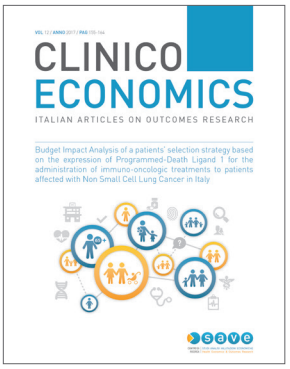
VOL 12 / ANNO 2017 / PAG 155-164

CLINICO ECONOMICS

ITALIAN ARTICLES ON OUTCOMES RESEARCH

Budget Impact Analysis of a patients' selection strategy based on the expression of Programmed-Death Ligand 1 for the administration of immuno-oncologic treatments to patients affected with Non Small Cell Lung Cancer in Italy

save
CENTRO DI RICERCA | STUDI ANALISI VALUTAZIONI ECONOMICHE
Health Economics & Outcomes Research



ClinicoEconomics è una rivista peer-reviewed di farmacoeconomia e di outcomes research sulle conseguenze economiche e di politica sanitaria di dispositivi medici e strategie farmacologiche.
Obiettivo della Rivista è quello di pubblicare in modo rapido e conciso lavori sull'impatto clinico ed economico in tutte le principali aree terapeutiche, valutazioni in tema di sicurezza, di efficacia nella pratica clinica, di costo-efficacia, di costo-utilità e di costo-beneficio nell'uso sostenibile dei farmaci e dei dispositivi medici.

www.clinicoeconomics.eu

Progetto grafico e impaginazione
newattitude comunicazione

save
CENTRO DI RICERCA | STUDI ANALISI VALUTAZIONI ECONOMICHE
Health Economics & Outcomes Research

www.savestudi.it

Volume n. 12 / 2017 alla Pubblicazione peer-reviewed open access
ClinicoEconomics Italian Articles on Outcomes Research (Print ISSN 2282-8087; Online ISSN 2282-8095) è una rivista annuale pubblicata da S.A.V.E. Studi Analisi Valutazioni Economiche S.r.l. via G. Previati 74, 20149 Milano, Italia - www.clinicoeconomics.info
Registrazione del Tribunale di Milano n. 368 del 14/07/2011

Budget Impact Analysis of a patients' selection strategy based on the expression of Programmed-Death Ligand 1 for the administration of immuno-oncologic treatments to patients affected with Non Small Cell Lung Cancer in Italy

U. Restelli[1,2], S. Artale[3], V. Pacelli[1,2], D. Croce[1,2]

[1] Centre for Research on Health Economics, Social and Health Care Management (CREMS) – LIUC – Cattaneo University, Castellanza (VA), Italy

[2] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3] Presidio Ospedaliero di Gallarate ASST - Valle Olona, Gallarate, Italy

Corresponding author:

Umberto Restelli, Corso Matteotti, 22 – 21053 Castellanza (VA), Italy – Tel. +39 0331 572 346 – E-mail: urestelli@gmail.com

ABSTRACT

BACKGROUND

Immuno-oncology represents a new strategy for the treatment of different types of tumors. Among cancer types and locations, of particular relevance is non-small cell lung cancer (NSCLC) due to its incidence and mortality rate. Within randomized clinical trials, the expression of programmed death ligand 1 (PD-L1) above a certain threshold has been identified as associated with a higher outcome for immuno-oncologic treatment compared with chemotherapy. The aim of the analysis presented is to assess the financial consequences of a patients' selection strategy, through the assessment of PD-L1 expression, for the treatment of patients affected by advanced previously treated NSCLC in Italy.

ABSTRACT

BACKGROUND

L'immuno-oncologia rappresenta una nuova strategia per il trattamento di diverse tipologie di tumore. Tra le tipologie e sedi tumorali, il tumore al polmone non a piccole cellule (NSCLC) risulta di particolare rilevanza in considerazione della sua incidenza e tasso di mortalità. In trial clinici randomizzati, l'espressione del "programmed death ligand 1" (PD-L1) oltre una certa soglia è stato identificato come associato ad un migliore outcome per i trattamenti immuno-oncologici, in confronto alla chemioterapia. L'obiettivo della presente analisi è la valutazione delle conseguenze finanziarie di una strategia di selezione dei pazienti attraverso la valutazione dell'espressione di PD-L1, per il trattamento dei pazienti affetti da NSCLC avanzato precedentemente trattati, in Italia.

METHODS

A budget impact model was implemented, assuming the Italian National Health Service perspective, considering a treatment algorithm related to the second and third lines of treatment. Two scenarios were compared: considering the assessment of PD-L1 expression or not. The costs considered (year 2017) referred to immune-oncologic treatments, adverse events' management and PD-L1 test.

RESULTS

The cost to treat the 9,216 patients considered in the analysis in the base case scenario is almost 137 million €, with a per capita cost of 14,898 €. The treatment selection strategy considered, based on PD-L1 expression, would lead to a cost to treat the whole population of almost 112 million € (per capita cost of 12,119 €), with a differential cost of – 26 million € compared with the base case scenario, with a 18.7% cost reduction.

CONCLUSIONS

A patients' selection strategy through the assessment of PD-L1 expression for the treatment of patients affected by advanced previously treated NSCLC in Italy would be sustainable, leading to a reduction of costs compared with a scenario in which such strategy is not considered.

KEYWORDS

non-small cell lung cancer, immuno-oncology, programmed death ligand 1, PD-L1, budget impact analysis

METODI

È stato strutturato un modello di valutazione di impatto sul budget, assumendo il punto di vista del Servizio Sanitario Nazionale, considerando un algoritmo di trattamento relativo alla seconda e terza linea. I due scenari comparativi sono stati caratterizzati dall'effettuazione del test di espressione del PD-L1 e dalla non effettuazione del test. I costi considerati (anno 2017) sono stati quelli relativi ai trattamenti oncologici, alla gestione degli eventi avversi e al test di espressione del PD-L1.

RISULTATI

Il costo per trattare i 9.216 pazienti considerati nell'analisi nello scenario di base è circa 137 milioni di euro, con un costo pro capite pari a 14.898 €. La strategia di selezione dei pazienti basata sull'espressione del PD-L1, porterebbe ad un costo per trattare i pazienti considerati pari a circa 112 milioni di euro (costo pro capite pari a 12.119 €), con un costo differenziale di – 26 milioni di euro in comparazione allo scenario di base (- 18,7% di riduzione dei costi).

CONCLUSIONI

Una strategia di selezione dei pazienti attraverso la valutazione dell'espressione di PD-L1 per il trattamento dei pazienti affetti da NSCLC avanzato precedentemente trattati in Italia sarebbe sostenibile, portando ad una riduzione del costo di gestione dei pazienti rispetto ad uno scenario che non considera tale strategia.

KEYWORDS

non-small cell lung cancer, immuno-oncology, programmed death ligand 1, PD-L1, budget impact analysis

BACKGROUND

Immuno-oncology represents a new strategy for the treatment of different types of tumors. Its therapeutic approach aims at potentiating "the patient's immune-response to tumor cells",[1] making the immune system "capable of identifying and eliminating cells expressing tumor associated antigens".[1]

Cancer immunotherapy dates back to 1863,[2] however, only in recent years it was considered as a primary approach for cancer treatment.[1] It represents a new paradigm, following the development of chemotherapies and of molecular targeted agents.[3] In the last decade, different monoclonal antibodies received a marketing authorization by the European Medicines Agency for the following therapeutic areas: breast cancer (i.e. bevacizumab, trastuzumab), cervical cancer (i.e. bevacizumab), chronic lymphocytic leukaemia (i.e. rituximab), classical Hodgkin lymphoma (i.e. nivolumab, pembrolizumab), colorectal cancer (i.e. bevacizumab, cetuximab, panitumumab), epithelial ovarian (i.e. bevacizumab), fallopian tube and primary peritoneal cancer (i.e. bevacizumab), gastric cancer (i.e. bevacizumab, trastuzumab), melanoma (i.e. ipilimumab, nivolumab, pembrolizumab), non-Hodgkin's lymphoma (i.e. rituximab), non-small cell lung cancer (i.e. bevacizumab, nivolumab, pembrolizumab), renal cell cancer (i.e. bevacizumab, nivolumab), soft tissue sarcoma (i.e. olaratumab), squamous cell cancer of the head and neck (i.e. cetuximab, nivolumab).

Among the aforementioned cancer types and locations, of particular relevance is non-small cell lung cancer (NSCLC) due to its incidence and mortality rate. Considering Italian data, in 2016 lung cancer is estimated to be the second most frequent cancer in males (15%, excluding skin carcinoma), the third most frequent in females (6%, excluding skin carcinoma) and the third most frequent overall (11%, excluding skin carcinoma).[4]

In terms of deaths due to cancer, those estimated to be attributed to lung cancer in 2016 are the most frequent in males (26%, excluding skin carcinoma), the third most frequent in females (11%, excluding skin carcinoma) and the most frequent overall (19%, excluding skin carcinoma).[4] Among lung cancer, NSCLC is estimated to account for 85%-90%.[5]

The monoclonal antibodies that received a marketing authorization by the European Medicines Agency for the treatment of NSCLC are bevacizumab ("advanced NSCLC in patients whose cancer cells are not mainly of the squamous type, where it is given with platinum-based chemotherapy" and "advanced NSCLC in patients whose cancer cells have a certain change (activating mutations) in the gene for a protein called EGFR, where it is given in combination with erlotinib"),[6] nivolumab ("NSCLC that has spread locally or to other parts of the body in patients who have previously been treated with other cancer medicines - chemotherapy")[7] and pembrolizumab ("NSCLC ... used specifically when the tumour produces a protein known as PD-L1 and has spread or cannot be surgically removed").[8]

Concerning the last two aforementioned monoclonal antibodies, nivolumab showed in a phase 3 randomized controlled trial improved overall survival, response rate, and progression free survival compared with docetaxel in patients affected with advanced previously treated squamous NSCLC;[9] and showed in a phase 3 randomized study longer overall survival compared with docetaxel in patients affected with advanced previously treated non-squamous NSCLC.[10] In a phase 2/3 randomized study, Pembrolizumab showed a longer "overall survival and a favourable benefit-to-risk profile in patients with previously treated, programmed death ligand 1 (PD-L1)-positive, advanced NSCLC" compared with Docetaxel;[11] and showed in a phase 3 randomized trial a "significantly longer progression-free and overall survival and with fewer adverse events", in patients affected with advanced untreated NSCLC with PD-L1 expression ≥ 50%, compared with platinum-based chemotherapy.[12]

The expression of PD-L1 above a certain threshold (50% in first line treatment and 1% in second line treatment) in the last two randomized trials reported above[11,12] is

associated with a higher outcome for immuno-oncologic treatment compared with chemotherapy.

Considering the difference in terms of costs between a treatment cycle with a monoclonal antibody and with chemotherapy, the possibility to identify which patients affected by NSCLC would not benefit in a significant way from the administration of an immuno-oncologic treatment, could increase the sustainability of National Health Services, without affecting the effectiveness of the services provided to patients. Therefore, the aim of the analysis presented is to assess the financial consequences of a patients' selection strategy, through the assessment of PD-L1 expression, for the treatment of patients affected by advanced previously treated NSCLC in Italy.

METHODS

A budget impact model was implemented to assess the sustainability of the patients' selection strategy for the eligibility of immuno-oncologic treatment of patients affected with NSCLC.

PATIENTS' POPULATION AND TIME HORIZON

The target population considered is composed of patients affected with already treated advanced squamous and non-squamous NSCLC without mutations. Furthermore, to select patients eligible to receive an immuno-oncologic treatment, we considered only those with <70 years and a performance status (PS) of 0-1, and with > 70 years and PS of 0-2 or < 70 years and PS of 2. Patients with a PS higher than 2 were excluded from the analysis, since international guidelines for the treatment of NSCLC consider them eligible to a best supportive care.[5]

We considered all patients eligible to a second line treatment and followed this population until the third line treatment. Therefore the time horizon considered is variable, based on the likely progression free survival of each oncologic treatment.

PERSPECTIVE AND INTERVENTION MIX

The perspective assumed in the analysis is that of the Italian National Health Service. Two different scenarios were implemented: a base case scenario in which we did not consider a patients' selection strategy based on the assessment of PD-L1 expression (base case scenario), and a comparative scenario in which we considered such treatment strategy starting from the second line of treatment (scenario 1).

To assign patients to second line treatments and, after disease progression, to third line treatments, a therapeutic algorithm was implemented, based on international guidelines,[5] on a previous algorithm implemented by Prof. Paz Ares, and adapted to the Italian context on the base of expert opinions related to real clinical practice. The expert opinion was collected through interviews to the director of the oncology department of a public hospital located in Lombardy Region.

The treatment algorithm was implemented considering different cancer types (squamous and non-squamous) and patients' characteristics (patients with <70 years and a PS of 0-1; and with > 70 years and PS of 0-2 or < 70 years and PS of 2), since NSCLC treatments guidelines recommend different therapies on the base of the aforementioned criteria. The choice of second line treatments depends on the first therapy administered to patients, therefore the algorithm was modelled starting from first line. The algorithm implemented per each tumor type and patients characteristics is reported as the Supplementary Material.

In the base case scenario, the choice of treatments was conducted in the hypothesis that the level of PD-L1 expression is unknown. In scenario 1, patients were further divided in two groups: those for whom the PD-L1 expression is ≥ 1% and those for whom the PD-L1 expression is < 1%. For the first group (PD-L1 ≥ 1%) the possibility to receive pembrolizumab as second or third line therapy was considered, while for the second group (PD-L1 < 1%), the possibility to receive immuno-oncologic treatments was excluded.

The first line therapies considered were cisplatin + gemcitabine, cisplatin + pemetrexed, carboplatin + gemcitabine, gemcitabine, vinorelbine, docetaxel, car-

boplatin. The second and third lines therapies considered were nivolumab, pembrolizumab, docetaxel, nintedanib + docetaxel, gemcitabine, vinorelbine.

COSTS AND CLINICAL INPUTS

The costs considered in the analysis were direct medical costs referred to year 2017, related to the therapy administered, to the management of each therapy's adverse events, and to PD-L1 test (only for scenario 1). Data collected from publications and referred to years different than 2017 were inflated at their 2017 value considering the annual inflation at average consumer prices in Italy as reported by the International Monetary Fund.[13]

The cost of each drug was based on the ex-factory price reported by the Italian Medicines Agency, considering a standard number of cycles, as reported in Table 1. To calculate the cost per each dose, we considered, on the base of the results of the Keynote-010 Study, a body mass index of 1.81 and a weight of 70.97 Kg.

The adverse events considered for each treatment were nausea, anemia, diarrhea, fatigue, febrile neutropenia, neutropenia, vomiting. The incidence of each adverse event was derived from phase II and III clinical trials, [10,11,14-16] as reported in Table 2. The cost to manage each adverse event was derived from literature.[17,18]

If AEs' incidence data were not available in literature, the minimum and maximum incidence values observed for treatments of the same class were considered (i.e. incidence of AEs of nivolumab for pembrolizumab; and incidence of vinorelbine for gemcitabine).

The last direct medical cost considered in the analysis was that of PD-L1 test. In Italy such test is not yet reimbursed by the National Health Service. Therefore we considered an hypothetical cost equal to 68 €, as referred to the code 91.40.8 of the Lombardy Region tariffs nomenclature.

ANALYTIC FRAMEWORK AND SENSITIVITY ANALYSIS

Patients within the model are assigned to a second line treatment for NSCLC following the algorithm described above. Of these patients, only 20% will receive a third

TABLE 1
Treatments' duration and cost considered in the analysis

Treatment	Treatment duration	Cost	Notes
Docetaxel	4.0 months	2,365 €	6 administrations of 75 mg multiplied by the patient's BMI. For each administration, a further cost of 9.7 € was considered (Italian nomenclature tariff, code 99.25). The number of administrations is based on the Progression Free Survival as in Herbst et al., 2016
Gemcitabine	12 weeks	1,183 €	9 administrations of 1,000 mg multiplied by the patient's BMI. For each administration, a further cost of 9.7 € was considered (Italian nomenclature tariff, code 99.25). The treatment duration is based on expert opinion.
Nintedanib + docetaxel	3.4 months	11,035 €	For docetaxel: 5 administrations of 75 mg multiplied by the patient's BMI. For each administration, a further cost of 9.7 € was considered (Italian nomenclature tariff, code 99.25). For Nintedanib: 200 mg twice daily for 5 cycles of 20 days. The number of administrations is based on the Progression Free Survival as in Reck et al., 2014
Nivolumab	3.5 months	18,624 €	8 administrations of 3 mg multiplied by patient's weight. For each administration, a further cost of 37.1 € was considered (10% of the value of DRG 410). The number of administrations is based on the Progression Free Survival as in Rahmer et al., 2015
Pembrolizumab	3.5 months	22,118 €	6 administrations of 2 mg multiplied by patient's weight. For each administration, a further cost of 37.1 € was considered (10% of the value of DRG 410). The number of administrations is based on the Progression Free Survival as in Herbst et al., 2016
Vinorelbine	9 weeks	1,732 €	3 oral administration of 60 mg multiplied by the patient's BMI, followed by 6 oral administration of 80 mg multiplied by the patient's BMI. The treatment duration is based on expert opinion.

Treatments' cost is based on the ex-factory prices reported by the "Gazzetta Ufficiale della Repubblica Italiana". Therefore, prices might be higher than in real world due to confidential agreements between producers and the Italian Medicines Agency. Nivolumab cost hypothesis: -30% of the ex-factory price.

TABLE 2
Cost and incidence of adverse events

Adverse event	Cost (€)	Incidence					
		Docetaxel	Gemcitabine	Nintedanib + docetaxel	Nivolumab	Pembrolizumab	Vinorelbine
Anaemia	4,207.8 [a]	1.62% [c]	5.19% (as Vinorelbine)	1.07% [f]	0.00% [d]	0.88% [c]	5.19% [g]
Diarrhea	450.9 [a]	2.27% [c]	0.60% [e]	6.44% [f]	0.00% [d]	0.59% [c]	2.60% [g]
Fatigue	0.0 [a]	3.56% [c]	7.79% (as Vinorelbine)	5.52% [f]	0.76% [d]	1.18% [c]	7.79% [g]
Febrile neutropenia	5,747.7* [b]	10.08% [d]	1.60% (as Vinorelbine)	7.06% [f]	0.00% [d]	0.00% (as Nivolumab)	2.60% [g]
Nausea	108.7 [a]	0.32% [c]	5.65%^ [e]	0.77% [f]	0.00% [d]	0.29% [c]	10.39% [g]
Neutropenia	176.2 [a]	12.30% [c]	26.00% [e]	12.12% [f]	0.00% [d]	0.29% [c]	45.45% [g]
Vomiting	470.3 [a]	0.78% [d]	5.65%^ [e]	0.77% [f]	0.00% [d]	0.00% (as Nivolumab)	7.79% [g]

a [17]; b [18]; c [11]; d [9]; e [14]; f [15]; g [16]
* Due to lack of data referred to NSCLC, we considered the cost of febrile neutropenia calculated by Brown and colleagues for the Italian context related to the management of locally advanced head and neck cancer.
^ Only an aggregated incidence of nausea/vomiting is provided in the publication, therefore half of the incidence was attributed to nausea and half to vomiting.

line therapy, on the base of experts' opinion, regardless of the therapy administered as second line treatment.

For each line of treatment the costs related to treatment, adverse management and PD-L1 test are considered. Patients assigned to different treatment might have different treatment duration, based on the data reported in Table 1. The percentage of patients with a PD-L1 expression ≥ 1% is considered to be 66%, as emerged in a randomized phase 2/3 trial.[11]

The impact on the budget of the Italian National Health Service is represented by the differential costs between scenario 1 and the base case scenario.

A univariate sensitivity analysis was conducted to identify the variables which influence the most the final result. The variables modified in the sensitivity analysis are: ±10% immuno-oncology drugs cost, ±20% adverse events' cost, +100% PD-L1 cost, ±5% PD-L1 test results ≥1%, patients from second line to third line of treatment equal to 30% and 10%.

The choice of the variables to be considered within the sensitivity analysis was based on the costs of immuno-oncologic treatments and on the costs and results of the PD-L1 test, which are the focus of the analysis. Furthermore, the percentage of patients accessing to the third line of treatment allowed to test how different patients conditions might impact on the final results; and the cost of adverse events' management, allowed to test how possible differences in terms of events management within different contexts might influence the budget impact.

RESULTS

The target population considered in the analysis was calculated starting from the 40,000 lung cancer's diagnoses estimated in Italy in 2016.[4] The number of patients affected with NSCLC is estimated to be 32,000 (80% of total lung cancers) and those with EGFR and ALK mutation was estimated to be 20%, based on expert opinion. Therefore, the number of patients affected with NSCLC with no mutation was estimated to be 25,600. 10% of these patients were estimated to have a PS > 2, and were excluded from the analysis, leading to a population eligible to first line treatment of 23,040 patients. The percentage of patients affected with squamous NSCLC was estimated to be 20% and

that of patients affected with non-squamous NSCLC 80%. 50.0% of patients affected with squamous NSCLC were considered with <70 years and a PS of 0-1, and 40.0% with > 70 years and PS of 0-2 or < 70 years and PS of 2. Among patients affected with non-squamous NSCLC, 63.0% were considered with <70 years and a PS of 0-1, and 27.0% with > 70 years and PS of 0-2 or < 70 years and PS of 2.

The number of patients eligible to second line treatment are 40% of the 23,040 patients eligible to first line treatment, being 9,216; of which 1,843 affected with squamous NSCLC and 7,373 affected with non-squamous NSCLC.

The total cost of second and third lines of treatment are reported in Table 3.

The cost to treat the 9,216 patients considered in the analysis in the base case scenario is almost 137 million €, with a per capita cost of 14,898 €. The treatment selection strategy considered, based on PD-L1 expression, would lead to a cost to treat the whole population of almost 112 million €, with a differential cost of – 26 million € compared with the base case scenario, with a 18.7% cost reduction. The per capita cost in Scenario 1 is equal to 12,119 €.

The sensitivity analysis conducted showed a minimum cost variation of - 19.7 million € (decreasing of 10% the immuno-oncologic drugs cost) and a maximum cost variation of - 32.1 million € (increasing of 10% the immuno-oncologic drugs cost). The results of the sensitivity analysis are reported in Table 4.

TABLE 3
Total cost for each scenario and differential cost

Scenario	Total cost	Per capita cost
Base case	137,299,835 €	14,898 €
Scenario 1	111,687,443 €	12,119 €
Difference	- 25,612,392 €	- 2,779 €
% difference	- 18.65%	

DISCUSSION

A patients' selection strategy through the assessment of PD-L1 expression for the treatment of patients affected by advanced previously treated NSCLC in Italy would be sustainable, leading to a reduction of costs compared with a scenario in which such strategy is not considered.

To our knowledge the analysis presented is the first assessment of the sustainability of the use of PD-L1 expression test for the selection of patients eligible to immuno-oncologic treatments for NSCLC in Italy.

The sensitivity analysis conducted showed how the variable that influence the most the variance of the final result is the cost of immuno-oncologic drugs, followed by the percentage of patients with a PD-L1 test result ≥ 1%. The direct medical costs related to adverse events' management, the cost of the PD-L1 test and the percentage of patients treated in third line have a limited impact on the variability of the results.

At an international level, Aguair and colleagues (2017),[19]

TABLE 4
Sensitivity analysis results

Scenario	Cost difference (Scenario 1 – Base case scenario)	% difference
Immuno-oncology drugs cost +10%	- 32.10 million €	- 19.8%
Immuno-oncology drugs cost -10%	- 19.74 million €	- 17.2%
Adverse events' cost + 20%	- 25.29 million €	- 18.3%
Adverse events' cost - 20%	- 25.93 million €	- 19.0%
PD-L1 test's cost +100%	- 24.99 million €	- 18.2%
PD-L1 test results ≥1% +5%	- 22.00 million €	- 16.0%
PD-L1 test results ≥1% -5%	- 29.23 million €	- 21.3%
Patients from second line to third line of treatment equal to 30%	- 26.26 million €	- 18.4%
Patients from second line to third line of treatment equal to 10%	- 24.96 million €	- 18.9%

assessed "the cost effectiveness and economic impact of second-line treatment with nivolumab, pembrolizumab and atezolimumab with and without the use of PD-L1 testing for patients selection" in the United States. The results of the analysis showed an improved result in terms of incremental cost-effectiveness ratio compared with docetaxel, leading to an increase of the efficiency of resources allocation due to the patients' selection strategy. Also in terms of sustainability, the selection of patients on the base of the PD-L1 expression lead to a positive result in terms of cost containment.

The analysis performed is to be considered relevant for decision makers, providing timely information on a debated topic, as that of the sustainability of the use of immuno-oncologic treatments. In consideration of the costs of such therapies, compared with standard chemotherapy, to be able to identify a target population that might maximize the therapeutic benefits of the use of immuno-oncologic treatments would lead to an increase in the efficiency of resources allocation. It is necessary to consider the need for the National Health Service to provide the most effective available treatment option to oncologic patients, preserving the sustainability of resources allocation. This is of particular relevance considering the 500 million € fund for oncologic treatments allocated by the Italian National Health Service.

The aforementioned patient's selection strategy, along with currently used managed entry agreements, both financial-based, as cost sharing, capping or payback; and performance-based risk sharing, as payment by result, success fee and risk sharing; would allow a more efficient allocation of economic resources.

The main limits of the analysis performed is the lack of real-world data referred to the therapies considered in the analysis (i.e. the progression free survival and overall survival are based on Randomized Controlled Trials) and to the costs considered, being ex-factory costs, that might be overestimated than the real costs of therapies.

A further limit is related to the treatment algorithm that, being based on the real clinical practice of the oncologic department considered, might not be generalized to each oncologic department in Italy. However, since the clinical practice of the oncologic department is based on the European Society for Medical Oncology's Clinical Practice Guidelines for diagnosis, treatment and follow-up for patients affected with NSCLC,[5] the authors consider the algorithm as representative of the Italian scenario.

ACKNOWLEDGEMENT

The analysis was performed with an a unrestricted grant of MSD Italia.

DISCLOSURE

UR declares no conflict of interests; SA declares fees from Astrazeneca, IPSEN, Labor Medical; VP declares no conflict of interests; DC declares honoraria for advisory board participations by MSD.

REFERENCES

1. Dempke WCM, Fenchel K, Uciechowski P, Dale SP. *Second- and third-generation drugs for immuno-oncology treatment-The more the better?* Eur J Cancer. 2017 Mar;74:55-72.
2. Lesterhuis WJ, Haanen JB, Punt CJ. *Cancer immunotherapy--revisited.* Nat Rev Drug Discov. 2011 Aug 1;10(8):591-600.
3. Martin-Liberal J, Hierro C, Ochoa de Olza M, Rodon J. *Immuno-Oncology: The Third Paradigm in Early Drug Development.* Target Oncol. 2017 Apr;12(2):125-138.
4. Associazione Italiana di Oncologia Medica, Centro nazionale per la prevenzione e il controllo delle malattie del Ministero della Salute, Associazione Italiana Registri Tumori. *I numeri del cancro in Italia 2016.* Il Pensiero Scientifico Editore, Roma, 2016.
5. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, Kerr K, Popat S, Reck M, Senan S, Simo GV, Vansteenkiste J, Peters S; ESMO Guidelines Committee. *Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol. 2016 Sep;27(suppl 5):v1-v27.
6. European Medicines Agency. *EPAR summary for the public* – Avastin. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000582/WC500029260.pdf [Accessed: 12 July 2017].
7. European Medicines Agency. *EPAR summary for the public* – Opdivo. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003985/WC500189768.pdf [Accessed: 12 July 2017].
8. European Medicines Agency. *EPAR summary for the public* – Keytruda. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003820/WC500190993.pdf [Accessed: 12 July 2017].
9. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.* N Engl J Med. 2015 Jul 9;373(2):123-35.
10. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR. *Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.* N Engl J Med. 2015 Oct 22;373(17):1627-39.
11. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB. *Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.* Lancet. 2016 Apr 9;387(10027):1540-50.
12. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. *Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer.* N Engl J Med. 2016 Nov 10;375(19):1823-1833.
13. International Monetary Fund, World Economic Outlook Database, April 2017. Available at: http://www.imf.org/external/pubs/ft/weo/2017/01/weodata/weorept.aspx?sy=2005&ey=2017&scsm=1&ssd=1&sort=country&ds=%2C&br=1&pr1.x=68&pr1.y=10&c=136&s=PCPIPCH&grp=0&a= (last accessed on the 19th July 2017).
14. Gatzemeier U, Shepherd FA, Le Chevalier T, Weynants P, Cottier B, Groen HJ, Rosso R, Mattson K, Cortes-Funes H, Tonato M, Burkes RL, Gottfried M, Voi M. *Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre, extended phase II study.* Eur J Cancer. 1996 Feb;32A(2):243-8.
15. Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barrueco J, Gaschler-Markefski B, Novello S; LUME-Lung 1 Study Group. *Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial.* Lancet Oncol. 2014 Feb;15(2):143-55.
16. Jassem J, Ramlau R, Karnicka-Młodkowska H, Krawczyk K, Krzakowski M, Zatloukal P, Lemarié E, Hartmann W, Novakova L, O'Brien M, Depierr A. *A multicenter randomized phase II study of oral vs. intravenous vinorelbine in advanced non-small-cell lung cancer patients.* Ann Oncol. 2001 Oct;12(10):1375-81. Erratum in: Ann Oncol 2002 Mar;13(3):493.
17. Banz K, Bischoff H, Brunner M, Chouaid C, de Castro Carpeño J, de Marinis F, Grossi F, Vergnenègre A, Walzer S. *Comparison of treatment costs of grade 3/4 adverse events associated with erlotinib or pemetrexed maintenance therapy for patients with advanced non-small-cell lung cancer (NSCLC) in Germany, France, Italy, and Spain.* Lung Cancer. 2011 Dec;74(3):529-34.
18. Brown B, Diamantopoulos A, Bernier J, Schöffski P, Hieke K, Mantovani L, Launois R, Griebsch I, Robinson P. *An economic evaluation of cetuximab combined with radiotherapy for patients with locally advanced head and neck cancer in Belgium, France, Italy, Switzerland, and the United Kingdom.* Value Health. 2008 Sep-Oct;11(5):791-9.
19. Aguiar PN Jr, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, de Mello RA, Lopes GL Jr. *The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC.* Ann Oncol. 2017 Sep 1;28(9):2256-2263.

CENTRO DI RICERCA | STUDI ANALISI VALUTAZIONI ECONOMICHE
Health Economics & Outcomes Research

www.clinicoeconomics.eu | www.savestudi.it | www.savedigital.it