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Treatment Pathways and Associated Costs of Advanced or Metastatic ALK+ Non-Small Cell Lung Cancer in Greece

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Abstract

Objective: To investigate the resource use and costs associated with the management of metastatic anaplastic lymphoma kinase inhibitors (ALK+) NSCLC in Greece.

Methods: The resource use was based on the outcomes of a Delphi panel with seven oncologists and unit costs derived from officially published sources.

Results: The average per patient cost in the current treatment pathway (chemotherapy, crizotinib, chemotherapy, palliative care) was estimated at €67,391. The average per patient cost in future scenario 1 (crizotinib, ceritinib, chemotherapy, palliative care) was estimated at €104,571 (treatment duration 26 months) while in future scenario 2 (chemotherapy, ceritinib, chemotherapy, palliative care) was estimated at €134,215 (treatment duration 29.3 months).

Conclusion: Ceritinib as second line treatment leads to an increase in total costs reflecting the longer survival.

Keywords: Non-Small Cell Lung Cancer; Lung Cancer; Greece; Drug Cost

Abbreviations: ALK: Anaplastic Lymphoma Kinase; BSA: Body Surface Area; CR: Complete Response; EMA: European Medicines Agency; FISH: Fluorescence in Situ Hybridization (test); IHC: Immunohistochemistry (test); NSCLC: Non-Small Cell Lung Cancer; OS: Overall Survival; PFS: Progression-Free Survival; PR: Partial Response; SD: Stable Disease; SIF: Social Insurance Fund; SPC: Summary of Product Characteristics

Introduction

Lung cancer is the most commonly occurring cancer in the world today, with an estimated 1.35 million incident cases, accounting for 12.4% of all cancers, and 1.18 million deaths [1,2]. In Greece, lung cancer was the leading cancer among men in 2012 and the third most common type of cancer in women, in terms of both incidence and mortality [3]. In addition, Greece has the highest incidence of lung cancer among people less than 45 years of age among the European Union countries [4].

Non-Small Cell Lung Cancer (NSCLC) accounts for 85-90% of all lung cancer cases [5,6] and is associated with high direct and indirect costs, which reflect the high incidence of the disease, the length of treatment, the high prices of drugs involved, and the therapy-induced toxic effects [7]. NSCLC patients have low survival rates and general poor prognosis [6,8].

Molecularly targeted therapies, such as anaplastic lymphoma kinase (ALK) inhibitors, have provided promising outcomes, especially in advanced disease [9-11]. It is estimated that ALK+ NSCLC patients constitute about 4%–5% of all NSCLC patients [12]. The accurate and timely identification of ALK positive (ALK+) patients has important therapeutic implications and is an important requirement for optimal management of NSCLC patients [5]. There are currently two treatments available for ALK+ patients. Crizotinib (Xalkori®) was approved by the European Medicines Agency (EMA) in October 2012 for the treatment of adults with previously treated ALK+ advanced NSCLC. Ceritinib (Zykadia®) is a new ALK inhibitor, which received marketing authorization by the EMA in May 2015 and is indicated for the treatment of ALK+ locally advanced or metastatic NSCLC previously treated with crizotinib.

The aim of this study investigate the resource use and costs associated with the management of the disease in Greece and to compare the current and future treatment pathways in advanced and metastatic ALK+ NSCLC.

Methods

The study was based on a two-step approach: first, identification of the local treatment pathways and associated resource use and second, estimation of total costs for each pathway, by assigning unit costs to

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resource use items. Only direct medical costs were considered in the analysis and the cost base year was 2014.

Resource use associated with pharmaceutical care, hospitalization, patient follow up and monitoring, lab and imaging tests, accompanying treatment, management of adverse events (AEs) and brain metastases was investigated for all four lines of treatment, including palliative care and maintenance treatment. Accompanying treatment referred to treatment received in order to manage disease symptoms and improve patient's quality of life. This mainly consisted of pharmaceutical treatment (corticosteroids, analgesics, erythropoietin, bisphosphonates, antibiotics, antithrombotics) and at-home-treatment with oxygen therapy and nebulizers. Palliative care was explored as fourth line of treatment and consisted of pharmaceutical treatment similar to accompanying treatment, blood transfusions, analgesic radiotherapy, and patient follow-up and monitoring, lab and imaging tests. Only grade 3/4 AEs were included in the analysis, as these require hospitalization and are associated with increased resource use.

Local treatment pathway and resource use

In order to map the local treatment algorithm and associated resource use, an expert panel was convened with seven leading oncologists, consisting of distinguished academics and directors of oncology units in public and private hospitals representing all major geographic regions of Greece.

A detailed questionnaire was developed, which was based on a review of the international literature on treatment pattern studies and clinical guidelines associated with the management of the disease. The questionnaire was developed with input from and was validated by a clinical expert. Data collection was performed during an expert panel and the data elicitation method was the Delphi technique, which aims at consensus-building [13]. This method uses multiple iterations and a feedback process that allows and encourages the selected Delphi participants to reassess their initial judgments about the information provided in previous iterations in light of other participants' input [13]. Data collected via the expert panel were analyzed in Excel®, and results were validated by all experts participating in the panel.

Duration of treatment was based on the expert panel for chemotherapeutic regimens, and the literature for ceritinib and crizotinib [10,11,14].

Unit costs

Unit costs were retrieved from publically available sources. The perspective adopted was that of the Social Insurance Funds (SIFs), thus all cost estimates reflect the economic burden of the disease to SIFs.

Unit costs for pharmaceutical, hospital, and medical treatment

Pharmaceutical costs consist of drug acquisition and administration costs. For drug acquisition costs, two sets of prices were used depending on the reimbursement status of the drugs. For all chemotherapeutic drugs and drugs under Law 3816/2010 (high cost drugs), hospital prices were calculated based on the Drug Price Bulletin 31.12.15 [15]; ceritinib price was obtained from the Price Bulletin 11.12.2015 [16] (the latest available Price Bulletin for new branded drugs); for outpatient drugs, prices reimbursed by SIFs were used, based on the Positive Reimbursement List [17,18].

Dosages and frequency of administration, as well as the administration setting and associated resource use, were based on drugs' summary of product characteristics (SPCs), and were adapted to the local clinical practice, based on input from the expert panel. Drug cost calculations were also based on three key assumptions, validated by the experts: a mean patient body surface area (BSA) of 1.7 m^2, mean patient weight of 70 kg and drug wastage.

The unit costs for hospitalization, day hospitalization and patient visits to the physician's surgery are listed in Table 1. Based on the expert panel, the two specialties that manage the disease in Greece are oncologists and pulmonologists. Unit costs for at-home treatments were based on Governmental Gazette 3054-18.11.2012.

Unit costs for lab and imaging tests

Unit costs of lab and imaging tests are presented in Table 2. These costs were subsequently weighted with the percentage of patients undergoing each test and the frequency per cycle (in the chemotherapy regimens) or per month (in the ALK-inhibitor regimens). In the cost-by-line-of-treatment calculations, the cost of ALK test, as well as the costs of imaging tests which are incurred only once at the beginning of treatment, were incorporated in first line treatment.

With respect to the detection of ALK rearrangements in patients with NSCLC, there are currently two technologies available in Greece: The fluorescence in situ hybridization (FISH) test and the immunohistochemistry (IHC) test. The most widely used test is the FISH test (80% of the patients), thus the weighted average cost of the test is €128.

	Unit cost (€)	Source
Day hospitalization	80	Governmental Gazette 2150, 27/9/2011
Cost of one day of hospitalization	70	Governmental Gazette 2456, 3/11/2011
Visits at physician's surgery	20	Presidential Decree 127/2005
Cost of brain surgery	2,336	DRGs-Governmental Gazette 946, 27.3.2012

Table 1: Unit costs for hospitalization and patient follow up.

Test	Unit costs* (€)
ALK-test	
FISH	150
IHC	40
Lab tests	
Urine test	1.76
FBC	2.88
K, Na, Ca, LDH, SGOT, SGPT, ALP, gGT, Bilirubin (Total, Direct)	24.8
Uric acid, albumin	7.22
Ur, Cr, Glu	7.8
Imaging tests	
Chest X-ray	2.9
Chest CT	45.0
Upper abdomen CT	45.0
Lower abdomen CT	45.0
Brain CT	45.0
Upper abdomen MRI	165.0
Brain MRI	165.0
Skeletal scintigraphy (bone scan)	25.8
PET scan	700

*Source: Prices reimbursed by Social Insurance Funds [18]

Table 2: Unit costs of lab and imaging tests per treatment cycle.

Based on input from the expert panel, the resource use associated with lab and imaging tests does not differentiate across treatment regimens, thus same costs have been used for all chemotherapeutic regimens. The average cost per cycle has also been used as a proxy for the monthly cost of lab and imaging tests in the treatment regimen with crizotinib and ceritinib.

Management of AEs costs

The calculation of the costs associated with the AEs considered all cost components: drugs, hospitalization, lab and imaging tests, medical follow up. For all categories, we sought the additional resource use associated strictly with the management of AEs, i.e., on top of the resource use associated with the regular disease management. The cost per AE, as well as the cost per average patient, was calculated based on the probability of developing each AE throughout the chemotherapeutic course of treatment. Management of grade 1/2 AEs was considered as part of the accompanying treatment; Grade 3/4 AEs were collected and analyzed as a standalone section, as these are usually associated with increased resource use (e.g. hospitalization).

For the chemotherapeutic regimens, the following AEs were considered: Neutropenia, febrile neutropenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, infections, and renal dysfunction. For ceritinib and crizotinib, no grade 3/4 AEs were taken into consideration, as, based on the expert panel, these are relatively rare and are mainly treated with dose modification, thus, entail no significant costs.

Unit costs for the management of brain metastases

The management of brain metastases is an additional cost component of ALK+ metastatic NSCLC, which can be quite significant, as it is associated with radiotherapy and brain surgery costs. Based on input from the expert panel, of the patients who will develop brain metastases, 70% will undergo radiotherapy, and 10% will receive both radiotherapy and surgery. Two alternative procedures (γ-knife and cyber-knife) with significant cost implications are followed in 20% of the cases (Table 3).

The additional average cost per patient treated for brain metastases was estimated as a stand-alone cost component and was subsequently added in the different treatment regimens' costs based on the percentage of patients developing brain metastases and the response to treatment. In particular, based on the expert panel, approx. 40% of all advanced or metastatic NSCLC patients will develop brain metastases, thus the average cost was weighted accordingly.

In the ceritinib-related scenarios, this cost was adjusted to reflect ceritinib's increased response rates, which lead to a reduction in patients with brain metastases. More specifically, for crizotinib pre-treated patients who are on ceritinib treatment, the disease control rate defined as Complete Response + Partial Response + Stable Disease (CR + PR + SD) was estimated at 61% [19]. This translates into a 39% of the patients with brain metastases who will eventually require treatment. The respective figure for crizotinib-naïve patients is 37% (CR + PR + SD = 63%) [19].

Results

Treatment pathways

The treatment pathway that is currently followed for the management of ALK+ advanced or metastatic NSCLC patients in Greece is first line chemotherapy, followed by crizotinib in second line. In the future, when ceritinib enters the local market, the treatment landscape is expected to change significantly. Two potential future treatment scenarios with ceritinib in the second line treatment were investigated (Table 4).

The most widely used first line chemotherapeutic regimen in Greece for the management of ALK+ NSCLC is carboplatin or cisplatin plus pemetrexed (73% of the patients undergoing first line chemotherapy). The average number of cycles for first line chemotherapy is six. The most widely used third line chemotherapeutic regimen in Greece for the management of ALK+ NSCLC is docetaxel, accounting for 83% of third line chemotherapy (Figure 1).

Maintenance treatment can follow either first line chemotherapy or third line chemotherapy. Following first line chemotherapy, 36% of patients will not receive maintenance treatment, while of those receiving the most widely used regimen is pemetrexed (Figure 2). Following third line chemotherapy, only 30% of the patients will undergo maintenance treatment.

Total per patient cost

The average per patient cost in the current treatment pathway was estimated at €67,391. Maintenance cost incorporates the fact that 36% of the patients do not undergo maintenance treatment. It is also weighted to reflect the different regimens used in maintenance treatment. Cost of brain metastases has been adjusted to reflect the average cost per patient, given that only 40% will develop brain metastases during the first and second lines of treatment (Table 5).

This treatment cost was estimated for a total duration of treatment of approx. 20 months, based on the number of cycles for chemotherapy treatment and the median progression-free survival (PFS) data for crizotinib [11]. Thus, it is important to note that this

	Unit cost (€)
Radiotherapy	400
γ-knife	6,500
cyber-knife	7,000
Radiotherapy & surgery	2,736

*Source: Prices reimbursed by Social Insurance Funds [18]

Table 3: Cost of treating brain metastases.

Line of treatment	Current treatment pathway	Future treatment pathways	
		Scenario 1	Scenario 2
1st line	Chemotherapy	Crizotinib	Chemotherapy
2nd line	Crizotinib	Ceritinib	Ceritinib
3rd line	Chemotherapy	Chemotherapy	Chemotherapy
4th line	Palliative care	Palliative care	Palliative care

Table 4: Treatment pathways.

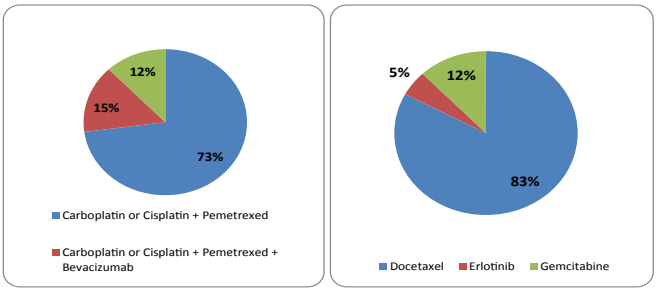

Figure 1: Treatment regimens in 1st and 3rd line chemotherapy.

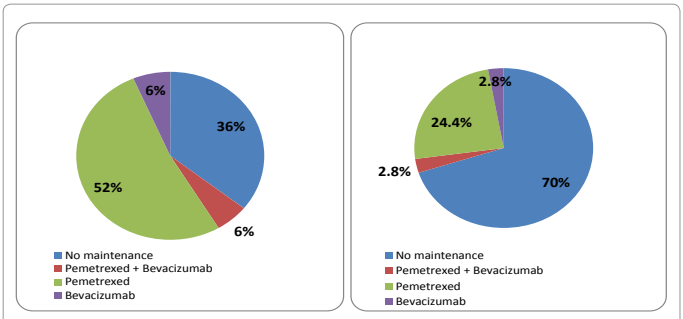

Figure 2: Patients on maintenance treatment following 1st and 3rd line chemotherapy.

Line of treatment	Regimen	Cost (€)	PFS (months)*
1st line	Chemotherapy	16,220.55	4.1
Maintenance treatment		5,922.04	2.4
2nd line	Crizotinib	35,927.47	7.7
3rd line	Chemotherapy	4,554.26	2.8
4th line	Palliative care	3,992.93	3.0
Extra cost of brain metastases		773.44	-
Total	-	**67,390.69**	**20.0**

*For chemotherapy, duration of treatment has been used as a proxy for PFS; for crizotinib, PFS data are taken from the literature; for palliative care, PFS reflects "Mean time to death" based on the expert panel

Table 5: Per patient cost in the current treatment pathway.

cost reflects the cost of the treatment pathway followed by a patient undergoing all four lines of treatment and all treatment cycles in each line, i.e., refers to the typical patient that receives all treatments and survives for at least 20 months.

In future scenario 1, the cost of treatment was estimated at €104,571 (Table 6). This cost was based on a total duration of treatment of approx. 26 months, which in turn is based on PFS data for crizotinib and ceritinib, given that these two agents are administered until disease progression. Median PFS for first line crizotinib (10.9 months) was taken from the study by Solomon and colleagues [14], while PFS for second line ceritinib patients who had previously received crizotinib (6.9 months) was taken from the study by Shaw and colleagues [10].

In future scenario 2, the cost of treatment was estimated at €134,216 (Table 7). The total duration of treatment was approx. 29.3 months, which was based on a median PFS for ALK-inhibitor naïve patients receiving ceritinib of 17 months. The latter represents a conservative downward adjustment of the ASCEND-1 trial results announced at ESMO 2014 (18.4 months) [20], since these referred to a population which included a considerable number of treatment-naïve patients.

Discussion

The present study investigated and provided an overall view of the resources and associated costs required to treat a typical patient with ALK+ advanced or metastatic NSCLC in Greece. To the best of our knowledge, this is the first study to analytically map all costs associated with the management of the disease in the local health care setting.

Per patient costs incurred by SIFs were estimated to range between €67,391 in the current treatment pathway and €134,216 in future scenario 2. It is important to note that these costs did not take into consideration obligatory discounts (6.5%), rebates or claw backs associated with drugs, thus, they reflect the maximum possible pharmaceutical cost. In addition, the costs of chemotherapy were estimated under the assumption that the average patient undergoes through all cycles in each line of treatment. Patient drop-out rates due to mortality, non-response or treatment intolerance were not taken into consideration, confirming that the estimated costs reflect the maximum possible costs of managing the disease.

Furthermore, cost estimates for the ALK-inhibitors are based on trial data for median PFS, which were used as a proxy for treatment duration. Therefore, costs reflect to a large extent the cost of increased life expectancy, rather than the cost of the treatment. This is of great importance, given the high unmet need in terms of survival in the specific disease area. Lung cancer has one of the lowest survival outcomes compared with other cancers because most patients are diagnosed at an advanced stage with extremely poor prognoses [5]. Patients with metastatic disease have much lower survival rates than those presenting at an early stage. The 5-year survival rate for patients with advanced NSCLC is 1–10%. Overall, median survival for advanced NSCLC is 6–12 months [21,22], while ALK rearrangements tend to be present in NSCLC patients with no smoking habit, younger age and tumor stage IV [5]. Therefore, new treatments that could increase survival from 20 months (current treatment pathway) to 29.3 months (future scenario 2) should be considered by health care decision makers as indispensable.

Treatment options for ALK+ patients are currently limited: Crizotinib, a first-generation ALK inhibitor, and ceritinib, a second-generation ALK inhibitor, are the only two drugs with an indication to treat this specific sub-population. Clinical data have shown that most patients treated with crizotinib progressed within 9 months [6]. Ceritinib, was shown to be highly active in patients with advanced *ALK*+ NSCLC, regardless of the presence of resistance mutations in *ALK* [10]. In addition, recent observational studies have shown that median overall survival (OS) in ALK+ NSCLC patients treated with one or more ALK inhibitors ranged from 40 to 49.4 months [23,24]. This outstanding long OS probably applies to patients who receive more than two ALK inhibitors during the course of their disease and is subject to sampling bias; however, it could be indicative of the magnitude of the additional clinical benefit of treatment with ALK inhibitors. Therefore, based on clinical and real world evidence, it is anticipated that insertion

Line of treatment	Regimen	Cost (€)	PFS (months)*
1st line	Crizotinib	51,047.41	10.9
2nd line	Ceritinib	41,902.04	6.9
3rd line	Chemotherapy	4,554.26	2.8
Maintenance treatment		2,772.20	2.4
4th line	Palliative care	3,992.93	3.0
Extra cost of brain metastases		301.64	-
Total	-	**104,570.49**	**26.0**

*For chemotherapy, duration of treatment has been used as a proxy for PFS; for ceritinib and crizotinib, PFS data are taken from the literature; for palliative care, PFS reflects "Mean time to death" based on the expert panel

Table 6: Per patient cost in the future treatment pathway under scenario 1.

Line of treatment	Regimen	Cost (€)	PFS (months)*
1st line	Chemotherapy	16,220.55	4.1
Maintenance treatment		5,922.04	2.4
2nd line	Ceritinib	103,239.58	17.0
3rd line	Chemotherapy	4,554.26	2.8
4th line	Palliative care	3,992.93	3.0
Extra cost of brain metastases		286.17	
Total		**134,215.53**	**29.3**

*For chemotherapy, duration of treatment has been used as a proxy for PFS; for ceritinib, PFS data are taken from the literature; for palliative care, PFS reflects "Mean time to death" based on the expert panel

Table 7: Per patient cost in the future treatment pathway under scenario 2.

of ceritinib in the local market will significantly improve clinical outcomes of disease management.

This study aimed at estimating and comparing the costs associated with the different treatment pathways. Results showed that inclusion of ceritinib will lead to an increase in per patient costs. However, the eligible patient population for ceritinib is small: Patients with ALK+ NSCLC constitute approx. 3.9% of all lung cancer patients [12]. Therefore, the anticipated budget impact for SIFs is expected to be significant but manageable.

The current study includes only direct medical costs, which reflect partly the total economic burden of NSCLC. Indirect costs constitute another significant component of the societal burden of the disease, which in the US have been estimated at US $118.4 billion. The study by Yabroff et al. showed that the cost of lost productivity due to lung cancer was the main indirect cost driver and was estimated to be US $8,282 per patient in the initial year and US $14,870 in the last year of a patient's illness.

Using PFS data as a proxy for treatment duration, estimating the cost on the basis that a patient undergoes through all lines of treatment and not incorporating indirect costs in the analysis constitute limitations of the present study. In addition, this study does not take into consideration patients' quality of life and how this is affected by the new treatments. However, despite limitations, this study can serve as a basis for future economic evaluation studies in the management of ALK+ NSCLC in Greece. Further research is required to determine the cost-effectiveness of ceritinib in the local market. The outcomes of this work can help understand the local management and associated costs of NSCLC and provide input for health care decision making in Greece, especially in the current period, where Health Technology Appraisal (HTA) and negotiation committee are being developed.

Conclusions

Advanced or metastatic ALK+ NSCLC is an expensive to treat disease with a poor prognosis and high unmet need. Inclusion in the market of ceritinib as second line treatment, leads to an increase in total costs reflecting the longer treatment duration, associated with longer survival rates. Future research is required to determine the cost-effectiveness of ceritinib in Greece.

Transparency

Declaration of funding

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Availability of data and materials statement

All data and supporting documents will be available upon request.

Ethics approval and consent to participate

No patient level data were used in the study. The expert panel only provided data on resource use for the management of the average patient treated for NSCLC in Greece; thus, no Ethics Committee consent was requested, as the conduct of the expert panel is not subject to any approval according to the Greek legislation.

Competing Interests

All authors declare that they have no competing interests.

Authors' Contributions

MG and HK designed the study, conducted the analysis and developed the paper.

IB, VG, PK, GK, PM, ES and KS consisted the expert panel, provided input during the analysis and reviewed the final manuscript.

DK and AM coordinated the study, provided input and reviewed the analysis, results and manuscript.

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