particular non-small cell lung cancer. Sequencing of the human genome has permitted the identification of epigenetic mutations, tumor suppression gene inactivation, and oncogene driver mutations, which could be potential targets for therapy. Studies have shown a longer overall survival in patients with oncogenic driver mutations who received targeted therapies respect those patients with driver mutations who did not receive targeted therapies. Therefore,

molecular testing for a range of biomarkers should be included in the routine diagnosis evaluation of patients with non-small cell lung cancer. (Martin Reck MD PhD, 2017)

The last decade researches focused on mutations of the epidermal growth factor receptor (EGFR) and the rearrangement of the anaplastic lymphoma kinase (ALK) gene, which have led to the development of targeted agents in order to inhibit these particular mutations.

Mutations in the EGFR gene cause the overexpression of EGFR receptor that activates a cascade, leading to proliferation and survival of the tumor. Mutations on the EGFR gene are identified in 40-80% of non-small cell lung cancer. (Bryan Chan, 2014) Targeted drugs known as EGFR tyrosine kinase inhibitors (TKIs) inhibit EGFR receptor. Some of these drugs include gefitinib, afatinib, and erlotinib, and are given orally as first line treatment in patients presenting EGFR mutations.

The rearrangement of the anaplastic lymphoma kinase (ALK) gene is presented in 3-7% of NSCLC and produces an abnormal protein that promotes malignant growth and proliferation of the tumor. (Bryan Chan, 2014). Some of the drugs that target the abnormal protein are known as ALK tyrosine kinase inhibitors and include crizotinib, ceritinib, alectinib, and are given orally as first line treatment in patients with ALK translocation.

Another targeted therapy for non-small cell lung cancer include drugs that target tumor blood vessels growth. These drugs known as angiogenesis inhibitors, inhibit the angiogenesis process induced by cancer cells. Bevasizumab, is a monoclonal antibody that targets the vascular endothelial growth factor (VEGF), a protein produced from the cancer cells and induces the creation of new blood vessels that help tumor to grow.

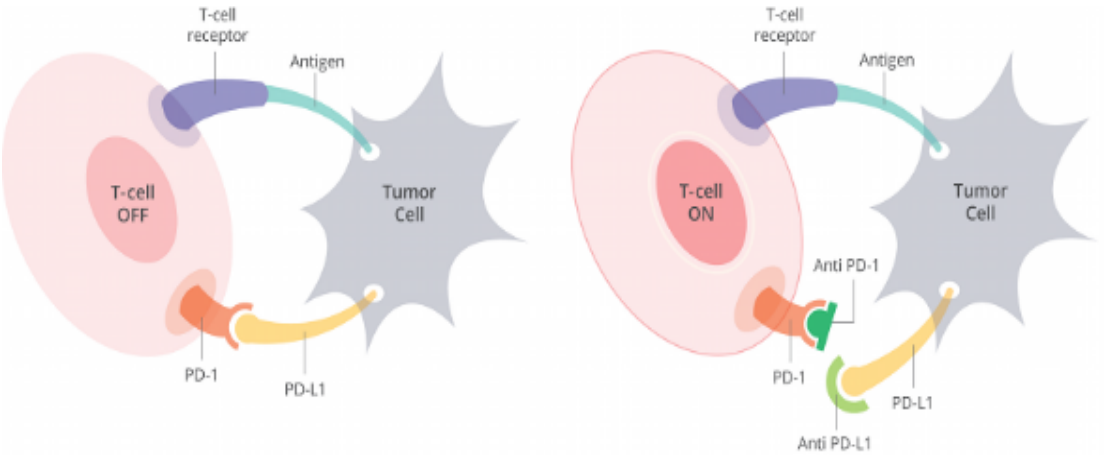
1.6.5 Immunotherapy

Until a few years ago, the only therapeutic option for patients with metastatic non-small cell lung cancer (NSCLC) was platinum based chemotherapy or targeted therapy, used for some specific molecular alterations in driven oncogenes that have been identified in NSCLC adenocarcinoma. Recent understanding of the molecular mechanisms leading to cancer immune evasion has led to the development of a new class of drugs known as **immune checkpoint inhibitors** (**ICIs**), which has shown a significant improvement in overall survival (OS) as well us patients quality of life.

ICIs are proteins on the surface of lymphocytes and other immune cells, most notably on cytotoxic T-cells. When they bind to their specific ligand, they activate a cascade leading to activation or inhibition of the immune response. Tumor cells express in their surface altered proteins able to be recognized by the immune system T-cells as antigens. Through binding of T-cell receptor with the antigen expressed on tumor cells, lymphocytes are able to mediate tumor cell lysis, however multiple immune escape strategies are taking place within the tumor microenviroment. The predominant mechanism by which NSCLC evade detection and elimination by immune system is through the expression of programmed death ligand 1(PDL-1) in tumor cells surface, which binds to its receptor, programmed cell death protein 1(PD-1) expressed to the surface of lymphocytes, which leads to the inhibition of the lymphocytes and as a consequence the absence of immune response.

Figure 1.7

Immune checkpoint inhibition



Immunohistochemical tests have revealed high PDL-1 expression on tumor cells of many tumors including NSCLC. This high PDL-1 expression can explain how activation of PDL-1/PD-1 pathway is an immune resistance mechanism used by cancer cells to escape from immune system. This can explain the use of PD-1/PDL-1 ICIs in the treatment of tumors expressing high levels of PDL-1, which directed against PD-1 or PDL-1 can block T-cells inhibition and restore immune response. PD-1/PDL-1 ICIs are monoclonal antibodies (MoAbs) approved by regulatory authorities for the treatment of NSCLC. We have three monoclonal antibodies, nivolumab, pembrolizumab and atezolizumab used as second line treatment in patients with NSCLC, of which

pembrolizumab was recently approved also as first line treatment in NSCLC. (Francesco Passiglia, 2018)

- ***Nivolumab*** is a human monoclonal IgG4 anti PD-1 antibody, and it is the first ICI approved by food and drug administrator (FDA) for treatment of pretreated with platinum chemotherapy, patients with metastatic NSCLC as second line treatment. The clinical activity was confirmed from two phase III randomized clinical trials, CHECKMATE 017 for squamous NSCLC and CHECKMATE 057 for non-squamous NSCLC, which have demonstrated the improvement in patient's survival respect chemotherapy for both squamous and non-squamous histology types.
- ***Pembrolizumab*** is a human monoclonal IgG-4 anti PD-1 antibody. The KEYNOTE 001 clinical trial showed a significant improvement in overall survival in pretreated patients with advanced NSCLC over chemotherapy, it was also evident early in the trial the efficacy correlated with PD-L1 positivity.as a result of these trial pemprolizumab was approved as second line treatment in pretreated patients with metastatic NSCLC who had an expression at least 1% of PD-L1. According to the results of phase III KEYNOTE 010 randomized clinical trial, pembrolizumad was the first ICI to be approved for first line treatment in patients with advanced NSCLC whose tumor cells express PD-L1 in more than 50%.
- ***Atezolizumab*** is a humanized IgG1 anti PD-L1 monoclonal antibody. Based on the results of OAK and POPLAR trial, where a clear improvement in overall survival was demonstrated against chemotherapy, atezolizumab was approved as second line treatment for NSCLC.

1.7 PD-L1 biomarker

Immunohistochemical test for tumor PD-L1 expression remains the only predictive biomarker approved, for response to ICIs in NSCLC. A longer overall survival and increase in response rates in patients with higher PDL-1 expression is demonstrated by several studies, however not all studies support this., as a significant number of PDL-1 positive patients did not respond to treatment, and about 30% of PD-L1 negative patients benefit from ICIs as compared with standard chemotherapy. (Francesco

Passiglia, 2018). This may be explained by the dynamic and heterogeneous nature of PD-L1 expression, which may lead to misclassification of PD-L1 status.

According to the US FDA, pembrolizumab must be used in conjunction with its companion PDL 1 test, it requires at least 1% PD-L1 expression to be used as second line treatment, and an expression of more than 50% of PD-L1 when used as first line treatment for NSCLC. As for nivolumab and atezolizumab, FDA did not specify any threshold PD-L1 positivity, consequently the use of PD-L1 test is not mandatory. Particularly in all studies conducted for nivolumab, a significant proportion of PD-L1 negative patients clearly benefitted from treatment with nivolumab. (Claud Grigg, 2016)

1.8 Patient's clinical characteristics for anti-PD-1/PD-L1 agents

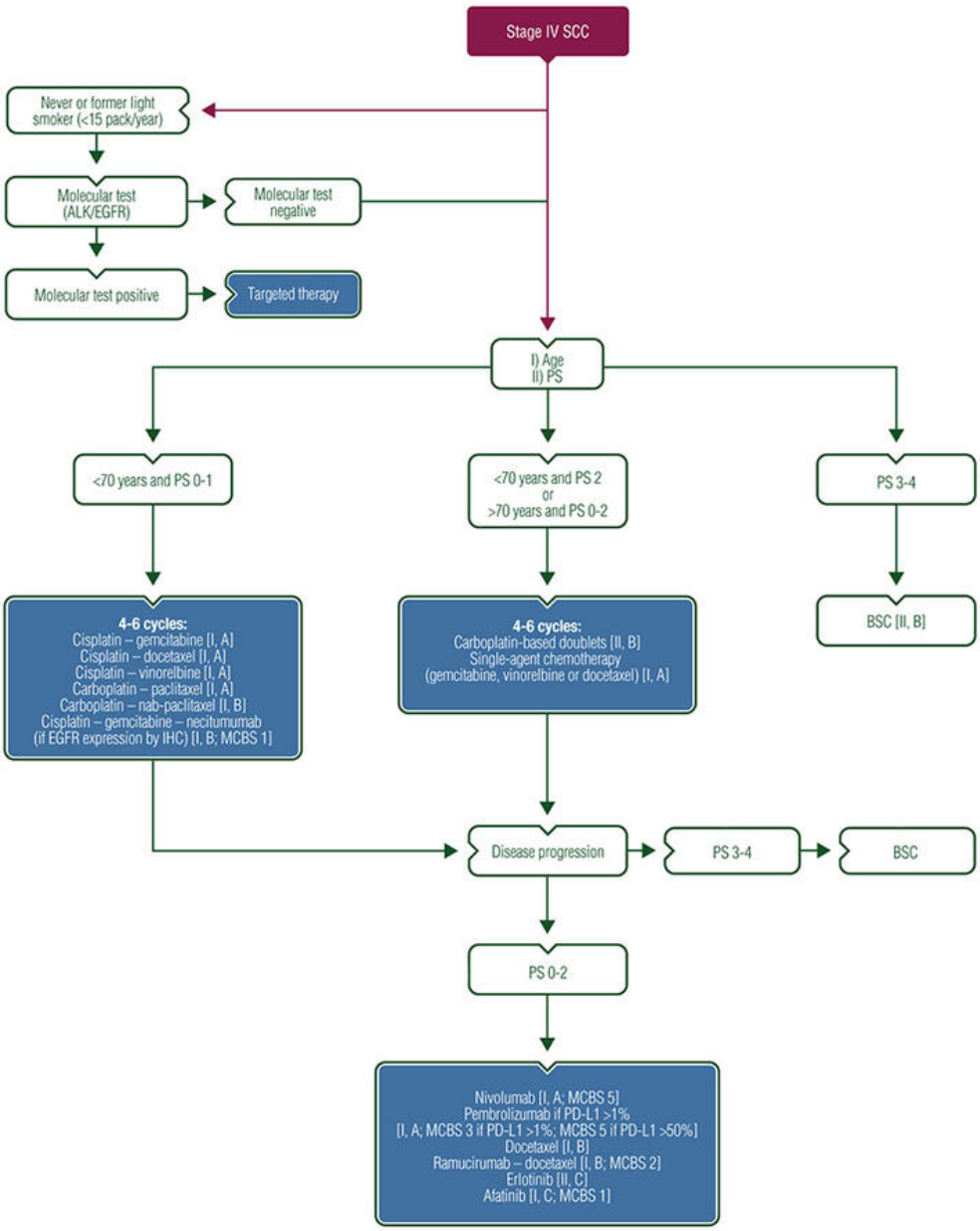
Not all patients with advanced non-small cell lung cancer are potential candidates for anti PD-1/PD-L1 therapy, a selection of patients that are most likely to benefit from this treatment should be made based on some clinical characteristics of the patients.

Age should not be used as a factor for selecting patients for anti-PD-1/PD-L1 therapy, particularly as these drugs offer a less toxicity respect chemotherapy. In many studies an improved survival was evident in patients treated with anti-PD-1/PD-L-1 therapies versus chemotherapy, regardless of the age group assessed. **Smoking status** should also not be used for patient selection. Most patients included in clinical trials for anti-PD-1/PD-L 1 in NSCLC were current or former smokers, and some of the trials analyzing the responses according to smoking status noticed a reduced benefit of the drugs in never smokers. It is likely that **PD-1 expression** may cause a difference in the treatment response rather than the **histology of the tumor**. Improvement in overall survival (OS) and progression free survival (PFS) with the use of ICIs in NSCLC appears in both squamous and non-squamous histological types versus chemotherapy. **Eastern Cooperative Oncology Group Performance Status (ECOG PS)** is a factor for patient selection for anti-PD-1/PD-L1 treatment. Patients with PS0 and PS1 were included in most randomized clinical trials of anti-PD-1/PD-L1 and no differences in survival have been demonstrated from the clinical data. Therefore, clinical evidence for patients with PS≥2 is limited, consequently treatment with anti PD-1/PD-L1 is recommended for patients with PS0-1 but not for those having a PS≥2. The patients with untreated **brain metastases, severe kidney of liver dysfunction, active autoimmune disease** that

requires a chronic systemic treatment, are not potential candidates for anti PD-1/PD-L1 treatment. (Rafael Califano, 2018)

Figure 1.8

Treatment algorithm for stage IV squamous NSCL

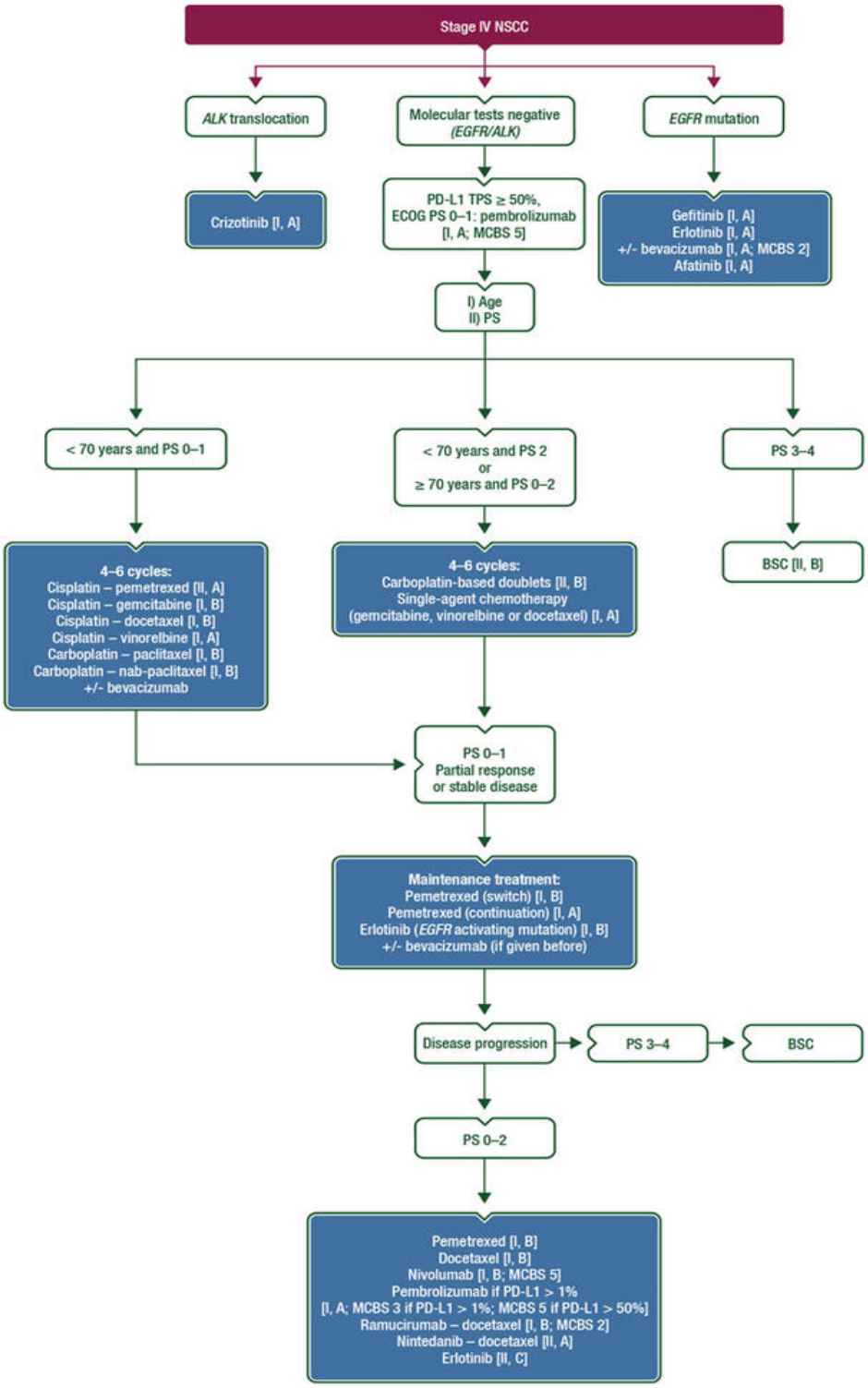


ALK, anaplastic lymphoma kinase; BSC, best supportive care; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; MCBS, Magnitude of Clinical Benefit Scale; PD-L1, programmed death-ligand 1; PS, performance status; SCC, squamous cell carcinoma.

Source: European Society of Medical Oncology (ESMO)

Figure 1.9:

Treatment algorithm for stage IV non-squamous NSCLC



ALK, anaplastic lymphoma kinase; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MCBS, ESMO Magnitude of Clinical Benefit Scale; NSCC, non-squamous cell carcinoma; PD-L1, programmed death-ligand 1; PS, performance status; TPS, tumour proportion score

Source: European Society of Medical Oncology (ESMO)

Chapter 2

Epidemiological Data: Incidence and Mortality of Lung Cancer

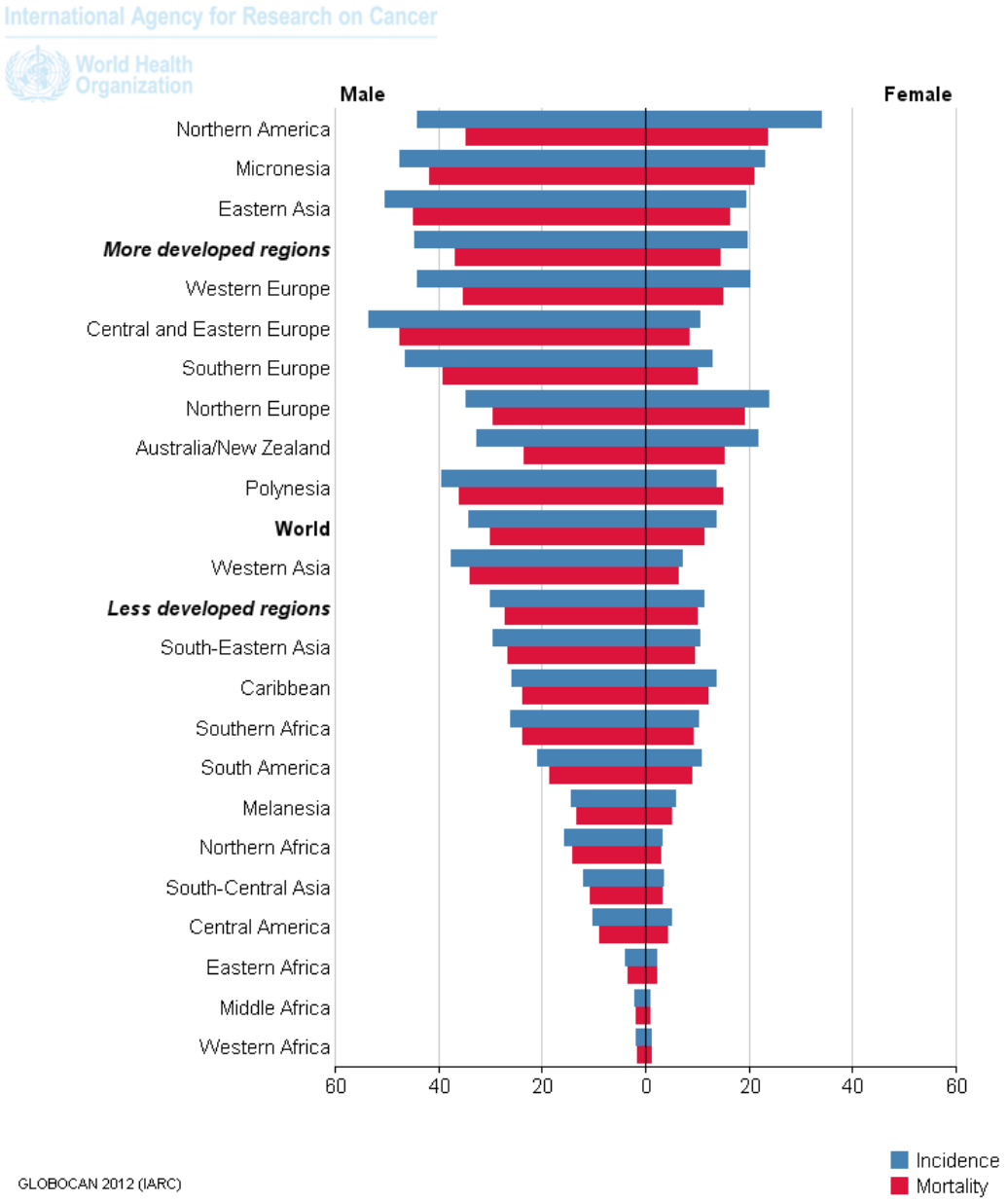
2.1 World data

Lung cancer is one of the most common malignant neoplasms all over the world and the most common cause of cancer deaths in both men and women in the past few decades. Lung cancer was considered to be rare in the beginning of the century but has now reached almost epidemic proportions. It is expected to cause 10 million deaths per year worldwide by the year 2030. A large number of lung cancers are associated with cigarette smoking, but other factors are also involved such as radiation, environmental pollution, and the Western nutrition and lifestyle. (Rengarajan et al, 2017)

The incidence, mortality and prevalence estimates for lung cancer were retrieved from the GLOBOCAN database, a project conducted from The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO). The aim of this project was to provide estimates on the incidence, mortality and prevalence of major types of cancer, at national level, for 184 countries of the world. The estimates are presented for 2012, which is the last available year of such a global statistic project for cancer. The data refer to population aged 15 years and older.

According to the GLOBOCAN database 13% of all new cancer cases are lung cancer, estimated to be responsible for nearly one in five deaths from cancer worldwide (1.59 million deaths, 19.4% of the total). Lung cancer has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (13% of the total), 58% of which occurred in the less developed regions. The disease is the most common in men worldwide (1.2 million, 16% of the total) with highest estimated age-standardised incidence rates in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000). Low incidence rates are observed in Middle and Western Africa (2.0 and 1.7per 100,000 respectively). In women the highest incidence estimated rates are observed in Northern America (33.8) and Northern Europe (23.7) while the lowest rates were again in Western and Middle Africa (1.1 and 0.8 respectively). (Figure 2.1)

Figure 2.1
Estimated worldwide age-standardised rates per 100,000

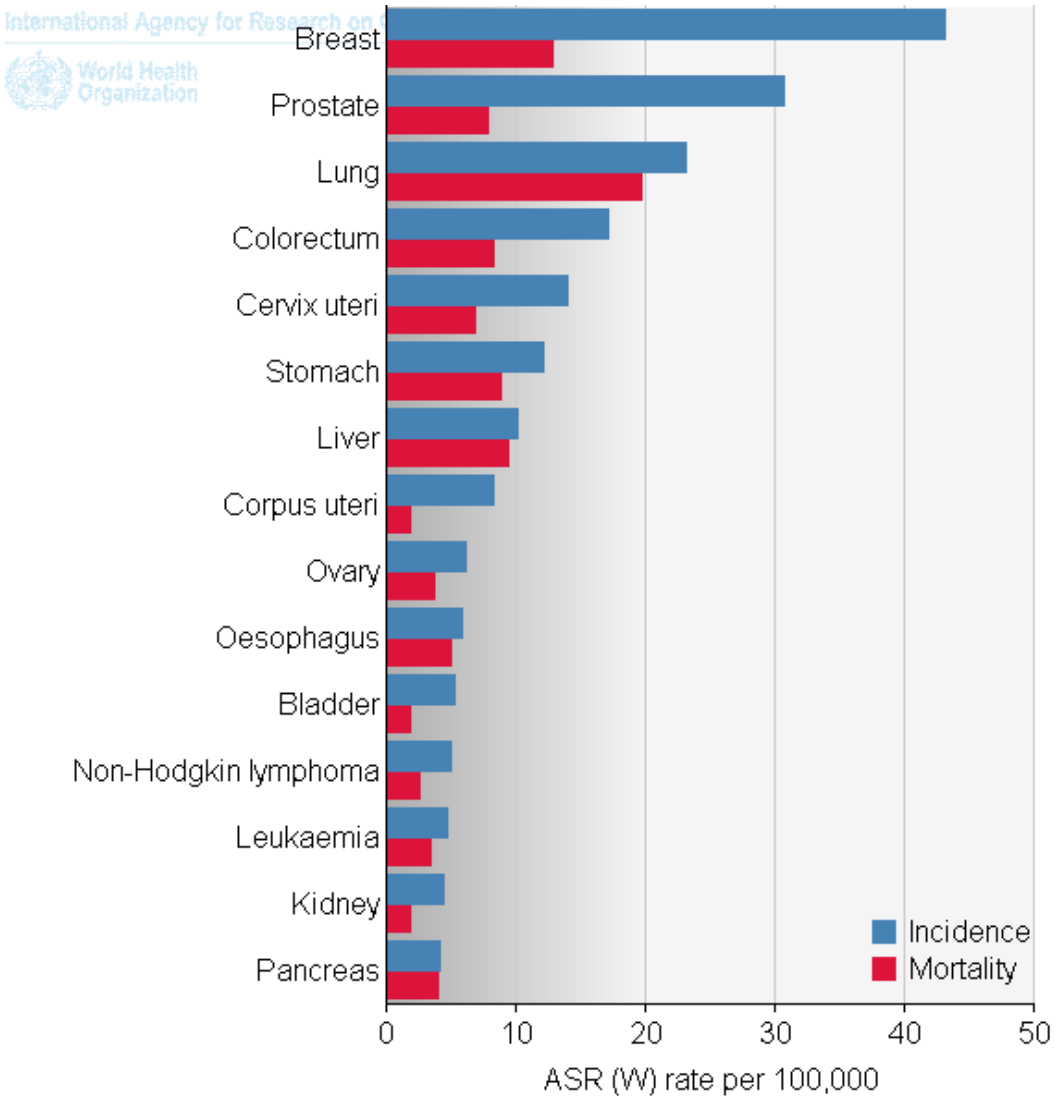


Source: Globocan 2012 (IARC)

As shown in Figure 2.2 below, lung cancer is the second most common cancer both in men and women (excluding skin cancer). Prostate cancer is the most common in men, and breast cancer in women.

Figure 2.2

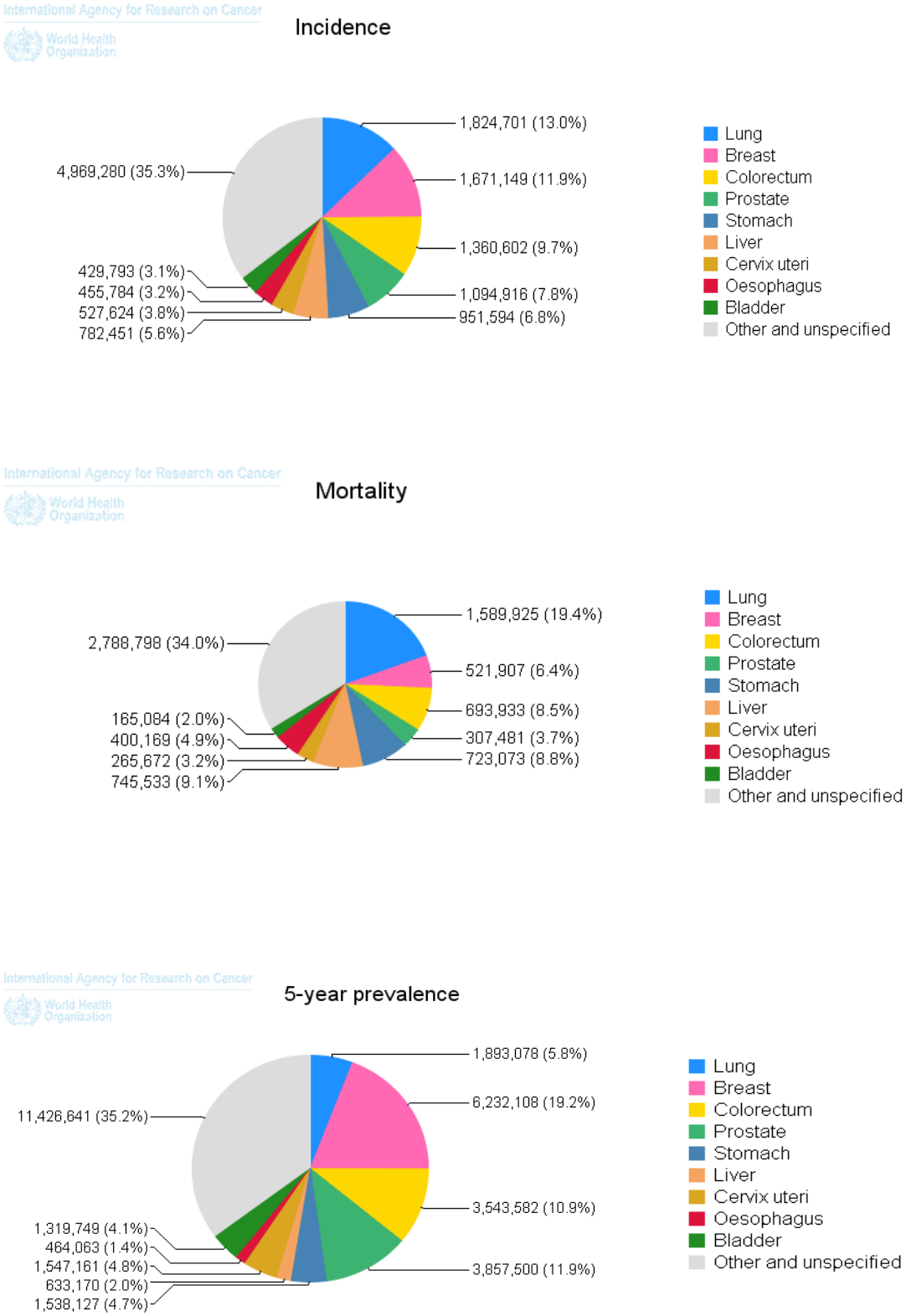
Estimated age –standardised incidence and mortality rates worldwide (both sexes)



Source: Globocan 2012 (IARC)

Figure 2.3

Estimated incidence, mortality, 5-year prevalence worldwide: both sexes



Source: Globocan 2012 (IARC)

According to the American Cancer Society's estimates for lung cancer in the United States for 2018 are about 234,030 new cases of lung cancer (121,680 in men and 112,350 in women) and about 154,050 deaths from lung cancer (83,550 in men and 70,500 in women). The chance that a man will develop lung cancer in his life time is about 1 in 15 while for a woman the risk is 1 in 17. Black men are about 20% more likely to develop lung cancer than white men and black women are 10% less likely to develop lung cancer when compared with white women. (American Cancer Society, 2018)

Lung cancer arises from the cells of the respiratory epithelium and can be divided into two broad categories, small cell lung cancer (SCLC) which accounts for 10-15% of lung cancer cases and non-small cell lung cancer (NSCLC) accounting for 80-85% of all lung cancer diagnoses. (American Cancer Society, 2018) Non small cell lung cancer is divided into 3 (three) major pathologic subtypes: adenocarcinoma (38,5% of all lung cancer cases), squamous cell carcinoma (20% of the total), large cell carcinoma (2,9% of the total). (Charles S. Dela Cruz et all, 2011)

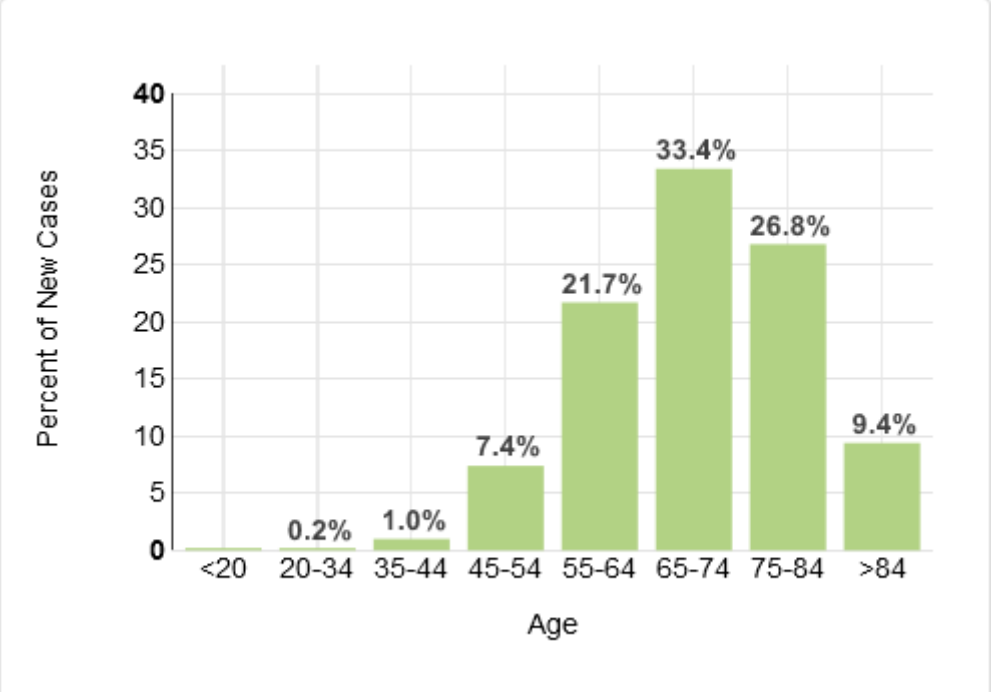
The 5-year survival rate for all people with all types of lung cancer is 18% (15% for men, 21% for women). However it is important to note that survival rates depend on several factors, including the subtype of lung cancer and the stage. For people with stage IA1 NSCLC, the 5-year survival rate is about 92%, for stage IA2 and IA3 the rate is 83% and 77% respectively. The survival rate for people with stage IB is about 68%, 60% for stage IIA and 53% for stage IIB. For stage IIIA the survival rate is about 36%, and about 26% and 13% for stage IIIB and IIIC respectively. In case of stage IV NSCLC the 5-year survival rate is approximately 1%. (American Cancer Society, 2018)

Although there has been some improvement in survival during the past few decades, the survival advances that have been realized in other common malignancies have yet to be achieved in lung cancer. A review of cancer statistics in 2011 noted a decrease in death rates from lung cancer in men by 2.0% per year from 1994 to 2006 while in women lung cancer death rates continued to increase by 0.3% per year from 1995 to 2005 but more recent data showed a decline over the past decades, -2,3% between 2006 and 2008. The lag in the decline of lung cancer rates in women compared with men has been attributed to the fact that cigarette smoking in women peaked two decades later than men. (Siegel R, 2011). Due to a decrease in smoking, death rates in 2018 have declined by 45% since 1990 in men and 19% in women since 2002. (American Cancer Society, 2018).

Lung cancer mainly occurs in older people, most people diagnosed with lung cancer are over 65 years old while a very small number of people get diagnosed younger than 45. (American Cancer Society, 2018). According to the Surveillance Epidemiology and End Results (SEER), median age at diagnosis for lung and bronchus cancer in the United States was 70 years old for the period from 2011 to 2015. The rates of age group cases are shown in Figure 2.4.

Figure 2.4

Rates of new cases by age group: Lung and Bronchus Cancer



Source: Surveillance Epidemiology and End Results (SEER) 18 2011-2015, Age-Adjusted

The World Health Organization estimates that lung cancer deaths will continue to rise worldwide, largely as a result of an increase in global tobacco use. Cigarette smoking is the principal risk factor for lung cancer. Despite the large proportion of all types of lung cancer attributed to the effect of cigarette smoking, in 2015 there were over 1.1 billion smokers worldwide, and if the current trends continue that number will increase to 1.9 billion by 2025. (WHO, 2015). Over 14 million people were diagnosed with cancer in 2012 and approximately 9 million people died of cancer in 2016. An estimated 22% of cancer deaths are attributed to tobacco use. (World Health Organization, 2018)

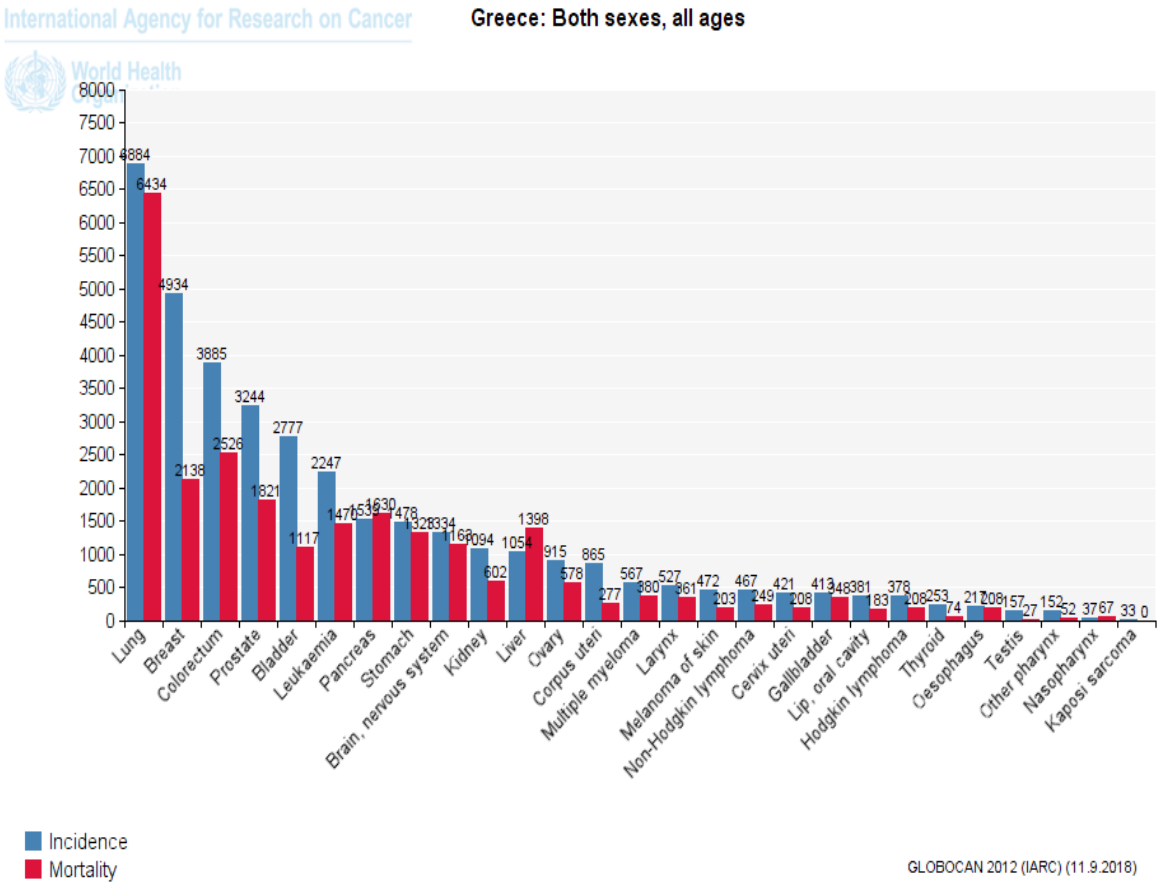
2.2 Epidemiological data in Greece

The data concerning lung cancer incidence in Greece are alarming, as Greece is the second country, after Poland, within the European Union (EU) with the highest consumption of cigarettes and the country with the highest incidence of lung cancer among people less than 45 years of age. (Foroulis Christoforos, 2012)

According to the world health organization (WHO) the smoking population in Greece increased from 2000 to 2009, while in other European countries the cigarette consumption decreased. Greece's smoking rates are the highest not only in the Europe but across all WHO regions globally. According to Euromonitor international the cigarette consumed by the Greek population reached a total of 27.7 billion cigarettes in 2010. Smoking constitutes the main direct etiologic factor for lung cancer and 30% of morbidity from cancer diseases (90% of lung cancer) are attributable to tobacco use. (Trichopoulos Dimitrios MD PhD, 2011)

Unfortunately cancer is a disease that remains incurable, the data follow are related to Greece and come from the GLOBOCAN Project conducted by the International agency for research on cancer (IARC) of the World health organization (WHO). The estimates of incidence, mortality and prevalence are based on the 2012, which is the last available year of such a global statistic project for cancer. As presented in Figure 2.5, the most common cancer in Greece for 2012 is the lung cancer with 6,884 new cases and 6,434 deaths, for both sexes, followed by breast cancer, colorectal cancer, prostate cancer and bladder cancer. The blue bars present the new cases and the red ones the deaths of all cancers in Greece.

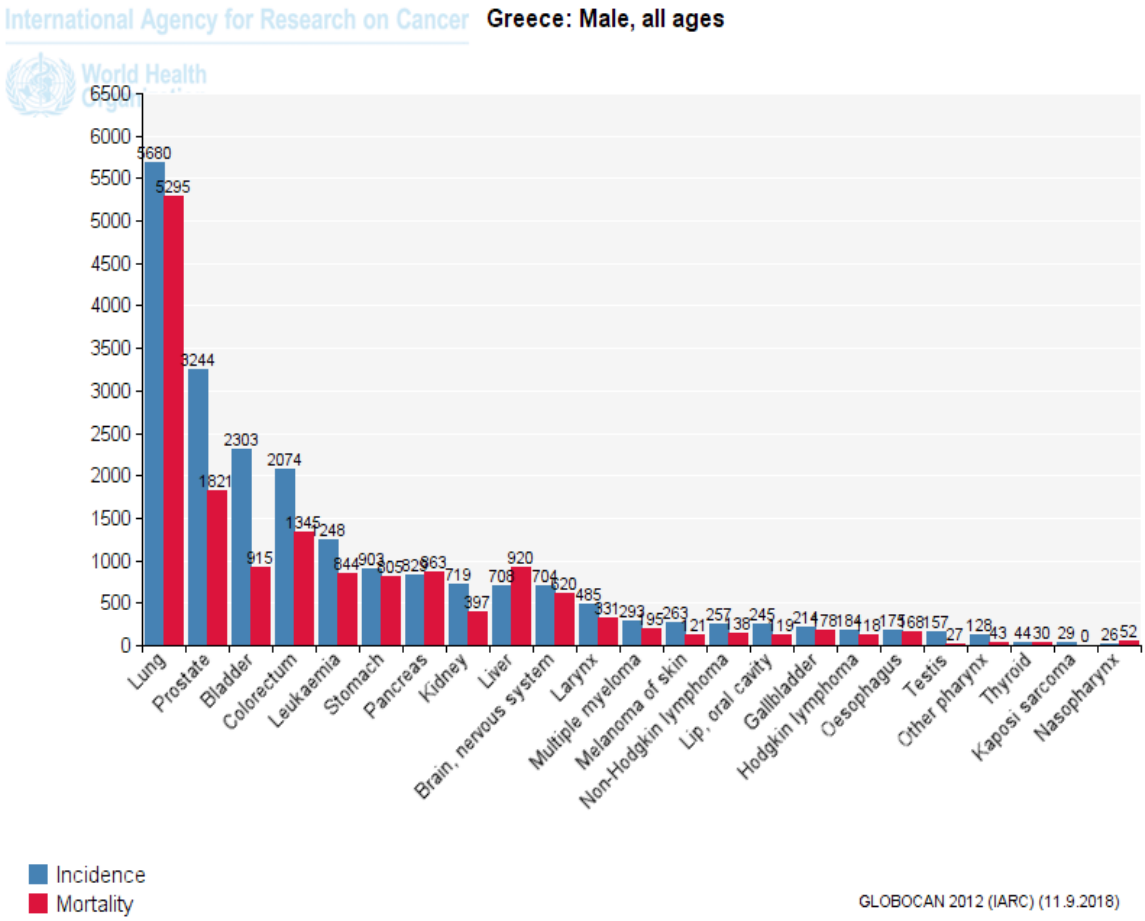
Figure 2.5
Greece Incidence and Mortality rates: both sexes



Source: GLOBOCAN 2012 (IARC)

From Figure 2.6 it is evident that in men, the most common neoplasm is lung cancer with 5,680 new cases and 5,295 deaths followed by prostate cancer, bladder cancer and colorectal cancer.

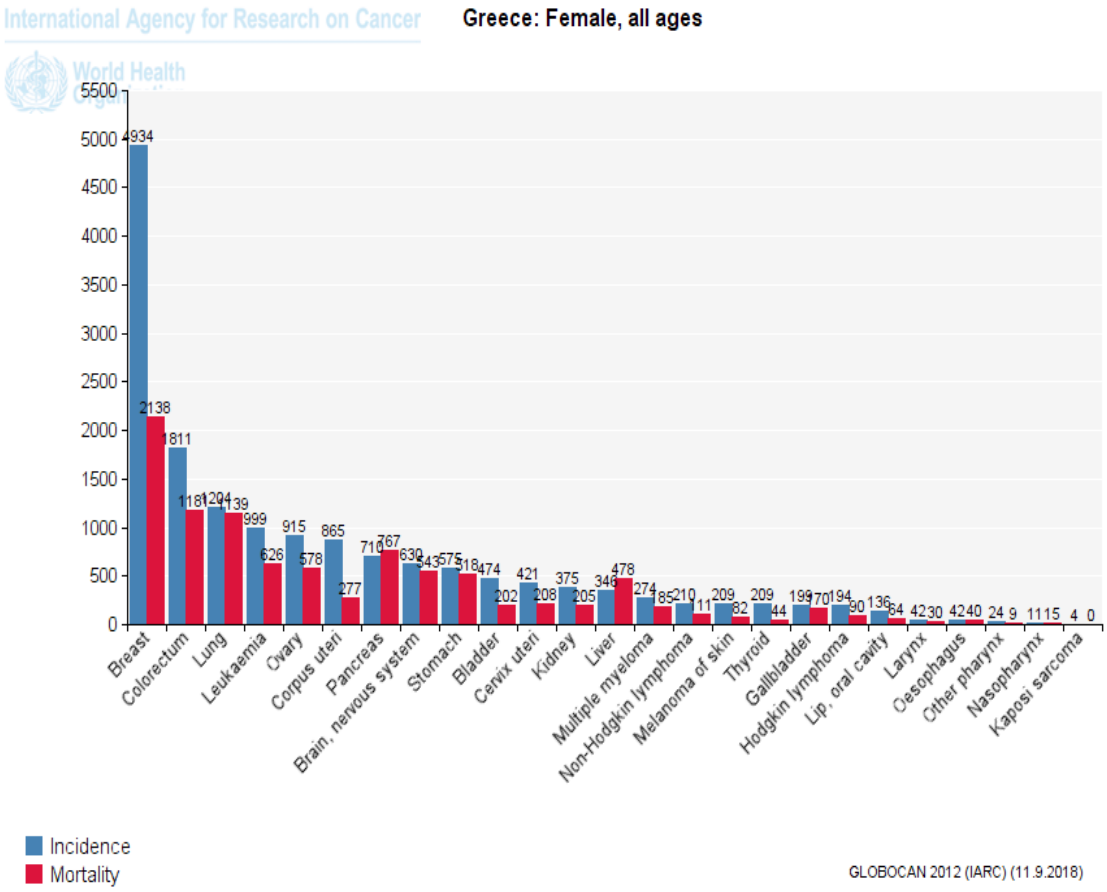
Figure 2.6
Greece incidence and mortality rates: male (all ages)



Source: GLOBOCAN 2012 (IARC)

In women, the most common neoplasm, as presented in Figure 2.7, is breast cancer followed by colorectal cancer and lung cancer. The incidence and mortality of lung cancer for women in Greece was 1,294 and 1,139 respectively for 2012.

Figure 2.7
Greece incidence and mortality: women (all ages)



Source: GLOBOCAN 2012 (IARC)

Cancer registries are essential in health care since they allow a better planning and evaluation of necessary health services. In Greece despite the high level of medical care there are no complete data on cancer registries. The Hellenic Society of Pathology having recognize the importance of such information in Greece, has conducted a 5-year pathology-based registry in Greece (2009-2013). During this study there have been registered 183,398 cancers and the pathology laboratories that participated comprise the 97.4% of all pathology laboratories in the national health care system, 6 out of 7 university hospital laboratories and 21 out of 21 major private hospitals and more than 80% of private pathology laboratories in Greece.

The collection of data started in November 2010 and was concluded in December 2016. Of the 183,398 register cases the 50,06% occurred in men and 49,94% in women.

The most common cancer types for both sexes were as follows: breast cancer (18,26%), colorectal cancer (15,49%), prostate cancer (13,49%) and lung cancer (10,24%).

In men, the most common neoplasms were as follows: prostate cancer (24,599 cases), colorectal cancer (15,993 cases), lung cancer (15,151 cases) and gastric cancer (5044 cases). In women, the most common neoplasms were as follows: breast cancer (32,959 cases), colorectal cancer (12,261 cases), thyroid cancer (8865 cases) and lung cancer (3530 cases). (Eleni Patsea, 2017) . The results of these research are summarized to the following tables. Table 2.1 shows the incidence rates of the most common neoplasms, while Table 2.2 presents the age-standardized incidence rates of the four most common neoplasms.

Table 2.1

Incidence of the most common neoplasms in males and females during 5-year period 2009-2013

Most common neoplasms during the 5-year period (incidence)		
	Male	female
Breast cancer	*	32,959
colorectal cancer	15,993	12,261
Prostate cancer	24,599	*
Lung cancer	15,151	3530
Gastric cancer	5044	*
Thyroid cancer	*	8865

*not among the most common neoplasms

Source: Hellenic society of pathology

Table 2.2.

Age standardizes incidence rates for the four most common neoplasms.the rates are standardized to the 2011 population.

Age-standardized incidence rates			
Breast cancer/100,000 standard population	Prostate cancer/100,000 standard population	Colorectal cancer/100,000 standard population	Lung cancer/100,000 standard population
119,4	90	52 Male:45,7 Female:44,8	35,1 Male:46,8 Female:13,6

Source: Hellenic society of pathology

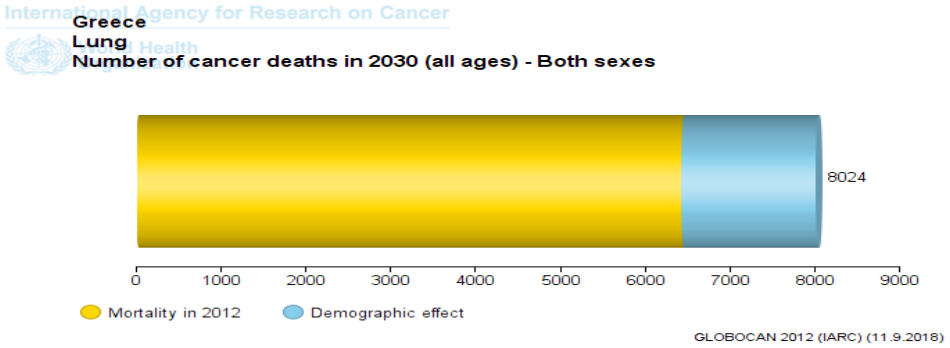
According to the GLOBOCAN 2012 project estimated cancer incidence in Greece the four most common cancers in both sexes are lung cancer, breast cancer colorectal cancer and prostate cancer.in male are lung cancer, prostate cancer, bladder cancer, colorectal cancer while in female are breast cancer, colorectal lung cancer and leukemia. There are some differences between the GLOBOCAN data and the data of the 5-year cancer registry report. The differences arise from the fact that the 5-year study conducted by the Hellenic society of pathology is based on real incidence as registered in the pathology laboratories in Greece, while the GLOBOCAN data are an estimation based on the registered numbers of neighboring countries, with which Greece nay have significant differences in environmental, lifestyle and genetically related cancer risk factors.

2.3 Predicts for 2030

The international agency for research on cancer (IARC) predicts that by 2030, 8,024 people from both sexes will die from lung cancer in Greece. Of this 6,663 are expected to be male and 1,361 women. The results of these predictions are demonstrated in Figures 2.8 and 2.9.

Figure 2.8

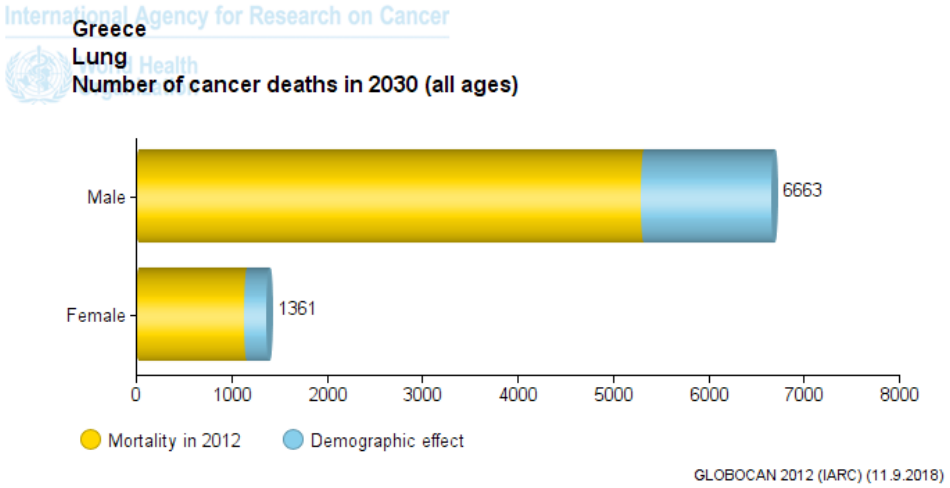
Predicted lung cancer mortality in Greece for 2030 both sexes (all ages)



Source: GLOBOCAN 2012 (IARC)

Figure 2.9

Predicted lung cancer mortality in Greece for 2030 (all ages)



Source: GLOBOCAN PROJECT (IARC)

In these figures the yellow part represents the 2012 data and the blue part the prediction for 2030. A 19,8% increase over the mortality rate in 2012 is observed. Particularly, the number of deaths is higher in men than in women.

Chapter 3
Health economics

3.1 Expenditure and Cost in Health Sector

The concept of health expenditure refers to any type of expenditure that is primarily for the purpose of improving or preventing a deterioration in the health status of a person or population (Culyer, 2015). This definition of *health expenditure* allows for the measurability of economic activities (health actions), according to the primary purpose and the results generated by the health system. The concept of activities also relates to serving the primary purpose of the health system but also concerns activities undertaken to improve or maintain a level in health (Canadian Institute for Health Information, 2002).

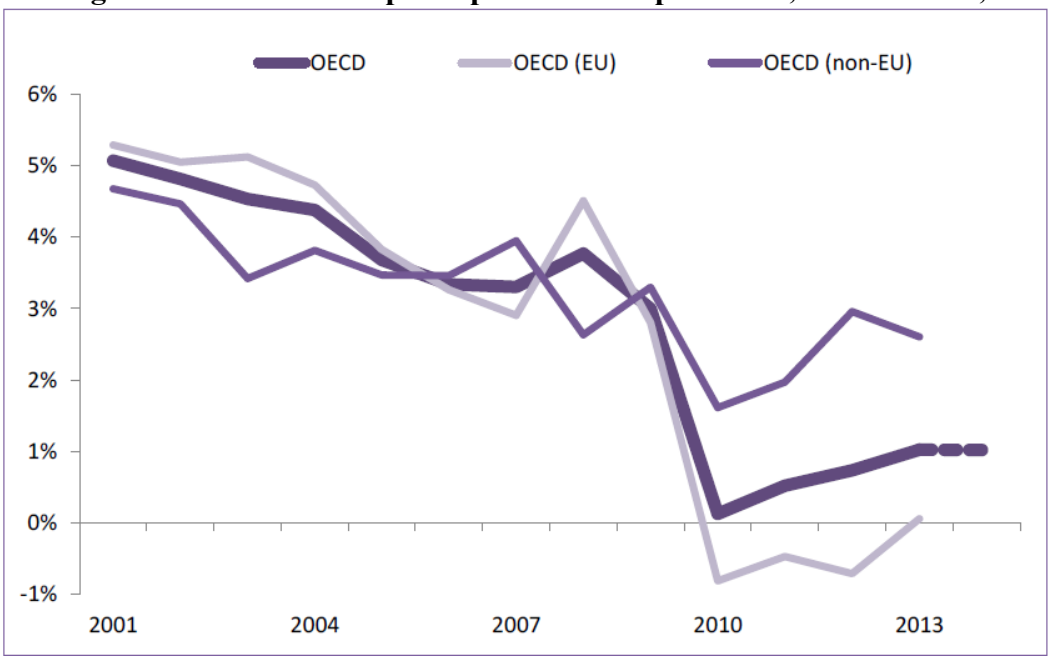
The health expenditures can be categorized into three main categories of expenditure, according to the international literature:

- Medical Expenses, which refer to doctors' fees, patient transportation costs, costs for various treatments, e.g. spa treatments etc.
- Hospital Costs, related to hospital costs, intervention costs, drug costs, cost of examinations, etc.
- Pharmaceutical Expenditure, which concerns expenditure on medicines, optic and orthopedic.

Increasing international health spending is a source of worry for governments seeking policies to curb this growth, as the surge in total spending reflects a rise in public health spending.

According to OECD data, the health expenditures increased slightly in 2013, with preliminary estimates showing the continuation of this trend in 2014. The slow rise stems from the postponement of the growth in health spending in 2010 following the global financial and economic crisis. However, many European countries have continued to see growth below the OECD average.

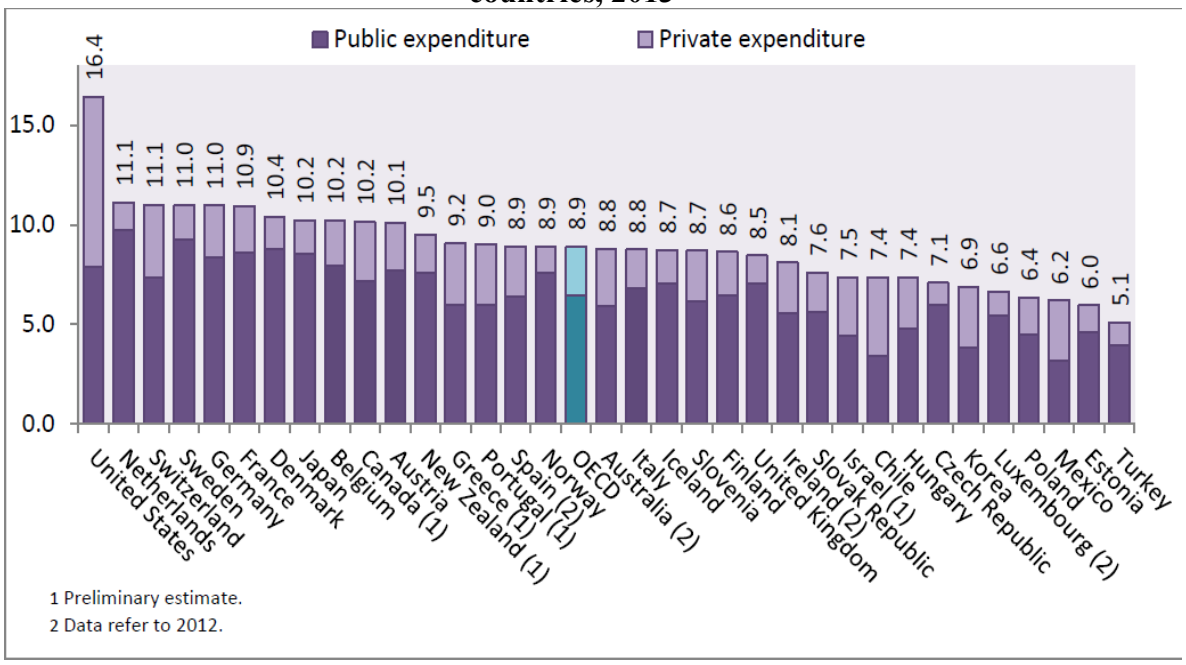
Figure 3.1
Average annual increase in per capita health expenditure, in real terms, 2001-2014



Source: OECD Health Statistics 2015

The health expenditure is estimated to have increased by 1.0% in real terms in all OECD countries in 2013, from 0.7% in 2012 and almost zero growth in 2010 (OECD (2017). However, growth rates in 2013 remained well below pre-crisis levels: between 2000 and 2009 the average increase in health spending reached 3.8%. Estimates for 12 OECD countries are presented in Figure 3.1 and indicate that slow growth continued in 2014 with an increase in health expenditure of around 1.0% (OECD Health Statistics 2015).

Figure 3.2
Health expenditures (excluding investment) as a percentage of GDP, OECD countries, 2013



Source: OECD Health Statistics 2015

More spending on health or more people or spending more natural resources does not necessarily mean better performance. That is why the ranking of countries is different. Throughout the OECD, policy makers have a keen interest in understanding how well their population's health is and how well their health systems are capable of delivering good results. A glance at indicators shows that great progress has been made (OECD (2017).

People in OECD countries live longer than ever, with a life expectancy of more than 80 years on average, thanks to improved living and living conditions and progress in health care. While the average public share of health expenditure remained stable (around 73%), the need to reduce public deficits in some countries has led to a shift to private sources of funding through changes in the right, changes to the benefits package and introduction or extension of fees use (OECD (2017).

In all sectors of the health system growth reductions were observed relative to pre-crisis levels. The end of patents for some medicines along with cost-cutting policies in many countries has reduced pharmaceutical spending in real terms. Expenditure on prevention services has also generally declined. The isolation from some countries of

some primary care services has led to less significant reductions in out-patient spending. Outside the OECD, health spending has risen sharply in countries like China and Indonesia, as the approach to universal health coverage remains.

Health is provided to the public, through an organized system, the health system. In the case of a system, attention is needed both in the structure and process dimension, since it concerns the way in which the structure of the system is structured to produce a result (Sarah, Whitehead., Shehzad, 2010).

The international practice has shown that cost control by itself is not effective unless it increases the efficiency of health systems. By controlling the growth rate of health expenditure and given resources, what is the most efficient way to heir distribution and use? The aim of health systems in recent years is to use efficiently the elements of the structure of the system, which through the rational application of procedures will lead to the efficiency of the systems and the quality of the provision of health services to the citizen.

The economic evaluation and efficiency of the system health, are the subject of health economics and their study is important in an economic environment with severe fiscal problems. The economic evaluation essentially identifies the efficiency of a system, program or intervention, identifying the cost-benefit, where the cost is measured as the monetary value of the inputs used to complete a process, and the benefit as outputs measured as specific and tangible Results. As an economic assessment, we define the comparative analysis of alternative health care and health programs as compared to their cost, measured in monetary units, and the results, measured in monetary or physical units (life years gained, etc) (Reidpath, Olafsdottir, Pokhrel, Allotey, 2012).

3.2 Efficiency and Equality of Health Systems

A healthcare system can be considered as a macroeconomic unit as a healthcare system of a country with total health costs but also as a micro-economic unit, ie as a unit of production and provision of health services, as is the case, for example, within a

hospital's action. Whether it is macroeconomic or micro-economic, the concepts of efficiency and equity of systems (Sarah, Whitehead., Shehzad, 2010).

Health and healthcare production and delivery facilities. Some consider that due to both the broadness and the priority given to efficiency, the issue of equality has been greatly overcome (Culyer, 2015). The term of profitability comes from the Italian economist Vilfredo Pareto, according to which the allocation of resources is excellent when it is possible to change their distribution to improve the position of one without worsening the position of another man (UN, 2002).

The criterion of efficiency, is therefore met when the resources are used within a certain period of time in such a way that it is impossible to improve the well-being of one person without reducing the well-being of someone else. An analogous term, which can be incorporated into the concept of efficiency, is the effectiveness of therapeutic interventions, which mainly concerns the micro-level and attempts to demonstrate, by combining health and economic outcomes, that the allocation of resources to the health system owes take into account the maximum benefit on behalf of patients.

In the area of health, economic profitability is considered to be achieved when resources are distributed among health actions in such a way as to maximize the benefit. To the question "What is the best way to act, by assuming that it is worthwhile acting on a subject?", Precedes the question of "distributive efficiency" and which is "Worth to act?". It is clear that in the directions of the action a fundamental role is played by the prospect of the society in which the action develops, which indirectly and / or directly can put the health needs to be met but also ultimately assess whether or not the intervention of the competent bodies is effective.

In recent years we have seen effective health programs with very high costs, while many times using pharmaceutical formulations with controversial results (Reidpath, Olafsdottir, Pokhrel, Allotey, 2012). Similar effective treatments when used in developed countries are accessible only to small sections of the population due to costs, with the result that seemingly higher health costs do not affect the whole of society as a whole (Culyer, 2015).

It follows that effectiveness and efficiency are two different concepts, with the effectiveness of unilaterally focusing on the technical part, not counting who benefits, while efficiency includes the element of distribution and quality. Therefore, referring to efficiency in health services is not intended to control costs to the detriment of society as a whole. Instead, it aims to rationalize spending so as to benefit as much as possible the population.

The term health-related equality is a fairly abstract concept and it is relatively difficult to identify the constituent elements. In a general context, equality means access to health structures for all, regardless of gender, belief, economic status and place of residence. However, data from the World Health Organization lead to the conclusion of serious inequalities. These contradictions are even more pronounced within countries according to the socio-economic order of the citizens.

Medical and social sciences are increasingly engaged in the definition and measurement of equality while economists and politicians use life-quality indicators in planning and assessing social and health policies. Besides, the importance for the individual of quality of life is recognized and promoted by the UN through various proclamations and conventions (Reidpath, Olafsdottir, Pokhrel, Allotey, 2012).

According to the WHO, health and quality of life are influenced by a number of factors such as income and distribution, nutrition, educational, cultural and cultural level, lifestyle, climatic conditions, social relations, conditions work and residence and the quality of medical and hospital care.

To date, surveys show that groups with a lower level of health quality are less likely to benefit from the reforms being made. A politician equal discrimination by hierarchy of resource allocation for the benefit of these groups could alleviate health inequalities (Culyer, 2006). However, the above conclusion is overlooked in the debate on the elimination of inequalities.

The "Black Report" of the National Health System of Great Britain (DHSS, 1980) restricted the measures to address access to equality as a structure rather than as a process,

ignoring how a citizen can be led to access, from which starting point and with what later results. As a result of the above option, the inequality eventually exacerbated: in the case of uterine cancer, expenditure was directed to the staffing of the health system with general practitioners, thereby increasing accessibility, which however women were unable to take advantage of from lower socioeconomic strata (Brown, Brown, Sharma, 2004).

In the case of spending on prevention and information (primary care) there would be a better outcome at a lower cost (Sassi et al., 2001). This option summarizes the 90's philosophy: Excessive spending on structures without any process reform and without taking the outcome into account (Sassi et al., 2001). From this point of view, equality does not go hand in hand with efficiency as the linear interpretation of equality leads to an uneven distribution of costs. The traditional economic approach states that as the ability to cover the population increases, both the cost and the cost increase, so the profitability decreases.

Nevertheless, the concept of efficiency refers to the greater the coverage of the population, at constant cost, and is thus interwoven with the concept of substantial equality (Reidpath et al., 2001). With a different equality which accepts the existence of favorable discrimination in favor of weak socio-tax groups in order to achieve a fairer situation. Inclusion of equality into the basic criteria for assessing a health system presupposes the assumption that health is a social good.

This view was developed by the faculty of equality. According to this school, the production and distribution of health services should be based on the actual needs of the patients. Equality is thus linked to the concept of distribution efficiency, which seeks a fair distribution of resources.

The opposite is the liberal view, which considers that this distribution should be the same as all consumer goods based on market functioning. In all countries, depending on the historical and political circumstances, it is observed that equality of access or consumption of health services is achieved through State interventions. These interventions are at different levels and depend on the form of health systems, the degree of social policy exercise and the structure of the socio-political system.

However, they often have a common denominator to control the supply side of health services and to maximize the utility / benefit of society as a whole. The allocation of resources in order to increase efficiency and maximize social benefits is a fundamental goal of health systems, but it can not always be ensured that total utility is allocated according to actual health needs. Thus, that in the health systems where market mechanisms prevail, there are significant inequalities in the consumption of health services, with the result that most of the utility is allocated to the higher social- (Brown, Brown, Sharma, 2004).

Although the general objective of reducing health inequalities seems indisputable, the concepts of justice and the ways in which they should be implemented are not clear at all . More importantly, there is no consensus on how to deal with policies and can cause a conflict between the objectives of equality and efficiency. The dilemma of equality against efficiency is virtually ignored in political debate, often leading to uncoordinated crises in the development of health policies.

3.3 Types of economic evaluation in healthcare

3.3.1 Cost-Effectiveness Analysis (CEA)

The Cost-Effectiveness Analysis (CEA) is defined as "the analytical technique designed to systematically benchmark the overall costs and benefits of alternative therapeutic interventions in managing a disease" (Sarah, Whitehead., Shehzad, 2010). The cost of each intervention is measured in monetary units, while the benefit is defined in similar, physical units determined by a specific measurement and with the help of specialized tools.

The interventions under consideration may reduce the impact of the disease,

eliminate the symptoms of the disease, improve the quality of life of patients, and also extend life expectancy. The difference is usually calculated from the method of choice at the time of analysis, ie the intervention applied to the clinical practice usually to treat the disease in question.

Benchmarking is fundamental to economic science. Cost-effectiveness analysis is a typical approach to the problem of evaluating alternative interventions through opportunity costs. It is a key tool for rational distribution and a central reference to the health economics methodology. In other words, it seeks to assess different health technologies by comparing the difference in resources between alternative interventions, both socially and individually. The above cost is not the cost of acquiring / producing the technology but is periodically evaluated and time-shifted to the extent that new technologies are introduced into the clinical practice. With the implementation of the CEA, the best use is made of the limited resources that health systems can provide. There are three main objectives for this kind of analysis:

- The determination of the price of a technology,
- The definition of the level of compensation from the insurance funds;
- To issue guidelines to be used as a guide for healthcare professionals.

3.3.2 Cost-Benefit Analysis

According to the cost-benefit analysis, a therapeutic intervention is worth adopting when the social benefit outweighs the cost of intervention. Costs are calculated in the same way as in the previous analyses, but the benefits / results are measured in currency units in order to be more easily compared to the corresponding costs of the program (Reidpath, Olafsdottir, Pokhrel, Allotey, 2012).

In other words, the cost-benefit analysis compares the money spent for a medical intervention with the money earned from the implementation of this medical intervention. On the contrary, cost-effectiveness analysis does not make it clear whether the costs incurred are worth the results they give us. Thus, with the cost-benefit analysis, we can

find out, on the one hand, whether there is a net social benefit from a medical intervention, on the other hand whether this medical intervention offers greater benefit than alternative interventions. The cost-benefit analysis can also be used in comparisons of clinical practices of different medical specialties, as well as programs relating to the allocation of resources in general to the economy.

Benefits may include productivity at work, earning time for medical / nursing staff, saving medical expenses, or saving costs from patient incapacity. Benefits are generally classified in the literature as: Health, Productivity and Saving of Future Expenses (Reidpath, Olafsdottir, Pokhrel, Allotey, 2012).

However, the cost-benefit analysis does not attempt to link the quality of life associated with that particular state of health or clinical practice with spending or saving. It can incorporate productivity but not improve quality of life (Reidpath, Olafsdottir, Pokhrel, Allotey, 2012). In addition, it may also pose issues of resource efficiency in the economy to guide decision-making in choices that maximize it. Still, because this type of analysis gives value to all aspects of the results, effects and effects on third parties can also be valued.

The cost-benefit analysis is widely applied in financial assessments, and that is because, ultimately, the results are better understood when they are presented on the same basis as costs, that is, in monetary units. The cost-benefit analysis also takes place in our everyday life, in various small decisions that we need to take. It does not require much economic knowledge or economic thought, but it is based on the principles of economic prosperity, which incorporates ethical issues into economic analysis. In the context of its economic prosperity, we meet the Pareto principles of social well-being, where it appears that the program evaluated (sanitary or other) should be adopted if it does not create inequalities between the members of a society (Brown, Brown, Sharma, 2004).

3.3.3 Cost-Utility Analysis

The cost-utility analysis (CUA) Cost-utility analysis is a form of CEA, and it expresses health outcomes in the same way, but it also allows people to express their

preferences for these results. CUA measures quantitative (mortality) and qualitative (morbidity) effects of a medical intervention using a measurement scale. In this context, a comparison is made between the additional cost of two health programs and the added benefit to health. Typically, this measurement scale is the quality adjusted life years earned (QALYs). Not only is the number of years earned, but also their quality (Culyer, 2015).

The Cost-utility analysis is the return on the resources spent on the quality adjusted years of life earned. CUA is similar to CEA, but it differs in that it gives the proportion of costs and overall benefit gained from therapeutic intervention. The lengthening of life and its improved quality are considered. This form of economic evaluation can better respond to cases where health programs attempt to prolong life or reduce morbidity compared to mortality (Culyer, 2015).

In addition, data related to final outcomes (eg earned lives, etc.) can be used for the cost-utility analysis. Instead, intermediate outflows (eg, number of diagnostic tests) do not give the CUA data that can be expressed in a suitable unit of measurement. The most common unit of measurement in which the CUA results are expressed is € / QALY. CUA measures the cost of improving / lengthening life. Prolonging life is easily measured by evidence-based data, but improvement is more difficult to assess.

The utility analysis was first described in the 1940s as a means of determining uncertainty, and after about two decades it was also applied to health. This term, as used in economic science, is almost identical to preference. The utility is the importance that people attach to a particular state of health. It is a weighting of the state of health which represents the desire of individuals to find themselves in this situation. The value of utility is derived from a combination of factors such as the psychological state of the individual, the occupational status and other socio-economic factors related to the quality of life (Culyer, 2015).

It is to be expected that different people will attach different importance to different health situations, so different utility for each one. Utilities can be recorded either by clinicians, by patients or by the general public, but differences can be detected depending on the angle. They are considered more objective, however, those recorded by

patients. In addition, utility considerations are the uncertainty and the relative attitude of the individual towards risk (ie if he or she chooses to make choices or not).

An ethical model has been developed on how individuals make rational decisions in uncertainty, von Neumann and Morgenstern, which has been accepted in the relevant literature. According to this, the preferences of individuals are characterized by transition, independence and continuity (Culyer, 2015). Because, for health, future outcomes are characterized by uncertainty, this model is considered to be essential for the calculation of utility.

3.4 Health Expenditures in Greece and Worldwide

The Organization for Economic Cooperation and Development (OECD) recently published on end of 2017, entitled "Health at a Glance 2017", the latest comparable data and trends of key health and health performance indicators in its 35 Member States. This data "sheds light" on the performance of health systems with indicators reflecting health outcomes, non-medical health determinants, the quality of health services provided, the degree of access to healthcare as well as the economic and human resources consumed 2016 (or the nearest year) (OECD (2017).

In 2016, Health Expenditures (% of GDP) were estimated at 9.0% of GDP on average in all OECD countries, which remained unchanged in recent years (OECD (2017). Stabilization of Health Expenditures was achieved after a period of increase in health spending relative to that of the total economy of the OECD countries in the 1990s and 2000s. The United States retained the first place as it spent 17.2% Of health, more than 91.11% of the average in OECD countries35, 38.71% more than Switzerland (2nd place -12.4%) and 52.21% more than Germany (3rd place-11.3%).

Greece is at 25th place spending 8.3% of GDP on health, down 8.43% from the average in OECD countries35, 31.08% less than the average of the countries of Germany, Sweden, France, Japan, Canada and the Netherlands (MO-10.88%), while it is 93.02% higher than Turkey (35th place - 4.3%) and 56.60% , China and India (MO-5.3%). Analyzing Greece's Health Expenditures shows that Government / Compulsory spending

accounts for 57.83% of total spending, while Optional / Private cover 42.17%. Greece's Government / Compulsory spending is lower by 24.88% and Voluntary / Private higher by 51.8% of the average in OECD countries.

Per capita Health Expenditure in 2016, averaged US $ 4.003 in all OECD countries35 converted into Power Purchasing Power (PPP) (OECD (2017). Government / Compulsory expenditure accounts for the bulk of total expenditure by 73.37%, while Optional / Private costs amount to 26.63% of total expenditure. The United States is ranked No. 1 with USD 9,892, spending 147.11% more than the average of OECD countries35 and 87.66% more than the average of G7 (Group of Seven) (MO-5.271) , 14 USD).

Greece holds the 27th place with USD 2,223 per capita, of which USD 1,296 (58,3%) are Government / Compulsory and 927 USD (41,7%) of Optional / Private expenditure. Analyzing the data, Greece spends less 80,07% of the average OECD countries per capita, and 137,12% less than the average of the G7 countries, while spending more 104,32% on Turkey and 22.93% more than the average of the Baltic States (MD-1.808,33 USD).

According to the OECD, the average annual growth rate of per capita Health Expenditure, in real terms, from 2003 to 2016 (or the nearest year) has the opposite effect for Greece, with a growth rate of 5.4% in 2003-2009 in the period 2009-2016 it recorded a -5.0% consequence of the deep financial crisis and the debt crisis of the Greek economy. A similar but less dramatic picture is also seen in Portugal (2.2% vs. -1.3%).

The pharmaceuticals expenditures represent the 3rd largest spending among Health Expenditures, accounting for more than 1/6 (16%) of health spending on average in all OECD countries in 2015 (excluding hospital expenditure for pharmaceutical products). The cost of pharmaceuticals, is mainly covered by the state or compulsory insurance. In all OECD countries, these projects account for an average of about 57% of all pharmaceutical spending in retail, while 39% come from private payments and 4% from voluntary private insurance. Greece holds the 7th highest position in the private expense for pharmaceutical products by retail by type of financing by 48.3% while the lowest positions in the OECD countries30 are Luxembourg with 12.4% and Germany

with 15.7% (OECD (2017)

The total retail pharmaceutical expense account in OECD countries was more than 800 billion dollars in 2015 according to the OECD report. However, there are per capita pharmaceutical costs in different countries, reflecting differences in volume, pharmaceutical prices and the use of generic medicines. More specifically, the United StatesThey spent $ 1,162 per capita in 2015, an additional 110.13% more than the average of OECD countries31 and 103.15% more than Greece (OECD (2017).

Also, Switzerland (982 USD) and Japan (798 USD) spent significantly more on drugs per capita than other OECD countries31. At the other end of the scale, Denmark (282 USD), Israel (313 USD) and Estonia (326 USD) had relatively low expenditure levels (Table 5). Still, 80% of the total pharmaceutical spending at retail is held by Prescription Drugs while the remaining percentage is Non-Prescription Drugs.

The percentage of non-prescription medicines is relatively high in Poland (51.42% of the total), while Australia (33.45%) and Spain (30.79%) are quite high, and the average annual growth rate of per capita pharmaceutical expenditure in 2009 -2015 is significantly lower in the pre-crisis period 2003-2009 (2.5% vs. -0.5%). This decrease is mainly due to the drastic cuts in government spending as a measure to curb public spending. The largest decrease in per capita pharmaceutical spending was observed in countries with co-operation memoranda such as Greece (-6.5%), Portugal (-5.9%) and Ireland (-4.4%) (OECD (2017).

RESEARCH FRAMEWORK

Chapter 4

Analysis of the effectiveness and cost estimation of nivolumab treatment

4.1 Aim of the study

Non-small cell lung cancer is the most common histological type of lung cancer with approximately 80% of patients getting diagnosed in advanced stage. Over the past decade significant progress in molecular diagnostics and targeted therapy has been made, although the prognosis for patients with NSCLC remains poor. Until a few years ago, the only therapeutic option for patients with metastatic non-small cell lung cancer (NSCLC) was platinum based chemotherapy or targeted therapy. Recently the development of a new class of drugs known as **immune checkpoint inhibitors** (**ICIs**), is considered the new revolution in many types of cancer including NSCLC, as they have shown a significant improvement in patient's survival and quality of life.

Patients with advanced NSCLC, without driven mutations, who have disease progression during or after first-line platinum-based chemotherapy, can receive second-line therapy. *Docetaxel* was one of the most commonly used second-line regimens for advanced NSCLC, but since its approval 10 years ago little therapeutic progress has been made. Therefore, scientists are constantly searching for new treatment option that could improve survival and provide a better quality of life in patients with advanced NSCLC. *Nivolumab* is the first immunotherapeutic agent, approved in 2015 by the European medicines agency for its use as a second line therapy in patients with NSCLC as an alternative to docetaxel.

Nivolumab is a human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, marketed as OPDIVO by Bristol Meyers Squibb. Two randomized phase III studies, CheckMate 017 for squamous NSCLC and CheckMate 057 for non-squamous NSCLC, have been conducted in order to prove efficacy and safety of nivolumab compared to docetaxel. In both studies an increased overall survival and tolerance was shown as compared to docetaxel. Despite the clinical benefit of nivolumab, proven by scientific works, the high cost of the treatment remains a problem, especially in countries such as Greece dealing with the economic crises, the burden on the health

care budget of the insurance funds is high, while the out of the pocket payment is impossible.

The aim of these study is initially to document the population that was treated with nivolumab as second-line treatment, upon implementation in 14 ,private and public, health care centers all over Greece, to evaluate the effectiveness and the toxicities of nivolumab in this population, and finally to estimate the cost of the treatment at insurance prices.

4.2 Materials and Methods

This is a multicenter, retrospective study that was carried out in co-operation with the Hellenic cooperative oncology group (HeCOG), using real-world data of patients with advanced non-small cell lung cancer in Greece. Adult patients (>18 years old) diagnosed with NSCLC, mainly stage III-IV with both histological types (squamous and non-squamous) who had disease progression after at least one platinum-based chemotherapy and were treated with nivolumab, as second line therapy, at 3mg every 2 weeks were included.

Oncologists of 14 medical centers in Greece provided the patients data by reviewing their medical records. To collect the data the participating centers were invited to fill three main clinical research forms. The first one included demographical, biometrical, functional data (age, sex, smoking status, ECOG performance status), disease related data (histological tumor subtype, classification, localization), prior therapy characteristics, response to nivolumab and survival data. The second one was a registry of the toxicities caused by nivolumab treatment, and the third one included data corresponding to the follow-up of the patients. There were not collected data of PD-L1 expression, as for nivolumab FDA did not specify any threshold PD-L1 positivity, consequently the use of PD-L1 TEST was not mandatory.

The effectiveness was evaluated based on the progression-free survival (PFS) and overall survival (OS) outcomes, and the survival curves were estimated with the use of Kaplan-Meier method.

Categorical data are presented as frequencies with the corresponding percentages, while the median and range is presented for the continuous variables. Progression-free survival (PFS) was defined as the time interval (in months) from the initiation of the nivolumab treatment to the date of documented disease progression or the date of last contact. Based on the Response Evaluation Criteria In Solid Tumors (RECIST) disease progression is determined when the diameters of the lesions increase over 20%, but also when a new lesion appears during treatment. The progression of the disease was evaluated every 2 months through a CT-Scan examination. Overall survival (OS) was calculated as the time (in months) from the initiation of nivolumab treatment to the date of death. Alive patients were censored at the date of their last contact. Quality of life was not measures as the study was not designed to collect such a data even though they are important.

Time to event data were analyzed using the Kaplan-Meier product limit method and compared across subgroups (age, gender) with the long rank test. The association between factors of interest and progression/mortality rates were assessed using hazard ratios (HR) estimated with univariate Cox proportional hazard regression models. Analyses of PFS and OS were conducted in the entire cohort of 141 patients included in the current analysis, while the Objective response rate (ORR) was additionally assessed in the response evaluable population consisting of all patients with tumor evaluation by the investigators in the local hospitals/institutions. All tests were two-sided at an alpha 5% level of significance. The data cut-off date was October 9th ,2018. Analyses were conducted using the SAS (version 9.3, SAS Institute Inc., Cary, NC) software.

For the economic evaluation of the treatment only direct health care cost, in insurance prices, were included. The indirect costs, which burden patients and their families, were not included as the study was carried out retrospectively and from the perspective of the decision makers managing health care budgets. The cost data, in order to estimate the treatment cost for each patient, were collected by the Greek national sources, the database of METROPOLITAN Hospital and the available bibliography.

4.3 Patients and Treatment

A total of 141 patients were included in the study. The participating hospitals/institutions and the number of patients at each center are summarized in Table 4.2. The median age of the patients, when treatment with nivolumab was started, was 67.2 years. From the 141 patients 104 (73.8%) were male and only 37 (26.2%) were female.

The 107 (86.3%) of the patients were former or current smokers, and all of the patients had been previously treated with a platinum-based chemotherapy. In the study all histological subtypes were included, 54.8% of the patients had adenocarcinoma (non-squamous cell) while 38.7% had squamous cell carcinoma. At the time of diagnoses 64.8% of the patients were diagnosed in stage IV, 13.9% in stage IIIB and 6.5% in stage IIIA of NSCLC. All patients included in the analysis did not express any molecular abnormality, and no immunohistochemical test was implemented for the evaluation of patients PDL-1 expression, as it wasn't necessary in the routine clinical practice. The clinical characteristics of the patients are presented in Table 4.1.

Table 4.1

Selected patients and tumor characteristics at baseline

	Total (N=141)
Age^	67.2(45.9,89.7)
Sex	
Female	37(26.2)
Male	104(73.8)
Smoking*	
No	17(13.7)
Yes	107(86.3)
Histology*	
Adenocarcinoma	68(54.8)
Large cell	2(1.6)
Mixed	3(2.4)
Squamous cell	48(38.7)
Unclassified	2(1.6)
Undifferentiated	1(0.81)

	Total (N=141)
Stage*	
I	2(1.9)
II	10(9.3)
IIIa	7(6.5)
IIIb	15(13.9)
IIIb wet	4(3.7)
IV	70(64.8)

*Data not available for all subjects. Missing values: Smoking = 17, Histology = 17, Stage = 33.

Values presented as Median (min, max) or N (column %). ^ At initiation of Nivolumab treatment.

Table 4.2

Number of patients at each hospital participating in the analysis.

Organization Name	N	%
MITERA	30	21.28
METROPOLITAN - BAFALOUKOS	26	18.44
AGIOI ANARGYROI	24	17.02
IOANNINA UNIVERSITY	15	10.64
AGIOS SAVAS	14	9.93
AGIOI ANARGYROI - ARAVANTINOS	6	4.26
METROPOLITAN - SKARLOS	6	4.26
ALEXANDRAS	4	2.84
PATRA UNIVERSITY, RIO	4	2.84
YGEIA - RAZI	4	2.84
EUROCLINIC	3	2.13
THERMI	3	2.13
AG. ANDREAS - PATRA	1	0.71
EUROMEDICA GENIKI KLINIKI THESSALONIKI	1	0.71
Total	141	100.00

In the study all patients included received at least one cycle of nivolumab at a dose of 3mg/kg every 2weeks. The drug was initiated intravenously. Patients received the treatment until disease progression or interrupt of the treatment because of the adverse events or for another reason. The median follow-up period was 16.1 months. Nivolumab demonstrated a statistically significant benefit of OS and PFS. Table 4.3 presents a summary of OS and PFS results from the study.

Table 4.3

Follow-up time, overall survival (OS), progression-free survival (PFS)

Follow-up period (months)	
Median (95% CI)	16.1 (12.2-19.2)
Overall Survival (months)	
Median (95% CI)	19.7 (12.7-NE)
N (%) deaths	57 (40.4%)
Progression-free survival (months)	
Median (95% CI)	7.4 (5.9-11.6)

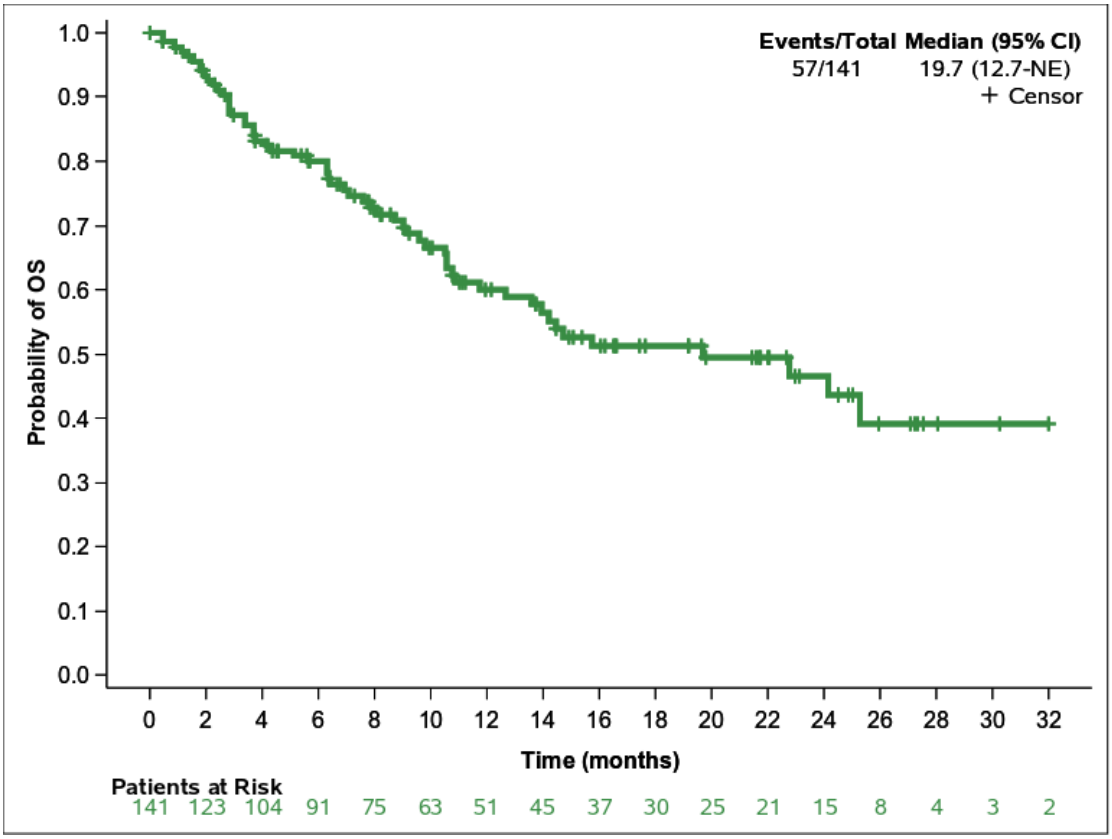
4.4 Efficacy

4.4.1 Effectiveness analysis (OS, PFS)

Time to event endpoints (OS, PFS) were analyzed using the Kaplan-Meier method, and compared across subgroups (sex, age) with the log-rank test. Figures 4.1 and 4.2 show the Kaplan Meier OS and PFS curve respectively of the study. The number of patients in each state of health are shown in Tables 4.4 and 4.5 which include the cumulative probability of survival by time and cumulative probability of survival without progression by time respectively. The studies maximum follow up period was 32.7 months.

Figure 4.1

Kaplan-Meier with respect to Overall Survival for all patients included in the analysis.



At the time of database analysis the median overall survival of all patients treated with nivolumab was 19.7 months (95%CI, 12.7-NE). The overall survival rate at 1 year was approximately 60%. From the OS survival curve (Figure 4.1) and the cumulative probabilities summarizes in Table 4.4, it is observed for the first 14 months a slow reduction in the survival rate. From month 14 to month 22 the rate remains almost stable with a very small reduction. From month 22 to 25 the rate presents a small reduction and for the rest of the following period the rate remains stable. At the end of the follow up period (32.7 months) the percentage of patients that did not express the event (death) was 39.15%.

Table 4.4

Probability of survival by time.

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.4600	.
0.4600	0.9857
0.4600	.
0.4600	.
0.4600	.
0.8900	0.9784
0.9200	.
0.9200	.
1.1500	0.9710
1.2500	0.9636
1.3800	.
1.5400	0.9561
1.8000	.
1.8000	0.9412
1.8400	.
1.9000	.
1.9700	0.9336
2.0700	0.9260
2.2600	0.9184
2.3000	.
2.3300	.
2.3900	0.9107

Months since Nivolumab initiation	Survival
2.5600	0.9030
2.6600	.
2.8200	.
2.8200	0.8874
2.8500	0.8796
2.9200	0.8718
2.9800	.
3.3800	0.8640
3.4100	0.8561
3.7000	.
3.7000	0.8404
3.7400	.
3.7700	0.8325
3.7700	.
4.1600	0.8245
4.1600	.
4.3000	0.8164
4.3600	.
4.5200	.
4.5900	.
4.5900	.
5.1500	0.8080
5.3800	.
5.6100	.
5.6400	0.7994

Months since Nivolumab initiation	Survival
5.6400	.
5.7000	.
6.3000	.
6.3000	0.7818
6.3600	0.7730
6.3600	.
6.3900	0.7642
6.6600	.
6.7900	.
6.9500	0.7551
7.0800	0.7460
7.2800	.
7.6100	0.7367
7.7400	.
7.8000	.
7.8400	0.7273
7.8400	.
7.9300	.
8.0700	0.7176
8.2000	.
8.2600	.
8.5600	.
8.7200	0.7075
9.0200	0.6974
9.0200	.

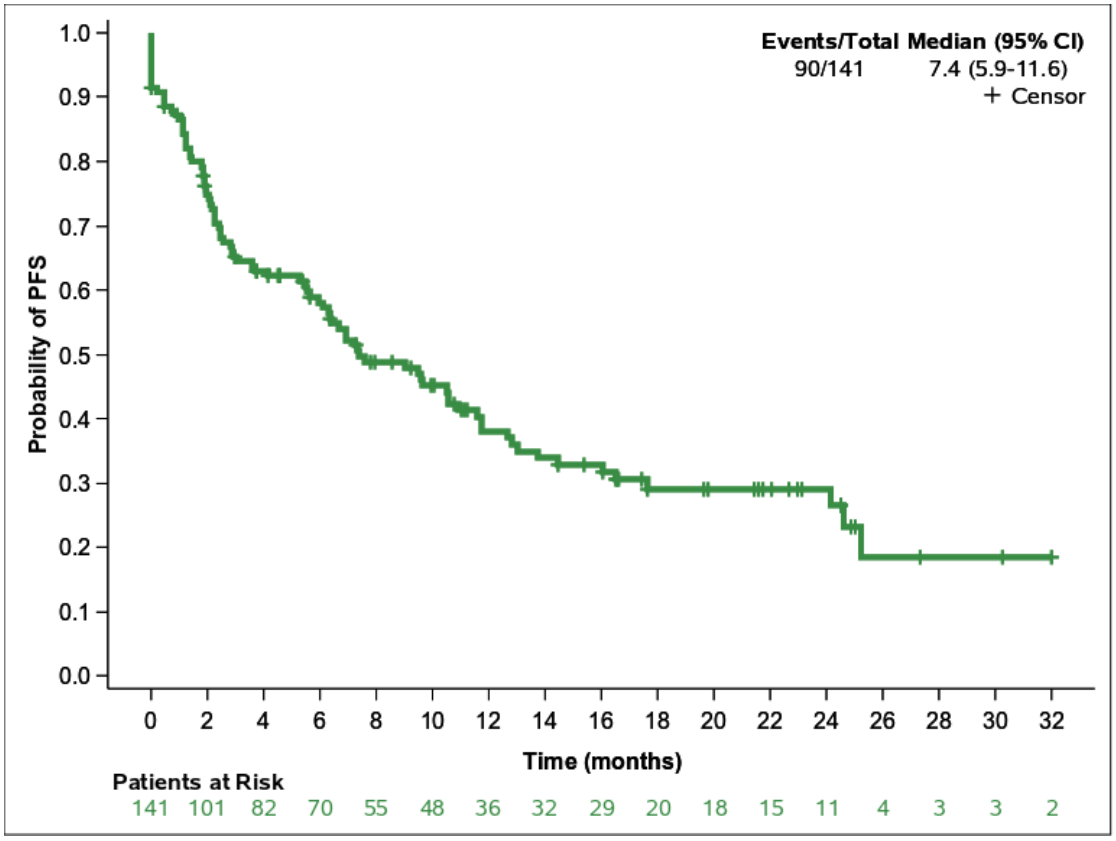
Months since Nivolumab initiation	Survival
9.1100	0.6871
9.2500	.
9.6100	0.6767
9.8000	0.6663
9.9300	.
10.0300	.
10.5200	0.6556
10.5600	0.6448
10.5900	0.6341
10.7500	0.6233
10.7900	.
10.8900	0.6124
11.0200	.
11.1100	.
11.2500	.
11.7400	0.6008
11.9300	.
12.1600	.
12.6600	0.5888
13.6100	0.5768
13.7700	.
13.7700	.
13.9300	0.5643
14.2000	0.5517
14.4600	0.5392

Months since Nivolumab initiation	Survival
14.4600	.
14.7200	0.5263
14.9500	.
15.0800	.
15.3800	.
15.7700	0.5125
16.0700	.
16.2000	.
16.5200	.
16.5900	.
16.6200	.
17.4400	.
17.6400	.
19.1800	.
19.1800	.
19.6400	.
19.6700	0.4935
19.7700	.
21.4400	.
21.5700	.
21.6700	.
21.7400	.
22.0000	.
22.0300	.
22.6900	.

Months since Nivolumab initiation	Survival
22.7900	0.4661
22.9800	.
23.1100	.
24.1300	0.4350
24.5200	.
24.5200	.
24.8500	.
25.0500	.
25.2800	0.3915
25.9300	.
27.0800	.
27.2500	.
27.3100	.
27.5400	.
28.0700	.
30.2600	.
32.5600	.
32.6600	0.3915

Figure 4.2

Kaplan-Meier with respect to PFS for all patients included in the analysis.



The median PFS of all patients treated with nivoluman was 7.4 months (95% CI, 5.9-11.6). The rate of progression-free survival at one year was approximately 38%. As it can be seen from the PFS survival curve in Figure 4.2 and the probability by time in Table 4.5, for the first 3 months the effectiveness of the treatment is low as we see a rapid decrease in the percentage of patients free of progression. From month 4 until month 16 treatment becomes more effective, a slower decrease in the number of patients free of progression is observed. From month 16 to month 24 in the survival curve we notice a plateau which is interpreted as a stable percentage of patients free of disease during this period. The same situation is also observed from month 16 to month 32. It can be said that patients have a better response to treatment after the third month, while for the first months an aggravation of the health status is observed.

Table 4.5

Probability of survival without progression by time.

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	0.9149
0.0000	.
0.2300	0.9077
0.4600	.
0.4600	.
0.4600	0.8863
0.4600	.
0.7200	0.8791
0.8900	0.8719
0.9200	.
1.0200	0.8646
1.1100	.

Months since Nivolumab initiation	Survival
1.1100	0.8501
1.1500	0.8428
1.2500	.
1.2500	.
1.2500	0.8210
1.3800	.
1.3800	0.8065
1.4400	0.7992
1.8000	0.7920
1.8400	.
1.8400	0.7774
1.8400	.
1.9000	.
1.9000	0.7628
1.9000	.
1.9700	.
1.9700	0.7480
2.0700	0.7406
2.1300	0.7331
2.1600	0.7257
2.2600	.
2.2600	.
2.2600	0.7035
2.4300	0.6961
2.4600	.

Months since Nivolumab initiation	Survival
2.4600	0.6813
2.5600	0.6739
2.8500	0.6665
2.8900	0.6591
2.9200	0.6517
2.9800	.
3.0200	0.6442
3.5700	0.6367
3.7000	0.6292
3.7400	.
3.7700	.
4.1600	0.6215
4.1600	.
4.5200	.
4.5900	.
4.5900	.
5.3100	0.6135
5.3800	.
5.5100	0.6053
5.5400	0.5971
5.6400	0.5889
5.6400	.
5.9300	0.5806
6.1300	0.5723
6.3300	0.5640

Months since Nivolumab initiation	Survival
6.3600	0.5558
6.3600	.
6.3900	0.5473
6.6900	0.5389
6.9200	0.5305
6.9500	0.5221
7.2100	0.5136
7.2800	.
7.3400	0.5051
7.3800	0.4965
7.6100	0.4880
7.8000	.
7.9300	.
8.5600	.
9.0200	0.4789
9.2500	.
9.5100	0.4697
9.5700	0.4605
9.6400	0.4513
9.9300	.
10.0300	.
10.5200	0.4417
10.5600	0.4321
10.5900	0.4225
10.7900	.

Months since Nivolumab initiation	Survival
10.9500	0.4127
11.0200	.
11.1100	.
11.2500	.
11.5700	0.4021
11.7400	0.3915
11.7700	0.3809
12.6600	0.3703
12.8200	0.3598
13.0500	0.3492
13.7700	0.3386
14.4600	0.3280
14.4600	.
15.3800	.
16.0700	0.3167
16.0700	.
16.4900	0.3050
16.5200	.
16.5900	.
16.6200	.
17.4400	.
17.6400	0.2911
17.6400	.
19.6400	.
19.7700	.

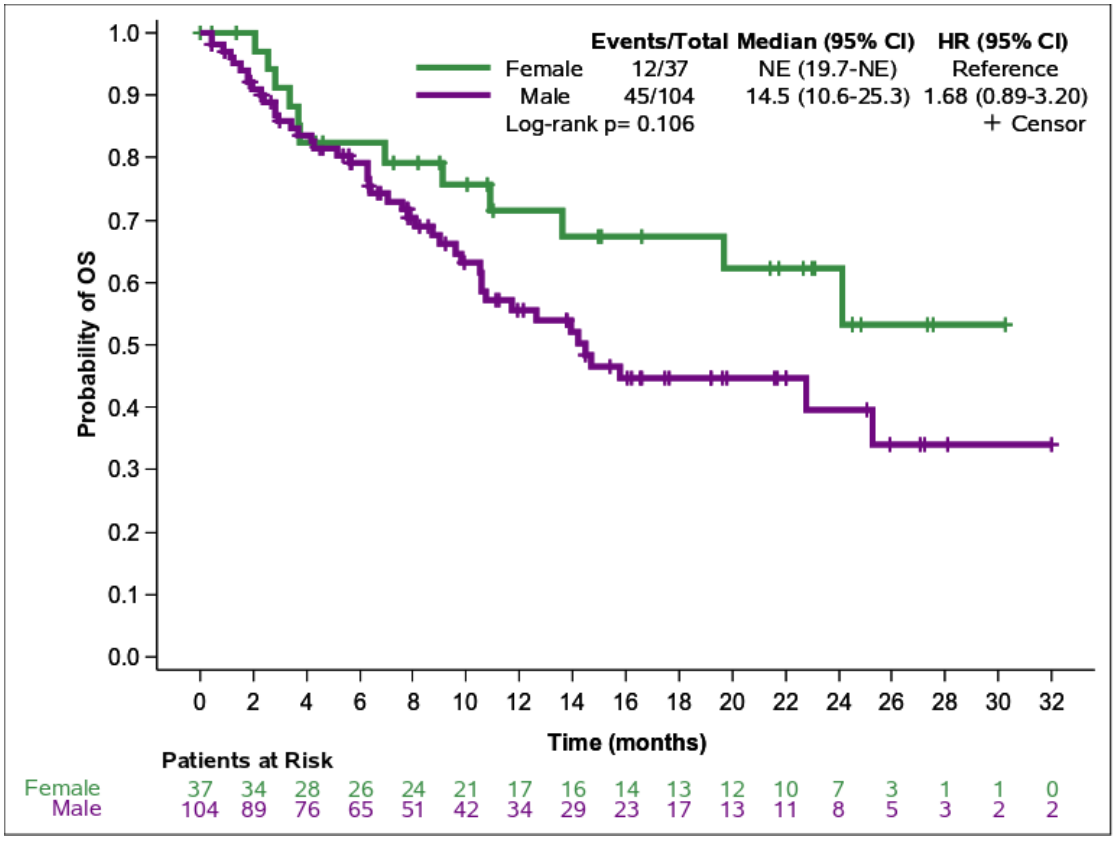
Months since Nivolumab initiation	Survival
21.4400	.
21.5700	.
21.7400	.
22.0300	.
22.6900	.
22.9800	.
23.1100	.
24.1300	0.2646
24.5200	.
24.5200	.
24.6200	0.2316
24.8500	.
25.0500	.
25.2500	0.1853
27.3100	.
30.2600	.
32.5600	.
32.6600	0.1853

4.4.2 Subgroup analysis

Subgroup analyses were performed for end points, OS and PFS, in order to observe if there is any statistically significant difference in the efficacy or nivolumab regarding gender (female, male).

Figure 4.3

Kaplan-Meier with respect to OS according to patient's sex.



***NE: not evaluated**

The median OS for male patients treated with nivolumab was 14.5 months (95% CI, 10.6-25.3) while for the female patients the median OS has not been reached yet. As it can be seen from the OS survival curves in Figure 4.3 and the cumulative probabilities in Tables 4.6 and 4.7, the overall survival was longer in the female group compared to the male group. Males have a higher risk to the event (death) respect to women with a hazard ratio of 1.68 (95% CI, 0.89-3.20) but it is not statistically significant. Since the significant level was set at the 5% no significant association was observed between patients sex at initiation of nivolumab treatment (using median value as cut-off) with overall survival (p=0.106).

Table 4.6

Probability of survival by time based on patient's sex (Female)

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.4600	.
1.3800	.
2.0700	0.9706
2.5600	0.9412
2.8500	0.9118
3.3800	0.8824
3.7000	0.8529
3.7700	0.8235
4.3600	.
4.5900	.
6.9500	0.7919
7.2800	.
8.2000	.
9.0200	.
9.1100	0.7559
10.0300	.
10.7900	.
10.8900	0.7161
11.0200	.
13.6100	0.6740
14.9500	.
15.0800	.

Months since Nivolumab initiation	Survival
16.6200	.
19.6700	0.6221
21.4400	.
21.7400	.
22.6900	.
22.9800	.
23.1100	.
24.1300	0.5332
24.5200	.
24.5200	.
24.8500	.
27.3100	.
27.5400	.
30.2600	0.5332

Table 4.7

Probability of survival by time based on patient's sex (Male)

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.4600	.
0.4600	0.9808
0.4600	.
0.4600	.

Months since Nivolumab initiation	Survival
0.8900	0.9710
0.9200	.
0.9200	.
1.1500	0.9610
1.2500	0.9509
1.5400	0.9409
1.8000	.
1.8000	0.9209
1.8400	.
1.9000	.
1.9700	0.9107
2.2600	0.9004
2.3000	.
2.3300	.
2.3900	0.8900
2.6600	.
2.8200	.
2.8200	0.8688
2.9200	0.8582
2.9800	.
3.4100	0.8475
3.7000	0.8367
3.7400	.
3.7700	.

Months since Nivolumab initiation	Survival
4.1600	0.8257
4.1600	.
4.3000	0.8146
4.5200	.
4.5900	.
5.1500	0.8031
5.3800	.
5.6100	.
5.6400	0.7913
5.6400	.
5.7000	.
6.3000	.
6.3000	0.7669
6.3600	0.7548
6.3600	.
6.3900	0.7424
6.6600	.
6.7900	.
7.0800	0.7296
7.6100	0.7168
7.7400	.
7.8000	.
7.8400	0.7035
7.8400	.

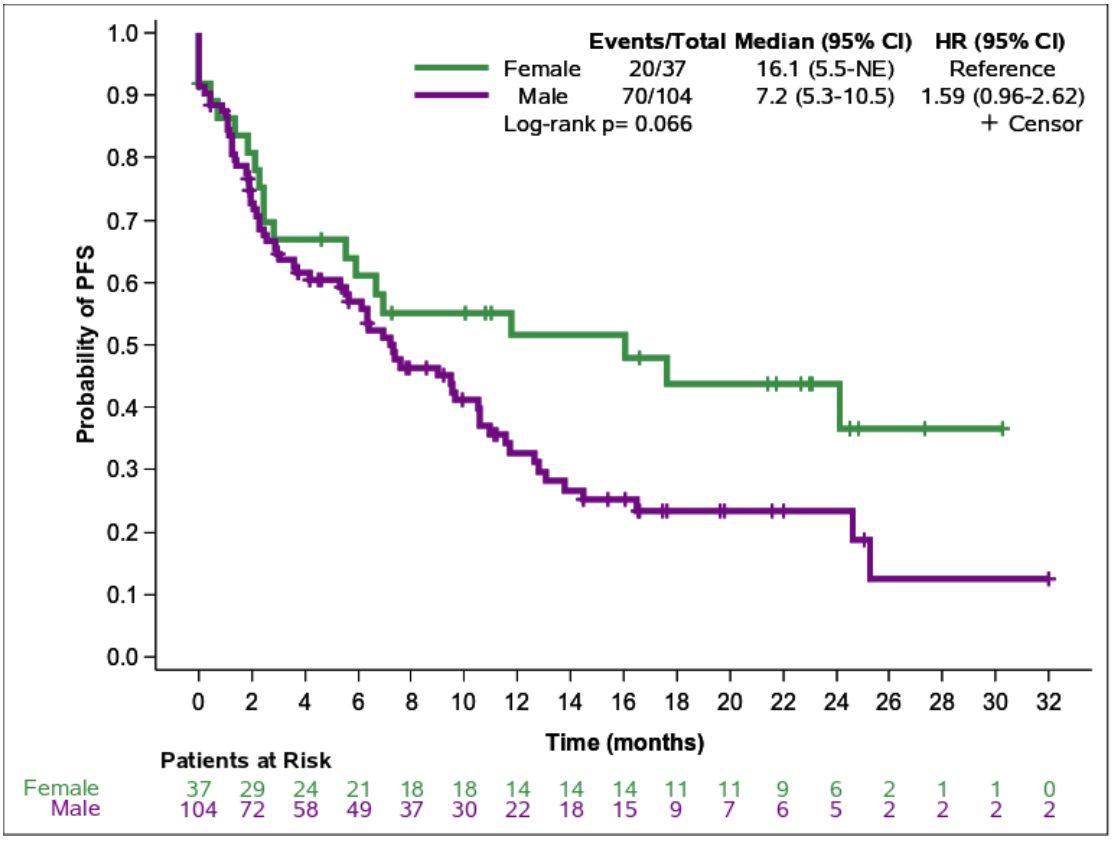
Months since Nivolumab initiation	Survival
7.9300	.
8.0700	0.6897
8.2600	.
8.5600	.
8.7200	0.6754
9.0200	0.6610
9.2500	.
9.6100	0.6463
9.8000	0.6316
9.9300	.
10.5200	0.6166
10.5600	0.6015
10.5900	0.5865
10.7500	0.5715
11.1100	.
11.2500	.
11.7400	0.5556
11.9300	.
12.1600	.
12.6600	0.5387
13.7700	.
13.7700	.
13.9300	0.5208
14.2000	0.5028

Months since Nivolumab initiation	Survival
14.4600	0.4849
14.4600	.
14.7200	0.4662
15.3800	.
15.7700	0.4468
16.0700	.
16.2000	.
16.5200	.
16.5900	.
17.4400	.
17.6400	.
19.1800	.
19.1800	.
19.6400	.
19.7700	.
21.5700	.
21.6700	.
22.0000	.
22.0300	.
22.7900	0.3972
25.0500	.
25.2800	0.3404
25.9300	.
27.0800	.

Months since Nivolumab initiation	Survival
27.2500	.
28.0700	.
32.5600	.
32.6600	0.3404

Figure 4.4

Kaplan-Meier with respect to PFS according to patient's sex



***NE: not evaluated**

The median PFS was 7.2 months (95% CI, 5.3-10.5) in the male group as compared with 16.1 months (95% CI, 5.5-NE) in the female group. As it is seen from the PFS survival curves in Figure 4.4 and the cumulative probabilities in tables 4.8 and 4.9, the PFS is longer in the female group compared to the male group. Males had a higher risk to the even (progression disease) .A trend was observed for unfavorable PFS in male, hazard ratio 1.59 (95% CI, 0.96-2.62), p=0,066.

Table 4.8

Probability of PFS by time based on patient's sex (Female)

Months since Nivolumab initiation	Survival
0.0000	1.0000

Months since Nivolumab initiation	Survival
0.0000	.
0.0000	.
0.0000	0.9189
0.0000	.
0.4600	0.8911
0.7200	0.8632
1.3800	0.8354
1.8400	0.8075
2.1300	0.7797
2.2600	0.7518
2.4600	.
2.4600	0.6962
2.8500	0.6683
4.5900	.
5.5400	0.6392
5.9300	0.6102
6.6900	0.5811
6.9200	0.5521
7.2800	.
10.0300	.
10.7900	.
11.0200	.
11.7700	0.5153
16.0700	0.4785

Months since Nivolumab initiation	Survival
16.6200	.
17.6400	0.4386
21.4400	.
21.7400	.
22.6900	.
22.9800	.
23.1100	.
24.1300	0.3655
24.5200	.
24.5200	.
24.8500	.
27.3100	.
30.2600	0.3655

Table 4.9

Probability of PFS by time based on patient's sex (Male)

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.

Months since Nivolumab initiation	Survival
0.0000	.
0.0000	.
0.0000	.
0.0000	0.9135
0.2300	0.9038
0.4600	.
0.4600	0.8846
0.4600	.
0.8900	0.8749
0.9200	.
1.0200	0.8651
1.1100	.
1.1100	0.8454
1.1500	0.8356
1.2500	.
1.2500	.
1.2500	0.8061
1.3800	0.7963
1.4400	0.7864
1.8000	0.7766
1.8400	0.7668
1.8400	.
1.9000	.
1.9000	0.7468
1.9000	.

Months since Nivolumab initiation	Survival
1.9700	.
1.9700	0.7267
2.0700	0.7166
2.1600	0.7065
2.2600	.
2.2600	0.6863
2.4300	0.6762
2.5600	0.6661
2.8900	0.6560
2.9200	0.6459
2.9800	.
3.0200	0.6357
3.5700	0.6254
3.7000	0.6152
3.7400	.
3.7700	.
4.1600	0.6046
4.1600	.
4.5200	.
4.5900	.
5.3100	0.5934
5.3800	.
5.5100	0.5819
5.6400	0.5705
5.6400	.

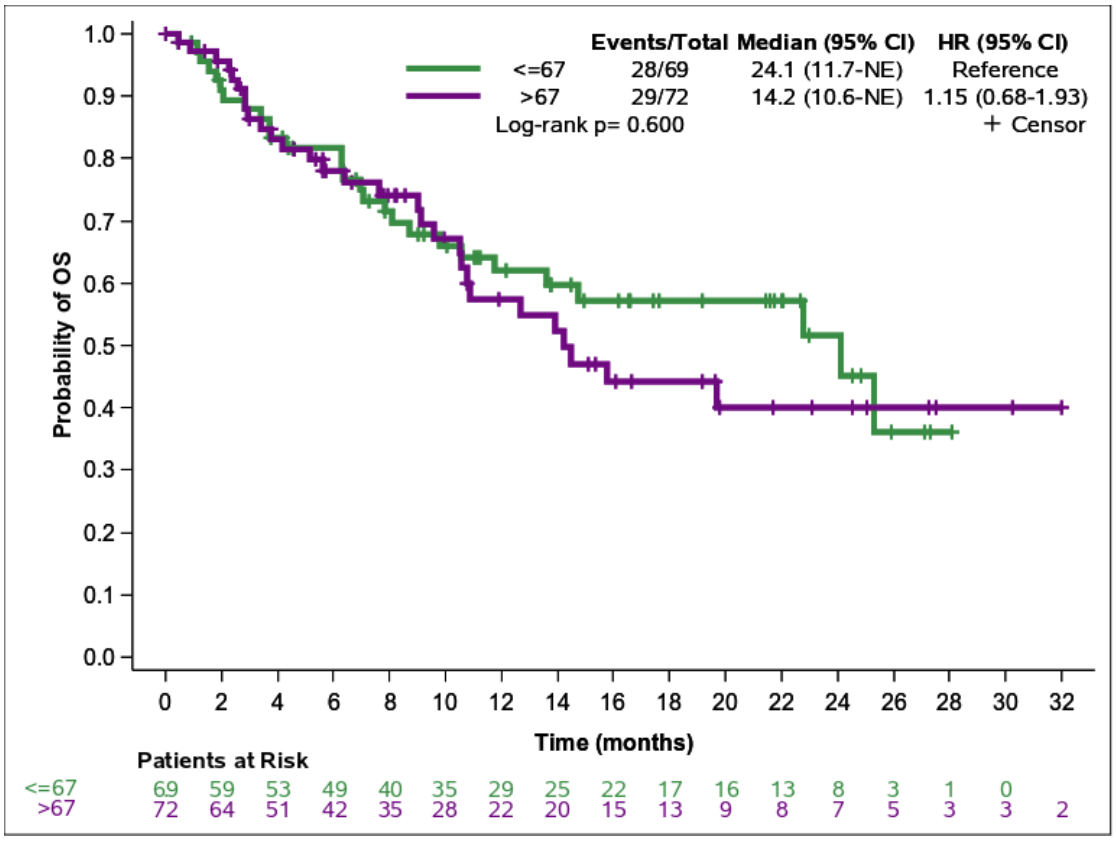
Months since Nivolumab initiation	Survival
6.1300	0.5589
6.3300	0.5473
6.3600	0.5356
6.3600	.
6.3900	0.5237
6.9500	0.5118
7.2100	0.4999
7.3400	0.4880
7.3800	0.4761
7.6100	0.4642
7.8000	.
7.9300	.
8.5600	.
9.0200	0.4513
9.2500	.
9.5100	0.4380
9.5700	0.4248
9.6400	0.4115
9.9300	.
10.5200	0.3978
10.5600	0.3840
10.5900	0.3703
10.9500	0.3566
11.1100	.
11.2500	.

Months since Nivolumab initiation	Survival
11.5700	0.3418
11.7400	0.3269
12.6600	0.3120
12.8200	0.2972
13.0500	0.2823
13.7700	0.2675
14.4600	0.2526
14.4600	.
15.3800	.
16.0700	.
16.4900	0.2346
16.5200	.
16.5900	.
17.4400	.
17.6400	.
19.6400	.
19.7700	.
21.5700	.
22.0300	.
24.6200	0.1876
25.0500	.
25.2500	0.1251
32.5600	.
32.6600	0.1251

Subgroup analysis was also performed for OS and PFS, in order to observe if there is any statistically significant difference in the efficacy or nivolumab regarding patient's age (>67, ≤67 years).

Figure 4.5

Kaplan-Meier with respect to OS according to patient's age at initiation of nivolumab treatment.



***NE: not evaluated**

The age subgroups were well balanced, at the beginning of the study 69 patients were included in the group ≤ 67 years, and 72 patients were included in the group > 67 years. The median OS was 14.2 months (95% CI, 10.6-NE) for the group > 67 years, and 24.1 (95% CI, 11.7-NE) for the group ≤ 67 years. As it is observed from the survival curves in Figure 4.5 and the cumulative probabilities in Tables 4.10 and 4.11 for the first eleven months the OS rates are similar with a slow decrease over time, curves are crossed several times during this period of time, from month 11 to the end of the follow up (32.7 month) the curves get separated. The group > 67 years had a higher risk to the event (death) compared to group ≤ 67, with hazard ratio 1.15 (95% CI, 0.68-1.93), but it was not statistically significant. Since the significant level was set at the 5% no significant

association was observed according to patient's age at initiation of nivolumab treatment (using median value as cut-off) with overall survival (p=0.600).

Table 4.10

Probability of survival by time based on patient's age at initiation of nivolumab (age= ≤67).

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.4600	0.9855
0.4600	.
0.9200	.
0.9200	.
1.1500	0.9703
1.2500	0.9552
1.5400	0.9400
1.8000	0.9249
1.9000	.
1.9700	0.9094
2.0700	0.8940
2.8500	0.8786
3.3800	0.8632
3.7000	.
3.7000	0.8324
3.7700	.
4.1600	.
4.3000	0.8164

Months since Nivolumab initiation	Survival
4.3600	.
4.5200	.
6.3000	.
6.3000	0.7830
6.3600	0.7664
6.7900	.
6.9500	0.7494
7.0800	0.7323
7.2800	.
7.8400	0.7149
7.8400	.
8.0700	0.6970
8.7200	0.6791
9.0200	.
9.2500	.
9.8000	0.6603
10.0300	.
10.5600	0.6409
11.0200	.
11.1100	.
11.2500	.
11.7400	0.6195
12.1600	.
13.6100	0.5974

Months since Nivolumab initiation	Survival
13.7700	.
13.7700	.
14.4600	.
14.7200	0.5725
14.9500	.
16.2000	.
16.5200	.
16.5900	.
17.4400	.
17.6400	.
19.1800	.
21.4400	.
21.5700	.
21.7400	.
22.0000	.
22.0300	.
22.6900	.
22.7900	0.5152
22.9800	.
24.1300	0.4508
24.5200	.
24.8500	.
25.2800	0.3607
25.9300	.

Months since Nivolumab initiation	Survival
27.0800	.
27.3100	.
28.0700	0.3607

Table 4.11

Probability of survival by time based on patient's age at initiation of nivolumab (age= >67).

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.4600	0.9859
0.4600	.
0.4600	.
0.8900	0.9714
1.3800	.
1.8000	0.9567
1.8400	.
2.2600	0.9417
2.3000	.
2.3300	.
2.3900	0.9263
2.5600	0.9109
2.6600	.

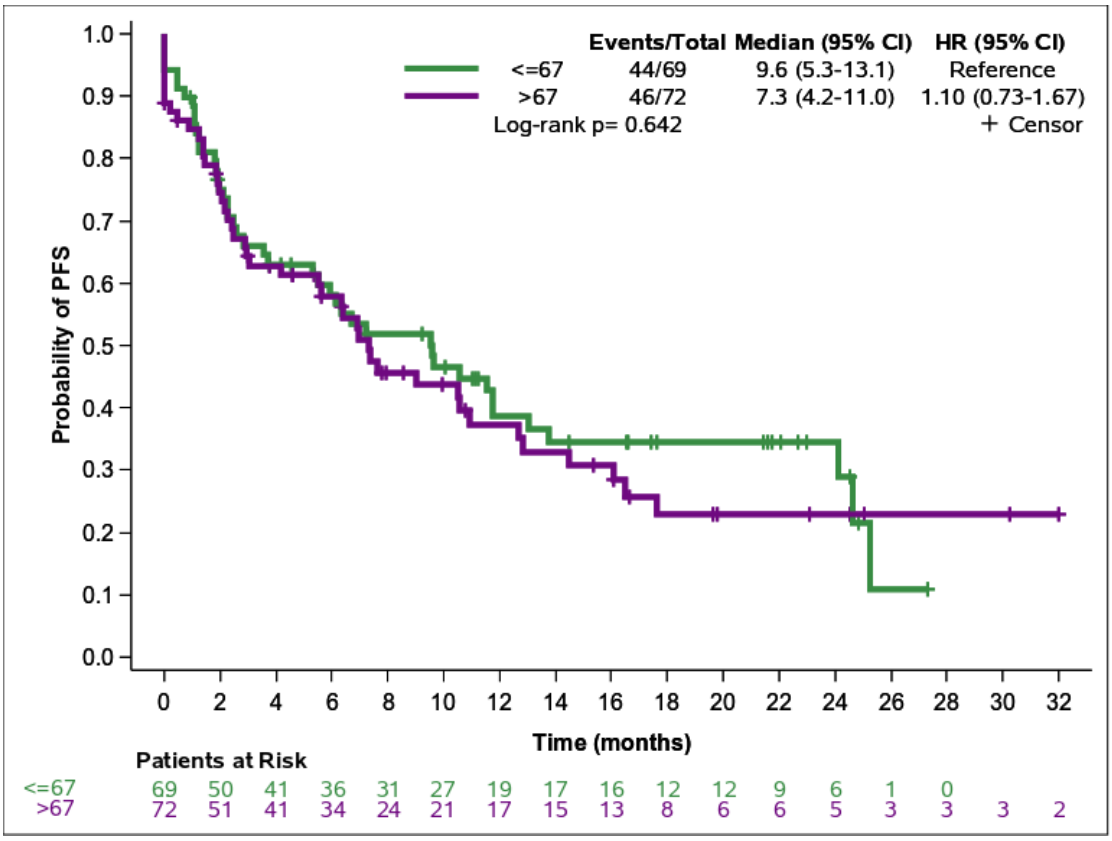
Months since Nivolumab initiation	Survival
2.8200	.
2.8200	0.8795
2.9200	0.8638
2.9800	.
3.4100	0.8478
3.7400	.
3.7700	0.8315
4.1600	0.8152
4.5900	.
4.5900	.
5.1500	0.7982
5.3800	.
5.6100	.
5.6400	0.7804
5.6400	.
5.7000	.
6.3600	.
6.3900	0.7614
6.6600	.
7.6100	0.7419
7.7400	.
7.8000	.
7.9300	.
8.2000	.
8.2600	.

Months since Nivolumab initiation	Survival
8.5600	.
9.0200	0.7187
9.1100	0.6955
9.6100	0.6723
9.9300	.
10.5200	0.6483
10.5900	0.6243
10.7500	0.6003
10.7900	.
10.8900	0.5753
11.9300	.
12.6600	0.5491
13.9300	0.5230
14.2000	0.4968
14.4600	0.4707
15.0800	.
15.3800	.
15.7700	0.4413
16.0700	.
16.6200	.
19.1800	.
19.6400	.
19.6700	0.4012
19.7700	.
21.6700	.

Months since Nivolumab initiation	Survival
23.1100	.
24.5200	.
25.0500	.
27.2500	.
27.5400	.
30.2600	.
32.5600	.
32.6600	0.4012

Figure 4.6

Kaplan-Meier with respect to PFS according to patient's age at initiation of nivolumab treatment.



The median PFS was 7.3months (95% CI, 4.2-11.0) for the group >67years, compared to 9.6 months (95%CI, 5.3-13.1) for the group ≤67 years. As it can be seen from the PFS survival curves in Figure 4.6 and the cumulative probabilities in Tables 4.12 and 4.13, for the first 7 months there is not a significant difference in the efficacy of nivolumab according to patient's age, the survival curves are moving together until the 7th month of treatment. From month 7 to the end of the follow up the survival curves slightly differentiate. The group > 67 years had a higher risk to the event (progression disease) compared to group ≤ 67, with hazard ratio 1.10 (95% CI, 0.73-1.67), but it was not statistically significant. Since the significant level was set at the 5% no significant association was observed according to patient's age at initiation of nivolumab treatment (using median value as cut-off) with progression free survival (p=0.642).

Table 4.12

Probability of PFS by time based on patient's age at initiation of nivolumab (age= ≤ 67 years).

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.0000	.
0.0000	.
0.0000	0.9420
0.4600	.
0.4600	0.9130
0.7200	0.8986
0.9200	.
1.0200	0.8838
1.1100	.
1.1100	0.8544
1.1500	0.8396
1.2500	.
1.2500	0.8102
1.8000	0.7954
1.8400	0.7807
1.9000	0.7660
1.9000	.
1.9700	0.7510
2.1300	0.7359
2.2600	.
2.2600	0.7059

Months since Nivolumab initiation	Survival
2.4600	0.6909
2.5600	0.6759
2.8500	0.6608
3.5700	0.6458
3.7000	0.6308
3.7700	.
4.1600	.
4.5200	.
5.3100	0.6146
5.5100	0.5985
5.9300	0.5823
6.1300	0.5661
6.3300	0.5499
6.6900	0.5338
7.2100	0.5176
7.2800	.
9.2500	.
9.5100	0.5003
9.5700	0.4831
9.6400	0.4658
10.0300	.
10.5600	0.4479
11.0200	.
11.1100	.
11.2500	.

Months since Nivolumab initiation	Survival
11.5700	0.4275
11.7400	0.4072
11.7700	0.3868
13.0500	0.3665
13.7700	0.3461
14.4600	.
16.5200	.
16.5900	.
17.4400	.
17.6400	.
21.4400	.
21.5700	.
21.7400	.
22.0300	.
22.6900	.
22.9800	.
24.1300	0.2884
24.5200	.
24.6200	0.2163
24.8500	.
25.2500	0.1082
27.3100	0.1082

Figure 4.13

Probability of PFS by time based on patient's age at initiation of nivolumab (age= >67 years).

Months since Nivolumab initiation	Survival
0.0000	1.0000
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	.
0.0000	0.8889
0.0000	.
0.2300	0.8748
0.4600	0.8607
0.4600	.
0.8900	0.8463
1.2500	0.8320
1.3800	.
1.3800	0.8033
1.4400	0.7889
1.8400	0.7746
1.8400	.
1.9000	0.7600
1.9700	0.7454
2.0700	0.7308

Months since Nivolumab initiation	Survival
2.1600	0.7161
2.2600	0.7015
2.4300	0.6869
2.4600	0.6723
2.8900	0.6577
2.9200	0.6431
2.9800	.
3.0200	0.6281
3.7400	.
4.1600	0.6128
4.5900	.
4.5900	.
5.3800	.
5.5400	0.5962
5.6400	0.5797
5.6400	.
6.3600	0.5626
6.3600	.
6.3900	0.5450
6.9200	0.5275
6.9500	0.5099
7.3400	0.4923
7.3800	0.4747
7.6100	0.4571
7.8000	.

Months since Nivolumab initiation	Survival
7.9300	.
8.5600	.
9.0200	0.4373
9.9300	.
10.5200	0.4164
10.5900	0.3956
10.7900	.
10.9500	0.3736
12.6600	0.3517
12.8200	0.3297
14.4600	0.3077
15.3800	.
16.0700	0.2840
16.0700	.
16.4900	0.2582
16.6200	.
17.6400	0.2295
19.6400	.
19.7700	.
23.1100	.
24.5200	.
25.0500	.
30.2600	.
32.5600	.
32.6600	0.2295

From subgroup analysis results we can conclude that the effectiveness of nivolumab had no statistically significant differences regarding age and patients sex. However it was a trend toward improved PFS regarding patient's sex , women's median PFS was 16.1 months while in male was 7.2 months (p=0.066).

4.4.3 Response Rates

The clinical activity of to nivolumab treatment was evaluated in the analysis. The overall response rate is the percentage of patients who responded to the treatment, either with the size minimization of the lesions (partial response PR), or with the lesions complete disappearance (complete response CR). Of the 141 patients included in the analysis, 8 (5.67%) have died early, 4 (2.84) couldn't be evaluated because of the missing data, and 3 (2.13) weren't evaluated because of treatment discontinuation. (Table 4.14)

Table 4.14

Best response according to investigator's assessments for all patients included in the analysis.

Best Response	N	%
CR	2	1.42
PR	33	23.40
SD	45	31.91
PD	42	29.79
Missing Data	4	2.84
No - Early tumor death	8	5.67
No - Treatment discontinuation prior evaluation	3	2.13
Non evaluable yet	4	2.84
Total	141	100.00

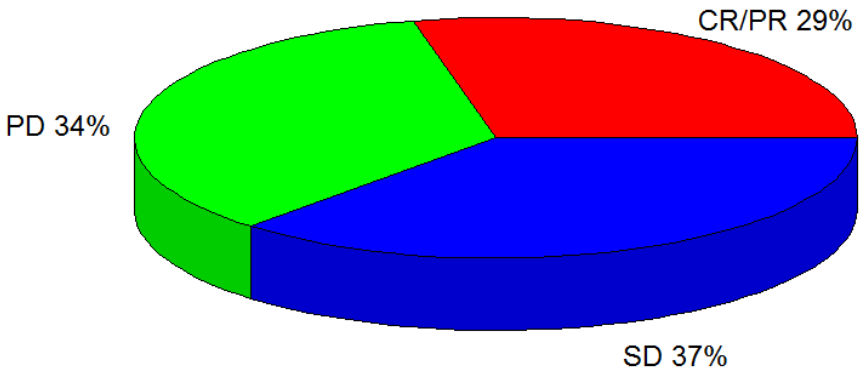
Table 4.15

Best response according to investigator's assessments among response evaluable patients.

Best Response	N	%
CR/PR	35	28.68
PD	42	34.43
SD	45	36.89
Total	122	100.00

Figure 4.7

Pie chart of best response in the response evaluable patients.



Among 122 patients evaluated, 2 had complete response and 33 had partial response (CR/PR, 28.68%), 45 (36.89%) had stable disease (SD) and 42(34.43%) had progression disease (PD).The response rates according to investigator's assessments are summarized in Table 4.15 and Figure 4.7.

4.4.4 Safety

In addition to the effectiveness it is essential to evaluate the toxicity profile of nivolumab as evidenced in everyday clinical practice. The most common toxicities seen with checkpoint inhibitor treatment are immune-mediated as a result of increased T cell activation and subsequent injury not only to cancer cells but also to healthy cells leading to disorders such as dermatitis, colitis, pneumonitis, hepatitis, thyroiditis, encephalitis and others. Common toxicities seen with cytotoxic chemotherapy such as diarrhea, fatigue, hematologic toxicity can also be seen with checkpoint inhibitors but to a lesser degree and severity. Grade 3-4 toxicities reported in the current study are listed in Table 4.16.

Table 4.16

Treatment related adverse events (grade3-4)

Incidence of grate 3-4 toxicities	**N**	**%**
Vomiting (grate 3)	1	0,71
Neutropenia (grate 3)	1	0,71
Thrombocytopenia (grade 4)	1	0,71
Anemia (grade 3)	2	1.42
Diarrhea (grade 3)	2	1.42
Fatigue (grade 3)	3	2.13
Dyspnea (grade 3)	1	0.71
Pneumonitis (grade 3)	1	0.71
Hypothyroidism (grade 3)	1	0.71
Colitis (grade 3)	1	0.71
Pleural effusion (grade 3)	1	0.71
Diabetes (Hyperglycemia) (grade 3)	1	0.71
Infection clinic (grade 3)	2	1.42

During this study treatment related adverse events were extracted from patient's medical files. Only in 18 (12.78%) patients were reported grade 3-4 adverse events which has an impact in the continuation of nivolumab therapy. The only grade 4 toxicity was

thrombocytopenia reported in one patient. In two patients grade 3 anemia was documented, while another two suffered from grade 3 fatigue.

4.5 Treatment cost

The current study is carried out from the perspective of decision makers managing health care expenditures, only direct health care cost, in insurance prices, are included expressed in euros (€). In order to estimate the cost of second line treatment with nivolumab in NSCLC patients, data were collected from the patients' medical files, Greek national sources, the database of Greek general hospitals and the available bibliography. An expert panel of oncologists was also available to provide advice about managing of treatment's adverse events. The costs estimated include cost of nivolumab drug, administration cost, cost of imaging and laboratory tests, and cost of treatment's adverse events. The unit prices used in this analysis refer to hospital enviroment and relate to 2017 year. The costs were calculated per patient, initially for a treatment cycle, which was set at a month, and at the end the total cost of the treatment per person.

Cost of nivolumab drug: The dose of nivolumab was calculated based on patients weight in kg. In this study data regarding patient's weight were available only for 66 of the 141 patients and the median weight was estimated at 76kg (min-max: 48-116). We used this weigh for the calculation of the median dose. Nivolumab was given intravenously in a dose of 3mg/kg every two weeks, consequently the total dose per administration was calculated at 3mg/kg*76kg= 228mg. Since April 2018 the European commission approved replacing nivolumab weight-based dosing with a fixed 240mg dose every two weeks. The unit costs of the drug are based on the Galinos website, according to the 20/12/2017 drug repricing of the Ministry of Health as corrected in 09/02/2018. The costs of nivolumab are listed in Table 4.17 below.

Table 4.17

Costs of nivolumab drug

Drug name	Dose per administration	Cost per vial (€)	Total vials per dose	Frequency of administration	Cost per dose	Total cost per month
NIVOLUMAB	3mg/kg*76kg=228mg	1 vial 4mL (10mg/mL)=434,74	6*4mL	Q2W	2.608.44	5.216,88

Since during study the dose was calculated based on the weight the smallest and more economic vials were used for the treatment. After administration of the drug there may be left some that has to be used within 24h, since the medicine in the vial is paid in full, leftovers are unnecessary expenses. This approach explains the use of the smallest and more economic vials.

Cost of administration: nivolumab is administrated intravenously and it does not require a hospitalization for its administration, but it takes place in the short stay units of the hospital. The cost of the short stay includes all the costs associated with the administration of the treatment, the prophylactic treatment if necessary, and the consumption of all medical supplies. The cost comes from eoppy site and it is in accordance to the Presidential Decree 187/05, Official Government Gazette issue no 231/A/05. (Table 4.18)

Table 4.18

Cost of nivolumab administration

Drug name	Type of administration	Cost of hospital short stay unit	Total cost per month
NIVOLUMAB	i.v.	40,00 €	Q2W: 80,00 €

Costs of laboratory tests: as part of the treatment it is necessary to conduct the necessary laboratory at determined time intervals, in order to evaluate the patient's state of health. A full blood test and specific biochemistry examinations that include evaluation of creatinine, urea, ALT/AST, ALP, Tbil, Na^+, K^+, Ca^{2+} are required each time before administration of nivolumab treatment. In addition hormonological laboratory examinations are necessary in order to evaluate thyroid function. This hormonological tests are conducted every 4 weeks and include measurement of FT_3, FT_4, TSH levels. The costs are summarized in Table 4.19.

Table 4.19

Costs of laboratory examinations

Type of laboratory test	Description of examinations	Cost (€)	Total cost of the tests	Frequency per month	Total cost per month	Source: Presidential Decree
Complete Blood count	hemoglobin-number of red blood cells-hematocrit-erythrocyte markers-number and type of white blood cells-number of platelets and platelet's markers	2,88	2,88	2	5,76	157/18, 157/24
Biochemistry tests	Creatinine	4,05	44,69	2	89,38	DB3E/92/19-01-2017
	Glucose	2,26				157/46
	Urea	2,26				157/45
	LDH(lactate dehydrogenase)	4,75				81/26
	ALT (alanine transaminase)	4,49				DB3E/92/19-01-2017
	AST(aspartate transaminase)	4,49				DB3E/92/19-01-2017

	ALP(alkaline phosphatase)	5,02				157/225
	Tbil (Bilirubin)	2,88				DB3E/92/19-01-2017
	Na^+	5,22				DB3E/92/19-01-2017
	K^+	5,22				DB3E/92/19-01-2017
	Ca^{2+}	4,05				157/50
Hormonological laboratory examinations	FT_3 (triiodothyronine)	12,00	44,92	1	44,92	OGG(FEK)3100/2011
	FT_4 (thyroxine)	20,54				OPAD 12414/26-04-2011
	TSH (thyroid stimulating hormone)	12,38				157/190
Total Costs per month					**140,06**	

Cost of disease re-staging: before initiation treatment with nivolumab and at specific time intervals during treatment, it is necessary to re-evaluate the stage of the disease. Restaging is carried out through a number of imaging tests which are conducted once every 2-3 months at the physician's discretion. In the current study imaging tests were conducted at baseline and thereafter every 2months. In Table 4.20 are listed the specific imaging tests and their costs. Contrast agents are also included to the costs since they are administrated before imaging tests.

Table 4.20

Cost of disease re-staging

Imaging test/contrast agent	Frequency per month	Unit cost (€)	Total cost per month (€)	Source: presidential decree
Thorax CT scan	0.5	71,11	35,5	81/19, 49976/05-12-2012
Abdomen CT scan	0.5	71,11	35,5	81/20, 49976/05-12-2012
Pelvis CT scan	0.5	71,11	35,5	81/22, 49976/05-12-2012
Brain CT scan	0.5	71,11	35,5	81/17, 49976/05-12-2012
Bone scan (γ camera)	0.5	60,00	30,00	G32/3672/96, OGG (FEK)3100/2011
Iodinated Oral contrast agent	0.5	4,75	2,38	81/25
Iodinated i.v. contrast agent	0.5	9,51	4,76	81/26
Total cost per month			**179,14**	

Cost of adverse events: in the current study only grade 3-4 adverse events were included as extracted from medical files of the patients. Grade 3 and 4 adverse events have a high impact in the cost of the treatment, most of them require a long hospitalization in addition to pharmaceutical treatment and the specific examinations that are necessary in order to be managed. In the current study only 18 from the 141 patients expressed a grade 3-4 adverse event. The percentage of patients in each adverse event was very low,

specifically for most of grade 3-4 adverse events was less than 1%. The toxicity results are summarized in table 4.16. Due to the very low incidence of grade 3-4 adverse events their costs were not included in the analysis. The results regarding the safety of nivolumab in the current study confirm that nivolumab safety is favorable compared to the standard of care treatment chemotherapy (docetraxel) both for the incidence of all adverse events but also for the appearance of all grades.

The cost of palliative care was not included in the analysis as there are no available data regarding these costs. Both individual costs and total costs of the treatment per month for each patient are summarized in Table 4.21.

Table 4.21

Total cost of nivolumab second-line treatment

Individual costs/ per month	€
Cost of the drug	5.216,88
Administration cost	80,00
Cost of laboratory tests	140,06
Re-staging cost	179,14
Adverse events cost	-
Total treatment cost per month	**5.616,08**
Total cost per year	**67.392,96**

The costs included in this analysis are related only to the second line treatment with nivolumab and include the cost of the drug, the administration cost and the cost of all laboratory and imaging tests necessary to evaluate the course of the illness. None of the costs related to progression disease were includes as patients who had a disease progression received third line treatment.

Chapter 5

Conclusions

The current study represents the first clinical evaluation of nivolumab effectiveness in a real-world health environment in Greece. It is a study conducted in collaboration with the Hellenic Cooperative Oncology Group (HeCOG), and describes the experience of using nivolumab, as second line treatment for advanced NSCLC, in real clinical practice of 14 healthcare centers all over Greece. Patients with all histological types (squamous38,7%, non-squamous 54,8%), who have received previously at least on platinum based chemotherapy were included. A higher proportion of male patients and current/former smokers was observed.

The most important finding of the study was the efficacy of nivolumab that appears to be higher in an unselected non-clinical trial population, as compared to what has been published in the two randomised phase III clinical trials, Checkmate 017 and Checkmate 057. In this clinical trials histological types of NSCLC were analyzed separately. Checkmate 017 evaluated the efficacy of nivolumab compared to docetaxel in patients with squamous NSCLC. Median OS was 9.2 months for nivolumab and 6 months for docetaxel (HR: 0.62, 95%CI 0.47-0.80). The median PFS was 3.5 months with nivolumab while for docetaxel was 2.8 months (HR: 0.62, 95%CI, 0.47-0.81). In the Checkmate 057 trial non-squamous patients were included. The median OS was 12.2 months for nivolumab and 9.5 months for docetaxel (HR 0.75, 95% CI 0.63-0.91), while the median PFS was higher for docetaxel treatment, 4.2 months for docetaxel versus 2.3 months for nivolumab.

In our study the median OS was 19.7 month (95%CI, 12.7-NE), the median PFS was 7.4 months (95% CI, 5.9-11.6). Among the 122 patients that were evaluated according to the investigators assessments 25% had CR/PR, 34% had PD and 37% had SD. In the subgroup analysis conducted no statistical significant differences were observed regarding age and gender.

In the current study only grade 3-4 toxicities were included since they may lead to therapy interruption or even hospitalization. Based on patient's medical files a prevalence of 12.78% of immune related toxicities was reported. This safety profile favors nivolumab and is similar or even lower to those reported in the clinical trials.

In real world data, Areses Manrique et al presented an analysis of pretreated patients with advanced NSCLC who received nivolumab as second-line treatment. In this analysis both histological types were included, among the 163 evaluable patients 1.6% had CR, 23.9% had PD, 25.5% had SD and 35.6% had PD. The median PFS was 4.83months (95% CI, 3.69-5.97) while the median OS was 12.85 months (95% CI, 9.07-16.62). In the subgroup analysis no statistical significance was demonstrated for tobacco status, gender, age and histology, although a statistical significance was revealed in OS regarding two other parameters, CNS metastases and PS status. Median OS for patients with CNS metastases was 5.09 months (95%CI, 0.3-9.8) while for patients without CNS metastases was 1,48 months (95%CI, 11.5-17.3) P=0.0001. As for performance status, patients with PS2 had median OS 3.4 months (95%CI, 2.3-4.4), while for patients with PS1 the median OS was 11.79 months (95%CI, 8.5-15), and for patients with PS0 was not reached, P=0.006. In this analysis they concluded that nivolumad has a meaningful survival benefit and a favorable safety profile as second-line treatment for patients with advanced non-small cell lung cancer.

Another RWD analysis was conducted by Caple-Armero et al, in order to evaluate the efficacy of nivolumab compared to docetaxel in clinical practice. In this analysis patients with both histological types were included. The results showed a superior PFS in patients treated with nivolumab compared to those treated with docetaxel. Median PFS was 84 days (95% CI,39-300) for nivolumab and 61 days for docetaxel (95% CI, 48-76). The median OS for docetaxel was 129 days (95% CI, 106-300) but for nivolumab OS was not reached. In this study nivolumab showed a superiority in terms of efficacy compared to standard of care docetaxel, but the limitations of these study were the small sample size and the limed follow up period, thus the comparison with the results of our study is not possible.

Another purpose of our study was to examine costs related to nivolumab treatment as second line therapy for advanced NSCLC, since it is considered as a very expensive drug although its notable incremental effectiveness.

In the current analysis only the direct costs in insurance prices were included. The total cost of managing the disease per month was estimated at 5.616,08€ per patient and the annual cost was 67.392,96€ per patient. The costs of grade 3-4 toxicities that can lead to patient's hospitalization and increase the treatment cost, were not included since none of the toxicities had an incidence ≥5. It is important to mention that in a study conducted

by Ortega-Joaquin et al in Spain the cost of managing grade 3-4 toxicities with an incidence ≥5 deriving from nivolumab treatment as second line was lower than the cost of standard of care docetaxel (122,17€ nivolumab vs 691,61€ docetaxel / per patient).

We did not collect data regarding quality of life since the study is retrospective and a large percentage of patients were not alive at the time of the analysis. We also didn't consider the impact PD-L1 testing would have in the cost of nivolumab treatment, since the guidelines do not specify any threshold for patient's PD-L1 positivity.

Prescribing ICI agents based in patients PD-L1 positivity or the discovery of new biomarkers for the selection of patients that would benefit from this expensive drugs may increase treatment effectiveness and reduce the total cost to the health care system.

Recently the recommended dose of nivolumab has changed to a 240mg flat dose, this may reduce the unnecessary expenses caused by the quantity of the drug left in the vial. Previously nivolumab was given intravenously based on patient's weight consequently there were leftover in the vials used. It was estimated that in 2016 in USA the pharmaceutical companies would earn approximately 1.8 billion dollars from the left over cancer drugs.

The economic burden on the health care system and society deriving from lung cancer is very high, not only because of the high prevalence of lung cancer but because of the high cost per cycle and the long duration of the treatment. The restricted health care resources make necessary the government negotiation with the pharmaceutical companies on the price of the new drugs as well as the pharmacoeconomic analysis in order to consider whether it worth to add a new expensive drug that prolongs patient's life for a few more months.

In our analysis the conduction of a cost effectiveness analysis was not possible because of the missing real-world data of docetaxel in Greece. The most important limitations of our study were the retrospective nature, the unselected population and the missing restaging data of approximately 10% of patients before initiation of nivolumab therapy. Nevertheless nivolumab demonstrated its meaningful survival benefit and the favorable toxicity profile in clinical practice.

There are other drugs used for the treatment of NSCLC as monotherapy and in combination. With the aim to maximize value for money spent in health care system and

benefit for patients and society, a prospective analysis designed to collect appropriate health outcomes as well as health economic and quality of life data is under consideration.

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