Journal of Medical Economics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijme20

Detection of genomic alterations in liquid biopsies from patients with non-small cell lung cancer using FoundationOne Liquid CDx: a cost-effectiveness analysis

Dolores Isla, Rosa Álvarez, María Arnal, Edurne Arriola, Aitor Azkarate, Eider Azkona, Rosario García-Campelo, Pilar Garrido, Ernest Nadal, Ana L. Ortega, David Carcedo, María Crespo, Jesús Lavara, Fernando Córcoles & Reyes Bernabé

To cite this article: Dolores Isla, Rosa Álvarez, María Arnal, Edurne Arriola, Aitor Azkarate, Eider Azkona, Rosario García-Campelo, Pilar Garrido, Ernest Nadal, Ana L. Ortega, David Carcedo, María Crespo, Jesús Lavara, Fernando Córcoles & Reyes Bernabé (2024) Detection of genomic alterations in liquid biopsies from patients with non-small cell lung cancer using FoundationOne Liquid CDx: a cost-effectiveness analysis, Journal of Medical Economics, 27:1, 1379-1387, DOI: 10.1080/13696998.2024.2413289

To link to this article: https://doi.org/10.1080/13696998.2024.2413289

JOURNAL OF MEDICAL ECONOMICS
2024, VOL. 27, NO. 1, 1379–1387
https://doi.org/10.1080/13696998.2024.2413289
Article 0144-RT/2413289

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Detection of genomic alterations in liquid biopsies from patients with non-small cell lung cancer using FoundationOne Liquid CDx: a cost-effectiveness analysis

Dolores Isla[a], Rosa Álvarez[b], María Arnal[c], Edurne Arriola[d], Aitor Azkarate[e], Eider Azkona[f], Rosario García-Campelo[g], Pilar Garrido[h], Ernest Nadal[i], Ana L. Ortega[j], David Carcedo[k], María Crespo[k], Jesús Lavara[l], Fernando Córcoles[l], and Reyes Bernabé[m]

[a]Hospital Clínico Universitario Lozano Blesa, IIS Aragón, Zaragoza, Spain; [b]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [c]Hospital Provincial de Castellón, Castellón, Spain; [d]Hospital del Mar-CIBERONC, Barcelona, Spain; [e]Hospital Universitario Son Espases, Palma de Mallorca, Spain; [f]Hospital Universitario de Cruces, Baracaldo, Spain; [g]Complexo Hospitalario Universitario A Coruña, La Coruña, Spain; [h]Hospital Universitario Ramón y Cajal, Madrid, Spain; [i]Institut Català d'Oncologia, L'Hospitalet De Llobregat, Spain; [j]Hospital Universitario de Jaén, Jaén, Spain; [k]Hygeia Consulting SL, Madrid, Spain; [l]Roche Farma S.A, Madrid, Spain; [m]Hospital Universitario Virgen del Rocío, Sevilla, Spain

ABSTRACT

Objective: Liquid biopsy (LB) is a non-invasive technique to detect genetic alterations by next-generation sequencing (NGS) when tissue biopsy is not available. This study aims to estimate in the Spanish setting, the cost-effectiveness of using FoundationOne Liquid CDx (F1L CDx), a novel blood-derived LB test based on NGS, versus non-molecular diagnosis (non-mDx) in patients with advanced non-small cell lung cancer (NSCLC) in whom tissue sampling is not feasible.

Methods: A joint model was developed combining a decision-tree with partitioned survival models to calculate the costs and health outcomes over a lifetime horizon, comparing F1L CDx in LB versus non-mDx. Only direct costs (expressed in € of 2023) were included and a 3% discount rate for future costs and effects was considered. Health outcomes were expressed in Life Years (LYs) and Quality-Adjusted Life Years (QALYs). Utilities and treatment efficacy were obtained from the literature. An expert panel of 11 Spanish oncologists determined the treatment allocation and validated all model inputs and assumptions. Several sensitivity analyses were performed to assess the robustness of the results.

Results: In a hypothetical cohort of 1,000 patients, LB using F1L CDx would detect 386 alterations, so those patients could be treated with targeted therapies or enrolled in clinical trials. Cost-effectiveness results showed that F1L CDx provides greater effectiveness than non-mDx (+383.95 LYs and +305.94 QALYs), with an additional cost of €2,898,308. The incremental cost-utility ratio was €9,473/QALY gained. The probabilistic sensitivity analysis confirmed the robustness of the cost-effectiveness results.

Limitations: Various limitations inherent to cost-effectiveness analyses were described.

Conclusion: LB with F1L CDx test is a cost-effective strategy in Spain for patients with advanced NSCLC without tissue sample available for molecular diagnosis, improving the personalized treatment of these patients.

ARTICLE HISTORY
Received 23 July 2024
Revised 2 October 2024
Accepted 3 October 2024

KEYWORDS
Cost-effectiveness analysis; FoundationOne Liquid CDx; liquid biopsy; molecular testing; non-small cell lung cancer

JEL CLASSIFICATION CODES
C52; C5; C; I10; I1; I

Introduction

In recent years, personalized medicine has greatly impacted the management of advanced non-small cell lung cancer (NSCLC) through the development of very effective new-targeted therapies (TTs) that improve the survival and quality of life of these patients[1,2]. It is estimated that around 50–60% of patients with advanced NSCLC are eligible for TTs[3,4]. Therefore, the accurate and timely identification of oncogenic driver alterations is crucial to guide initial treatment decision-making[5].

Single-gene testing (SgT) has traditionally been performed routinely with techniques such as immunohistochemistry, fluorescence *in situ* hybridization, polymerase chain reaction (PCR), and Sanger sequencing methods[6]. However, next-generation sequencing (NGS) has become an efficient alternative for assessing several biomarkers in a single workflow and allows the detection of more alterations compared to SgT[3,7].

Tissue biopsy (TB) is the gold standard for detecting tumor genetic alterations, but it is associated with significant limitations such as insufficient tissue, biopsy scheduling limitations, the need for repeat biopsies, and long turnaround times[6]. TB failure/inadequacy can reduce significantly systemic treatment options in patients with NSCLC and may

CONTACT David Carcedo david.carcedo@hygeiaconsulting.com Hygeia Consulting SL, Madrid, Spain

Supplemental data for this article can be accessed online at https://doi.org/10.1080/13696998.2024.2413289.

result in worse clinical outcomes, particularly in patients harboring actionable drivers[8].

Liquid biopsy (LB) is a minimally invasive approach to detecting circulating tumor-derived components from body fluids, such as blood, that has emerged increasingly as an important tool in advanced NSCLC management. LB has demonstrated its potential to serve as an alternative to TB, particularly in cases where tissue samples are insufficient or inadequate for biomarker testing, or if re-biopsy cannot be performed safely[9,10].

Therefore, there is a high proportion of patients with advanced NSCLC in whom tissue sampling for molecular diagnostics is not feasible due to insufficient tissue for molecular testing, insufficient DNA in tissue samples requiring re-biopsies or tissue depletion in SgT[8]. In this context, LB offers potential advantages over TB like faster turnaround time and a minimally invasive and easily repeatable procedure for the patient that can capture the heterogeneity of the tumor[5]. Additionally, LB can also be used to monitor disease progression, and the therapy response and resistance[11].

FoundationOne Liquid CDx (F1L CDx) is an NGS-based *in vitro* diagnostic test that uses circulating cell-free DNA isolated from a blood sample to identify alterations by liquid biopsy, targeting 324 cancer-related genes[12].

The purpose of this economic analysis is to evaluate the cost-effectiveness of using F1L CDx in LB for detecting genomic alterations in patients with advanced NSCLC in whom tissue sampling for molecular diagnosis is not feasible, from the perspective of the Spanish National Health System (NHS).

Methods

Model design, assumptions and inputs, and clinical feasibility of the results were validated by a group of 11 expert oncologists representing the main Autonomous Regions of Spain. The analysis was performed according to the economic evaluation guidelines and the CHEERS checklist is provided in Supplementary material (Table S4)[13].

Model structure and target population

A joint model combining a decision tree with partitioned survival models (PSM) was developed. It is based on a previous model, which compared NGS versus SgT in the molecular assessment of advanced NSCLC using tissue samples[7,14].

The decision tree allows the determination of molecular alterations and the cost associated with this procedure in patients with advanced NSCLC, comparing the use of F1L CDx versus no-molecular diagnosis (non-mDx). Therefore, it covers the diagnostic phase since the patient is diagnosed with advanced NSCLC and molecular genetic testing is required until these results are obtained. Based on the molecular profiling results, a specific treatment is assigned, and the long-term costs and health consequences are estimated using PSM, one for each treatment and with three health states: progression-free, progressed-disease, and death. In addition, PD-L1 overexpression is determined by immunohistochemistry in parallel to F1L CDx and non-mDx (Figure S1,Supplementary material).

The PSM use monthly cycles and the analysis was performed using a lifetime horizon, so a 3% discount rate for both costs and health outcomes (life years [LYs] and quality-adjusted life years [QALYs]) was applied following Spanish guidelines[15]. The analysis was conducted from the perspective of the Spanish National Health System, so only direct medical costs were considered (€2023).

The hypothetical cohort of patients was defined as those with a confirmed diagnosis of advanced NSCLC but in whom a valid tissue sample is not available to identify possible genomic alterations.

The analysis included level I and II biomarkers according to the ESCAT classification: *EGFR, ALK, ROS1, BRAF^{V600E}, NTRK, ERBB2* (*HER2), MET^{ex14}, RET* and *KRAS^{G12C}*. ESCAT III biomarkers were not included as their clinical trials are ongoing and there is insufficient evidence to model their efficacy[16,17].

Decision tree inputs

The testing rate (percentage in which determination is finally performed), the prevalence of biomarker alterations (positivity rate) and PD-L1 expression were the main variables of the decision tree model.

F1L CDx testing rate was assumed to be 100% for all biomarkers and the testing rate for PD-L1 expression was considered 50%, although given the variability between experts, the uncertainty of this value was assessed in the sensitivity analysis (SA).

The positivity rate of biomarker alterations provided by experts is shown in Table 1, which were in line with other Spanish publications[7,18]. Since PD-L1 expression is determined in parallel to both comparators (F1L CDx and non-mDx) and given that PD-L1 overexpression can be found simultaneously with a biomarker alteration, Table 1 differentiates whether the alteration is accompanied by PD-L1 overexpression (TPS $\geq$ 50%) or not (TPS $<$ 50%). PD-L1 overexpression (TPS $\geq$ 50%) was estimated to be present in approximately 33% of patients with NSCLC.

Table 1. Positivity rates of biomarkers.

Biomarker	Positivity rates		
	Alteration present	Alteration and PD-L1 $<$ 50%	Alteration and PD-L1 $\geq$ 50%
EGFR mutation	12.80%	10.69%	2.11%
ALK fusion	3.21%	2.68%	0.53%
ROS1 fusion	1.50%	1.25%	0.25%
BRAF^{V600E} mutation	2.27%	1.90%	0.37%
NTRK fusion	0.42%	0.35%	0.07%
ERBB2 (HER2) mutation	2.30%	1.92%	0.38%
MET^{ex14} mutation	1.89%	1.58%	0.31%
RET fusion	1.31%	1.09%	0.22%
KRAS^{G12C} mutation	13.50%	11.27%	2.23%

EGFR: epidermal growth factor receptor gene; ALK: anaplastic lymphoma receptor kinase gene; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; BRAF^{V600E}: B-Raf proto-oncogene, serine/threonine kinase V600E mutation; NTRK: Neurotrophic tyrosine receptor kinase gene; HER2: human epidermal growth factor receptor 2 gene; MET ^{ex14}: MET proto-oncogene exon 14; RET: RET proto-oncogene; KRAS ^{G12C}: KRAS proto-oncogene G12C mutation; PD-L1: programmed death-ligand 1.

A specificity and sensitivity of 99% for F1L CDx is considered in the model, based on the data reported in the literature[12]. Therefore, it was assumed that false positives obtained with F1L CDx would erroneously receive a TT that is not effective, thus incurring an additional cost of 1 month of ineffective treatment with TT before switching to the correct treatment. False negatives are treated in the same way as true negatives based on their PD-L1 expression.

After the diagnostic phase, a specific first-line treatment is initiated. Based on the prevalence of alterations in the target population (Table 1) and the specificity and sensitivity of F1L CDx, a first-line treatment is allocated depending on the molecular profile of the patient. For non-mDx, patients are defined as wild-type (WT), so first-line treatment depends on PD-L1 expression. Table 2 shows the treatment allocation agreed upon the expert panel for the following groups of treatments: TTs (reimbursed by the NHS or accessed through other ways such as clinical trials or Named Patient Programs), immunotherapies (IT), chemo-immunotherapies (C-IT), chemotherapy (CH) and no treatment (tx).

PSM inputs

Once the treatment allocation has been established, the different PSM (one for each specific treatment) are used to assess long-term costs and health consequences. Specific treatments within each group described in the previous paragraph are listed below:

- TT: lorlatinib, selpercatinib, osimertinib, alectinib, crizotinib, dabrafenib + trametinib, larotrectinib, capmatinib, tepotinib, adagrasib, trastuzumab deruxtecan.
- IT: pembrolizumab, cemiplimab.
- C-IT: pembrolizumab + pemetrexed + platinum.
- CH: cisplatin + pemetrexed.

PSM are commonly used in oncology and the transition between health states based on the efficacy of treatments is associated with the evolution (extrapolation) of progression-free survival (PFS) and overall survival (OS) curves. Therefore, different parametric distributions (exponential, weibull, log-normal, generalized gamma) were fitted separately to the published PFS and OS data from the respective clinical trials for all the treatments included in the model[19–33]. Goodness-of-fit was assessed using the Akaike and Bayesian Information Criteria (AIC and BIC) (Table S1,Supplementary material). Based on these criteria the best-fitting model for each treatment was selected and included in the model to extrapolate PFS and OS (Table S2,Supplementary material).

To assess costs and health outcomes over the lifetime horizon, costs and utilities were assigned to PSM health states (progression-free, progressed-disease and death). The

Table 2. First-line treatment allocation based on the patient molecular profile.

Biomarkers and PD-L1 expression	TTs		IT	C-IT	CH	No tx
	NHS reimbursed	CT, UM, NPP				
EGFR						
EGFR+ and PD-L1 < 50%	88.56%	8.78%	0.00%	0.00%	0.00%	2.67%
EGFR+ and PD-L1 ≥ 50%	88.56%	8.78%	0.00%	0.00%	0.00%	2.67%
ALK						
ALK+ and PD-L1 < 50%	94.67%	2.67%	0.00%	0.00%	0.00%	2.67%
ALK+ and PD-L1 ≥ 50%	94.67%	2.67%	0.00%	0.00%	0.00%	2.67%
ROS1						
ROS1+ and PD-L1 < 50%	93.56%	3.67%	0.00%	0.00%	0.00%	2.78%
ROS1+ and PD-L1 ≥ 50%	94.00%	2.88%	0.00%	0.00%	0.00%	3.13%
$BRAF^{V600E}$						
$BRAF^{V600E}$+ and PD-L1 < 50%	0.00%	8.90%	0.00%	71.10%	14.45%	5.55%
$BRAF^{V600E}$+ and PD-L1 ≥ 50%	0.00%	8.51%	64.64%	9.72%	12.15%	4.97%
NTRK						
NTRK+ and PD-L1 < 50%	0.00%	48.00%	0.00%	20.00%	30.00%	2.00%
NTRK+ and PD-L1 ≥ 50%	0,00%	48.00%	10.00%	10.00%	30.00%	2.00%
ERBB2 (HER2)						
HER2+ and PD-L1 < 50%	0.00%	14.72%	0.00%	62.58%	17.30%	5.39%
HER2+ and PD-L1 ≥ 50%	0.00%	14.72%	44.38%	17.42%	18.43%	5.06%
MET^{ex14}						
MET^{ex14}+ and PD-L1≥ <50%	0.00%	25.67%	0.00%	60.11%	8.33%	5.89%
MET^{ex14}+ and PD-L1 ≥ 50%	0.00%	24.56%	43.33	19.33%	7.22%	5.56%
RET						
RET+ and PD-L1 < 50%	64.16%	31.35%	0.00%	0.00%	0.00%	4.49%
RET+ and PD-L1 ≥ 50%	64.49%	31.35%	0.00%	0.00%	0.00%	4.16%
$KRAS^{G12C}$						
$KRAS^{G12C}$+ and PD-L1 < 50%	0.00%	18.18%	0.00%	68.91%	6.73%	6.17%
$KRAS^{G12C}$+ and PD-L1 ≥ 50%	0.00%	17.08%	59.55%	11.01%	6.18%	6.18%
WT						
WT and PD-L1 < 50%	n/a	n/a	0.00%	86.98%	7.10%	5.92%
WT and PD-L1 ≥ 50%	n/a	n/a	79.43%	9.60%	5.26%	5.71%

TTs: targeted therapys; IT: immunotherapy; C-IT: chemo-immunotherapy; CH: chemotherapy; CT: clinical trials; NPP: Named Patient Programs; UM: unlicensed medicines in Spain; NHS: National Health System; tx: treatment; EGFR: epidermal growth factor receptor gene; ALK: anaplastic lymphoma receptor kinase gene; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; $BRAF^{V600E}$: B-Raf proto-oncogene, serine/threonine kinase V600E mutation; NTRK: Neurotrophic tyrosine receptor kinase gene; HER2: human epidermal growth factor receptor 2 gene; MET^{ex14}: MET proto-oncogene exon 14; RET: RET proto-oncogene; $KRAS^{G12C}$: KRAS proto-oncogene G12C mutation; WT: wild-type; PD-L1: programmed death-ligand 1.

utilities assigned were reported by Nafees et al.[34] being 0.814 for progression-free health state and 0.783 for patients with progressed-disease.

Regarding costs, first-line treatment of NSCLC is initiated according to the distributions in Table 2, and patients are on treatment according to the extrapolation of the PFS and OS curves described above. Costs associated with intravenous administration (if applicable) and costs associated with treatment-related adverse events (Tr-AEs) were included.

Healthcare resources consumption

The model included the healthcare resource consumption associated with the routine management of patients with NSCLC according to their health state (progression-free or progressed disease), as determined by the expert panel (Table 3).

In addition to the routine resource use described in the table above, the model also includes unscheduled healthcare resources associated with disease progression. The expert panel considered that 10% of patients are hospitalized for an average of 5 days for symptoms related to disease progression.

Subsequent treatments

After progression to first-line treatment, as patients move into the post-progression state, the model considers the costs of subsequent treatments received. Table S3 of the Supplementary material shows the distribution of subsequent treatments.

Unit costs

Unit costs of F1L CDx and PD-L1 test were €3,600 and €43.50 respectively.

All treatment costs (first-line and subsequent drugs) were expressed as the ex-factory price considering the corresponding deductions according to RDL 08/2010[35] when applicable. For those drugs where the dose is not fixed, a mean body surface area of 1.77 m^2 and a mean weight of 72 kg was assumed, besides a unit cost of €296.88 for intravenous administration[36].

Tr-AEs frequencies were obtained from the literature[20,21,23–27,29–31,33,37–41] and their unit costs from the Spanish healthcare database eSalud[36].

Healthcare resources unit costs were oncologist visit (€93.77), primary care visit (€39.70), home palliative care (€65.63), CT scan (€141.71), PET/CT scan (€741.56), brain magnetic resonance imaging (€465), complete blood count (€71.32) and hospitalization (€916.05)[36]. In this regard, the model also included the costs associated with end-of-life care received by the patient prior to death (€15,417.93)[42].

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were performed in order to assess the uncertainty of the variables used in the model and determine the robustness of the results.

One-way sensitivity analysis (OWSA) was conducted for all model variables to explore the effects on the incremental cost-utility ratio (ICUR) results. Model parameters were individually modified by ±10% or ±20% from the base case value. In addition to the OWSA, a scenario analysis was carried out to assess the uncertainty surrounding some of the model assumptions:

- *Alternative parametric curves:* log-normal distribution for OS and PFS and on the other hand, exponential distributions for both OS and PFS.
- *Sensitivity and specificity values:* 90% sensitivity and 80% specificity, given the lack of real-world data.

In the probabilistic sensitivity analysis (PSA), 1,000 simulations were performed using the Monte-Carlo method, in line with the recommendations in the literature[43]. A normal distribution for population characteristics data, a gamma distribution for costs and healthcare resources frequency and a beta distribution for utility values were applied. When the standard deviation of the parameters was not available,

Table 3. Use of healthcare resources for progression-free and progressed-disease states.

Health resource	Oral treatments		IV treatments		No treatment	
	% patients	frequency	% patients	frequency	% patients	frequency
Progression-free state						
Oncologist visit	98%	9.12	99%	16.08	0%	n/a
Primary Care visit	57%	3.67	64%	5.89	0%	n/a
Home Paliative Care	2%	1.78	7%	3.89	0%	n/a
CT scan	99%	4.48	99%	4.79	0%	n/a
PET/CT scan	39%	1.06	49%	1.19	0%	n/a
Brain MRI	63%	2.81	37%	2.15	0%	n/a
Complete blood count	98%	9.12	99%	16.08	0%	n/a
Progressed-disease state						
Oncologist visit	94%	12.55	93%	15.80	21%	4.63
Primary Care visit	69%	6.75	74%	7.25	44%	6.88
Home Paliative Care	23%	5.88	33%	8.50	45%	15.38
CT scan	98%	4.42	96%	5.01	23%	2.29
PET/CT scan	28%	1.07	26%	1.07	0%	0.00
Brain MRI	56%	2.42	34%	2.29	6%	0.88
Complete blood count	94%	12.55	93%	15.80	21%	4.6

CT: computed tomography; PET: positron emission tomography; MRI: Magnetic Resonance Imaging; IV: intravenous.

ranges of ±20% were considered for the random variation of each parameter according to the distribution described above.

Results

Base case

The results obtained show that if F1L CDx is used in a hypothetical cohort of 1,000 patients with advanced NSCLC in whom tissue-based testing cannot be performed, 386 oncogenic biomarker alterations would be detected and 52 patients could be enrolled in clinical trials of targeted therapies. If non-mDx is used, no alterations would be found, and patients would be treated as WT. Therefore, these patients would not benefit from inclusion in clinical trials of targeted therapies. The greatest benefit would be seen in the case of *EGFR* and *KRAS,* due to their higher prevalence, as 126 and 133 alterations would be detected using F1L CDx (Supplementary material, Figure S2).

Using F1L CDx in a hypothetical cohort of 1,000 patients, provides more life years (3,125 LYs; 3.13 LYs per patient) and quality-adjusted life-years (2,502 QALYs; 2.50 QALYs per patient) than non-mDx and with an additional cost of €2,898,308 (€2,898.31 per patient). The ICUR obtained of €9,473/QALY gained, shows that using F1L CDx in Spain would be cost-effective as it is below the cost-effectiveness threshold of €20,000–30,000/QALY commonly accepted in Spain[44,45].

Per-patient cost-effectiveness results for the lifetime horizon are shown in Table 4.

Table 4. Per-patient results of the case base.

	F1L CDx	Non-mDx	Increment
Total costs	€184,253.17	€181,354.86	€2,898.31
Diagnostic costs	€3,621.75	€21.75	+€3,600.00
Treatment costs	€180,631.42	€181,333.11	−€701.70
First-line treatment	€157,135.18	€161,149.11	−€4,013.92
Subsequent treatment	€6,506.04	€4,066.26	+€2,439.77
Healthcare resources	€16,990.20	€16,117.74	+€872.46
QALYs	2.50	2.20	+€0.31
LYs	3.13	2.74	+€0.38
ICUR (€/per QALY gained)	€9,473.36/QALY		
ICER (€ per LY gained)		€7,548.71/LY	

LYs: life years; QALYs: quality-adjusted life years; F1L CDx: FoundationOne Liquid CDx; non-mDx: non-molecular diagnosis; ICUR: incremental cost-utility ratio; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

In all the scenarios analyzed (alternative parametric curves, lower specificity and sensitivity values) the results show the robustness of the cost-effectiveness results of F1L CDx versus non-mDx.

Results of the OWSA are represented by a tornado diagram (Figure 1), showing how individual changes in each variable modifys the base case ICUR (€9,473/QALY). Variables affecting more the ICUR, were the discount rate for costs and effects, the PD-L1 testing rate, the alterations prevalence and F1L CDx cost. In any case, the results of the base case are robust.

Finally, Figure 2 shows the PSA results represented by an incremental cost-effectiveness plot, in which the ordinate axis represents the long-term incremental cost of F1L CDx versus non-mDx and the abscissa axis the represents incremental long-term QALYs of F1L CDx versus non-mDx.

All the simulations show that F1L CDx is a cost-effective strategy versus non-mDx considering a threshold of €30,000/QALY. Moreover, lowering the threshold to €20,000/QALY, 99% of the simulations still shows that F1L CDx is cost-effective versus non-mDx.

Discussion

NSCLC is the solid tumor with the largest number of identified therapeutic targets[46]. Biomarkers determination ensures that patients receive the best available therapeutic option, minimizing unnecessary treatments and associated toxicities[47]. With this objective, according to the last consensus of the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology (SEAP), *EGFR*, $BRAF^{V600E}$, $KRAS^{G12C}$ and MET^{ex14} mutations, *ALK, ROS1, RET* and *NTRK* translocations and PD-L1 expression must be detected in patients with non-squamous NSCLC. In addition, other emerging biomarkers such as the *ERBB2 (HER2)* mutation are recommended[46].

NGS is the only technique that can simultaneously detect multiple genetic alterations in either tissue or plasma, becoming the leading molecular testing strategy for advanced NSCLC[48,49]. Patients undergo complicated procedures to obtain NSCLC tissue such as needle biopsies and endoscopic or surgical procedures[50]. Additionally, molecular characterization obtained from tissue biopsy is often not feasible because the tumor is inaccessible, TB reveals insufficient tumor content, or when the patient's condition does not allow a TB[51]. This procedure has a failure rate of around 10–30% and up to half of the patients need multiple biopsies. Therefore, LB is an efficient and less invasive method of molecular profiling in comparison with TB[50], and has demonstrated its potential as an alternative in cases where tissue sampling is not feasible or is insufficient[52].

The results of this study show that LB using F1L CDx is a cost-effective strategy for advanced NSCLC diagnosis in Spain when molecular diagnosis is not feasible due to the insufficient amount or inadequate quality of tumor samples[51]. This would represent 5–30% of the population according to experts consulted. F1L CDx would also have a clear benefit in terms of QALYs that outweigh its higher cost associated (mainly because of the higher diagnostic costs) and more patients could potentially be treated with TTs or be enrolled in specific clinical trials.

To our knowledge, our study is unique in the Spanish context in analyzing the cost-effectiveness of LB strategy in patients with advanced NSCLC in whom molecular diagnosis is not feasible versus non-mDx, contributing to the precise selection of first-line treatments. New models or platforms for outcome-based contracting have recently been developed, and technologies that can reduce the risk of a drug's efficacy failing may have added value[53].

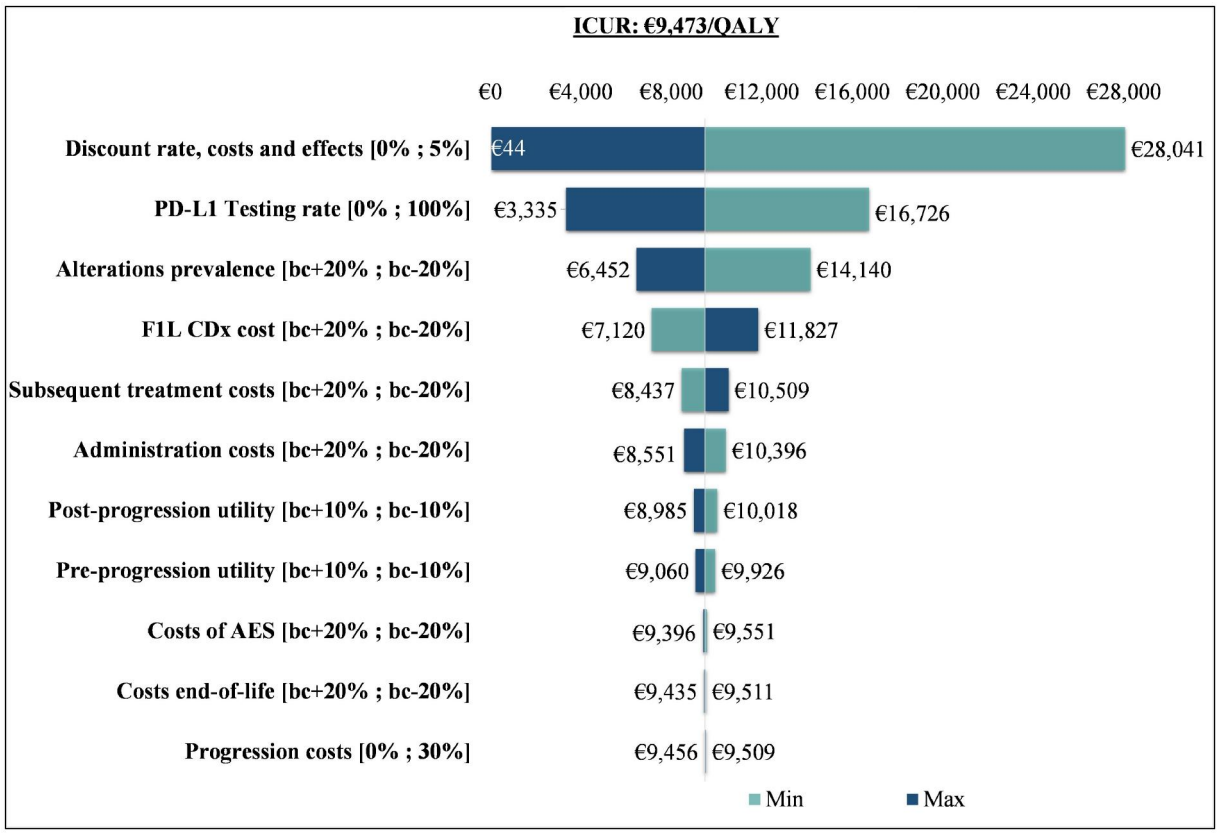

Figure 1. Tornado diagram of the sensitivity analysis.
F1L CDx: FoundationOne Liquid CDx; AES: adverse events; bc: base case; QALY: quality-adjusted life year; ICUR: incremental cost-utility ratio.

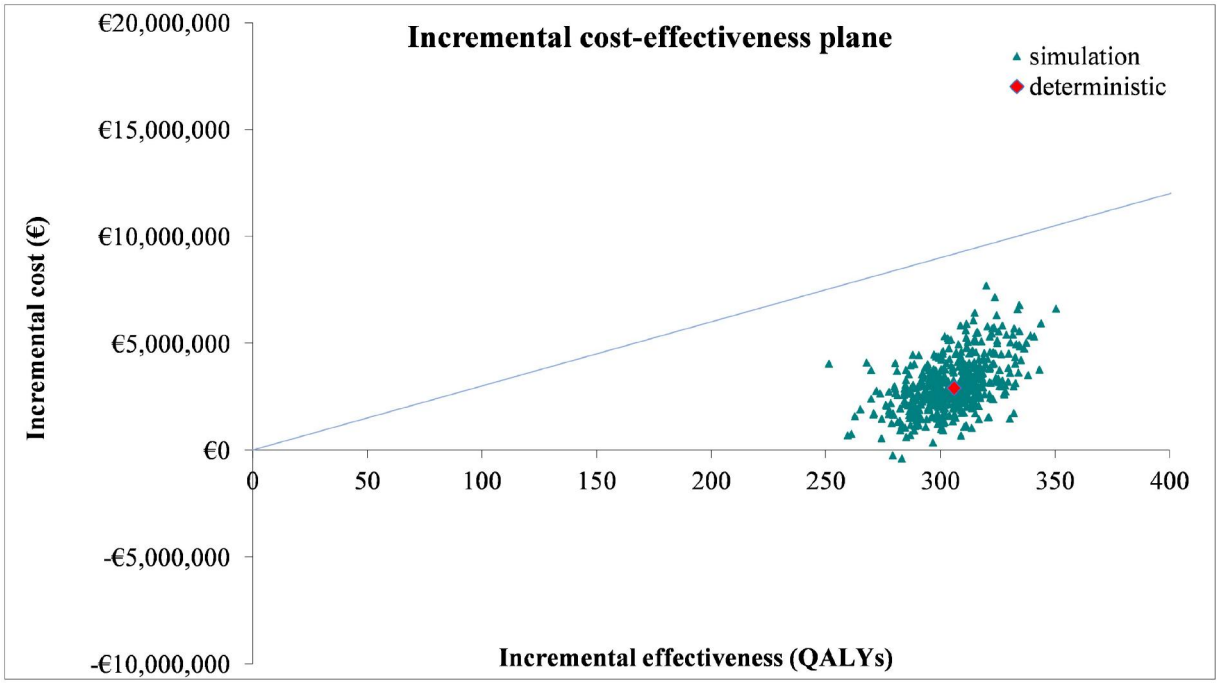

Figure 2. PSA results, represented by a cost-effectiveness plane.
QALYs: quality-adjusted life years.

Regarding sequencing in lung cancer, several studies have recently demonstrated that NGS is a cost-effective strategy for identifying biomarkers in cancer, as reported in two systematic reviews[54,55], some of which have been carried out in Spain[7,14].

In the specific case of LB, the systematic review of Fagery et al.[56] reported 24 publications in cancer management: 19 full economic evaluations, 4 budget impact analyses and one study with both an economic evaluation and

a budget impact analysis. LB was a cost-effective strategy in 15 (75%) considering different biomarkers, cancer types and stages, and economic analyses. Among these studies, eight were focused on lung cancer, which suggested that LB is potentially cost-effective in these patients[56]. Of these, a recent cost-effectiveness analysis in Germany showed that LB was cost-effective when added to TB, being slightly more expensive (€144,981 vs. €144,587) but more effective in terms of QALYs (1.20 QALYs vs. 1.19 QALYs). They concluded that the integration of LB as an add-on into the care pathway of advanced NSCLC has positive clinical effects[52]. Ezeife et al.[1] compared the addition of LB to TB versus TB alone in patients with advanced NSCLC, demonstrating that LB resulted in cost savings and led to more patients receiving appropriate TTs. Most of the cost savings resulted from the larger proportion of patients who received TTs with LB, reducing costs associated with the inappropriate use of costly chemoimmunotherapy[1]. We also highlight the health and budget impact analysis by Johnston et al.[57] as they also evaluate the introduction of F1L CDx in Canada and reported that F1L CDx would provide effective health outcomes with a minimal budget impact[57].

This model approach also has some limitations, some of them inherent to pharmacoeconomic models where complete clinical situations need to be reproduced. Some of the limitations of our study are the same as those reported in Arriola et al.[7] because both models have similarities. For example, testing rate, prevalence of alterations or treatment allocation were obtained from direct consultation with the panel of 11 Spanish experts, and therefore reflected their clinical practice from a less evidence-based perspective than using real-world data. In addition, since a lifetime horizon was considered, survival curves have to be extrapolated and this always involves some uncertainty, especially for those clinical trials with more immature data. For this purpose, several parametric models were tested and those that showed the best fit to the published data were selected. Moreover, for each treatment, its respective clinical trial was used to model survival curves, as there is no real-world data available for all treatments and there is no published network meta-analysis that brings all studies together. Another limitation relates to the inclusion of specificity and sensitivity in the analysis. We assume that there is no penalty in terms of costs and health outcomes for false negatives who are treated as true negatives, as they will receive an effective treatment such as immunotherapy or chemoimmunotherapy. Finally, indirect costs were not included in the analysis due to a lack of Spanish-specific evidence on productivity losses and caregiver burden in NSCLC. Had this been possible, it is expected that the results for F1L CDx would have been even better, as poor health is strongly linked to weak labor market success[58]. Similarly, the ESCAT III biomarkers were not included because there is no evidence of the efficacy of their target therapies, so it was not possible to model long-term health outcomes for these treatments.

Conclusions

LB using F1L CDx is a cost-effective strategy in Spain in those patients with advanced NSCLC in whom tissue biopsy samples are unavailable or insufficient for molecular testing. This method significantly improves the selection of optimal personalized treatments for these patients who may not otherwise benefit from targeted therapies or clinical trials.

Transparency

Declaration of funding

This work was supported by Roche Farma S.A. Roche Farma S.A played no role in the design of the study; collection, analysis, and interpretation of data; and in writing the manuscript.

Declaration of financial/other interests

DI: Consultant or Speaker Honoraria: Amgen, AstraZeneca, Bayer, Bristol-Myers, Boehringer, Roche, Janssen, Lilly, Merck, MSD, Pfizer, Sanofi, Takeda, Novartis; Clinical Trials: Amgen, AstraZeneca, Bayer, Boehringer, Bristol-Myers, Daiichi Sankyo, Roche, GSK, Janssen, Lilly, Merck, Mirati Therapeutics, MSD, Novartis, Pfizer, Sanofi; Research Grant: AstraZeneca, Bristol-Myers, Roche, GSK. **RA:** Advisory Role: Boehringer, Novartis, Roche; Speaker Role: Pharmamar; Coordinating PI: Boehringer, Cebiotex, Janssen Oncology, Novartis, Rain Therapeutics, Roche; Other: Conference registration from MSD Oncology. **MA:** No conflict of interests. **EA:** Consultant, Advisory or speaker Role: MSD, Bristol-Myers, Roche, Boehringer, Pfizer, Novartis, AstraZeneca, Lilly, Takeda; Co-founder: Trialing Health S.L; **AA:** Grant/Research Support: AstraZeneca, MSD; Speaker's Bureau: AstraZeneca, Roche, MSD, Bristol-Myers, Pfizer, Takeda; Consultant Role: Roche, Takeda; Coordinating PI: Amgen, Mirati, Bayer, Takeda, Pfizer, Roche, AstraZeneca. **EA:** No conflict of interests. **R-GC**: Consultant or Advisory Role: MSD, Bristol-Myers, Roche, Boehringer, Pfizer, Novartis, AstraZeneca, Lilly, Takeda; Speaker's Bureau honoraria: MSD, Bristol-Myers, Roche, Boehringer, Pfizer, Novartis, AstraZeneca, Lilly, Takeda; **PG:** Advisory Role: Abbvie, Amgen, AstraZeneca, Bayer, Bristol-Myers, Daichi, GSK, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Sanofi; Speaker Role: Amgen, Janssen, MSD, Novartis, Medscape, Takeda, TouchTime; Evaluator: EUnetHTA, EMA (assessment on lung cancer screening, scientific advisory group member for clinical immunological, oncology and lung cancer areas), RedETS; Steering Commiitee: Novartis, IO Biotech, Jannsen. **EN:** Funding grants: Roche, Pfizer, Merck Serono, Bristol-Myers; Advisory boards and Speaker Role: Roche, Bristol-Myers, Merck Sharp Dohme, Merck-Serono, Sanofi, Pfizer, Lilly, Amgen, Janssen, Daiichi-Sankyo, Boehringer, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, Bayer. **AL-O:** Advisory Role: Roche, Bristol-Myers, Merck. **DC:** Employment: Hygeia Consulting. **MC:** Employment: Hygeia Consulting. **JL:** Employment: Roche. **FC:** Employment: Roche. **RB:** Research Grant: Roche; Honorarias for lectures, presentations, or speaker's Bureau: Roche, Bristol-Myers, Pfizer, MSD, Amgen, Takeda, Astrazeneca; Advisory Role: Takeda, Roche, Bristol-Myers, Astrazeneca; Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Conception and design: DC, MC. Administrative support: JL, FC. Collection and assembly of data: DI, RA, MA, EA, AA, EA, R G-C, PG, EN, AL-O, RB. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

Acknowledgements

No assistance in the preparation of this article is to be declared.

Previous presentations

The preliminary results of this work were presented in a poster at the congress ISPOR EUROPE 2023 (12–15 November, Copenhagen, Denmark). https://www.ispor.org/heor-resources/presentations-database/presentation/euro2023-3784/133197.

ORCID

Dolores Isla http://orcid.org/0000-0002-2483-198X
Rosa Álvarez http://orcid.org/0000-0003-0935-8298
Edurne Arriola http://orcid.org/0000-0001-8960-7519
Aitor Azkarate http://orcid.org/0000-0002-6805-158X
Eider Azkona http://orcid.org/0000-0002-8524-2062
Pilar Garrido http://orcid.org/0000-0002-5899-6125
Ernest Nadal http://orcid.org/0000-0002-9674-5554
Ana L. Ortega http://orcid.org/0000-0002-5727-3371
David Carcedo http://orcid.org/0000-0002-2809-7399
Reyes Bernabé http://orcid.org/0000-0003-0312-9195

References

[1] Ezeife DA, Spackman E, Juergens RA, et al. The economic value of liquid biopsy for genomic profiling in advanced non-small cell lung cancer. Ther Adv Med Oncol. 2022;14:17588359221112696. doi: 10.1177/17588359221112696.

[2] Yuan M, Huang LL, Chen JH, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther. 2019;4(1):61. doi: 10.1038/s41392-019-0099-9.

[3] Guo H, Zhang J, Qin C, et al. Biomarker-targeted therapies in non–small cell lung cancer: current status and perspectives. Cells. 2022;11(20):3200. doi: 10.3390/cells11203200.

[4] Cheng Y, Zhang T, Xu Q. Therapeutic advances in non-small cell lung cancer: focus on clinical development of targeted therapy and immunotherapy. MedComm (2020). 2021;2(4):692–729. doi: 10.1002/mco2.105.

[5] Ionescu DN, Stockley TL, Banerji S, et al. Consensus recommendations to optimize testing for new targetable alterations in non-small cell lung cancer. Curr Oncol. 2022;29(7):4981–4997. doi: 10.3390/curroncol29070396.

[6] Tan AC. The role of liquid biopsy in the diagnostic testing algorithm for advanced lung cancer. Onco. 2022;2(3):181–185. doi: 10.3390/onco2030012.

[7] Arriola E, Bernabé R, Bernabé B, et al. Cost-effectiveness of next-generation sequencing versus single-gene testing for the molecular diagnosis of patients with metastatic non-small-cell lung cancer from the perspective of Spanish reference centers. J Clin Oncol Precis Oncol. 2023;7:e2200546. doi: 10.1200/PO.22.00546.

[8] Patel YP, Husereau D, Leighl NB, et al. Health and budget impact of liquid-biopsy-based comprehensive genomic profile (CGP) testing in tissue-limited advanced non-small cell lung cancer (aNSCLC) patients. Curr Oncol. 2021;28(6):5278–5294. doi: 10.3390/curroncol28060441.

[9] Penault-Llorca F, Kerr KM, Garrido P, et al. Expert opinion on NSCLC small specimen biomarker testing—part 2: analysis, reporting, and quality assessment. Virchows Arch. 2022;481(3):351–366. doi: 10.1007/s00428-022-03344-1.

[10] Nigro MC, Marchese PV, Deiana C, et al. Clinical utility and application of liquid biopsy genotyping in lung cancer: a comprehensive review. Lung Cancer (Auckl). 2023;14:11–25. doi: 10.2147/LCTT.S388047.

[11] Sehayek O, Kian W, Onn A, et al. Liquid first is "solid" in naïve non-small cell lung cancer patients: faster turnaround time with high concordance to solid next-generation sequencing. Front Oncol. 2022;12:912801. doi: 10.3389/fonc.2022.912801.

[12] Woodhouse R, Li M, Hughes J, et al. Clinical and analytical validation of foundation one liquid CDx, a novel 324-gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One. 2020;15(9):e0237802. doi: 10.1371/journal.pone.0237802.

[13] Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 explanation and elaboration: a report of the ISPOR CHEERS II Good Practices Task Force. Value Health. 2022;25(1):10–31. doi: 10.1016/j.jval.2021.10.008.

[14] De Alava E, Pareja MJ, Carcedo D, et al. Cost-effectiveness analysis of molecular diagnosis by next-generation sequencing versus sequential single testing in metastatic non-small cell lung cancer patients from a south Spanish hospital perspective. Expert Rev Pharmacoecon Outcomes Res. 2022;22(6):1033–1042. doi: 10.1080/14737167.2022.2078310.

[15] López Bastida J, Oliva J, Antoñanzas F, et al. Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias. Gac Sanit. 2010;24(2):154–170. doi: 10.1016/j.gaceta.2009.07.011.

[16] Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(4):339–357. doi: 10.1016/j.annonc.2022.12.009.

[17] Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020;31(11):1491–1505. doi: 10.1016/j.annonc.2020.07.014.

[18] Salas C, Martín-López J, Martínez-Pozo A, et al. Real-world biomarker testing rate and positivity rate in NSCLC in Spain: Prospective Central Lung Cancer Biomarker Testing Registry (LungPath) from the Spanish Society of Pathology (SEAP). J Clin Pathol. 2022;75(3):193–200. doi: 10.1136/jclinpath-2020-207280.

[19] Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med. 2020;383(21):2018–2029. doi: 10.1056/NEJMoa2027187.

[20] Drilon A, Subbiah V, Gautschi O, et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. J Clin Oncol. 2023;41(2):385–394. doi: 10.1200/JCO.22.00393.

[21] Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. N Engl J Med. 2018;378(2):113–125. doi: 10.1056/NEJMoa1713137.

[22] Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. N Engl J Med. 2017;377(9):829–838. doi: 10.1056/NEJMoa1704795.

[23] Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Ann Oncol. 2019;30(7):1121–1126. doi: 10.1093/annonc/mdz131.

[24] Planchard D, Besse B, Groen HJM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. J Thorac Oncol. 2022;17(1):103–115. doi: 10.1016/j.jtho.2021.08.011.

[25] Drilon A, W Tan DS, Lassen UN, et al. Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase fusion-positive lung cancers. J Clin Oncol Precis Oncol. 2022;6(6):e2100418. doi: 10.1200/PO.21.

[26] Wolf J, Seto T, Han J-Y, et al. Capmatinib in MET exon 14–mutated or MET-amplified non–small-cell lung cancer. N Engl J Med. 2020;383(10):944–957. doi: 10.1056/NEJMoa2002787.

[27] Paik PK, Felip E, Veillon R, et al. Tepotinib in non–small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med. 2020;383(10):931–943. doi: 10.1056/NEJMoa2004407.

[28] Bekaii-Saab TS, Yaeger R, Spira AI, et al. Adagrasib in advanced solid tumors harboring a *KRAS* ^{G12C} mutation. J Clin Oncol. 2023;41(25):4097–4106. doi: 10.1200/JCO.23.00434.

[29] Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in HER2-mutant non–small-cell lung cancer. N Engl J Med. 2022;386(3):241–251. doi: 10.1056/NEJMoa2112431.

[30] Makharadze T, Gogishvili M, Melkadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in advanced NSCLC: 2-year follow-up from the phase 3 EMPOWER-lung 3 part 2 trial. J Thorac Oncol. 2023;18(6):755–768. doi: 10.1016/j.jtho.2023.03.008.

[31] Reck M, Rodríguez–Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37(7):537–546. doi: 10.1200/JCO.18.00149.

[32] Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375(19):1823–1833. doi: 10.1056/NEJMoa1606774.

[33] Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. J Clin Oncol. 2023;41(11):1992–1998. doi: 10.1200/JCO.22.01989.

[34] Nafees B, Lloyd AJ, Dewilde S, et al. Health state utilities in non–small cell lung cancer: an international study. Asia Pac J Clin Oncol. 2017;13(5):e195–e203.

[35] Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF). Portal Farma, Botplus; 2023. Available from: https://botplusweb.farmaceuticos.com/

[36] Gisbert R, Brosa M. Healthcare cost database eSalud; 2023. Available from: http://www.oblikue.com/bddcostes/

[37] Sequist LV, Yang JCH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327–3334. doi: 10.1200/JCO.2012.44.2806.

[38] Solomon BJ, Bauer TM, Mok TSK, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. Lancet Respir Med. 2023;11(4):354–366. doi: 10.1016/S2213-2600(22)00437-4.

[39] Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056–1064. doi: 10.1016/j.annonc.2020.04.478.

[40] Socinski MA, Nishio M, Jotte RM, et al. IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. J Thorac Oncol. 2021;16(11):1909–1924. doi: 10.1016/j.jtho.2021.07.009.

[41] Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078–2092. doi: 10.1056/NEJMoa1801005.

[42] Nuño-Solinís R, Herrera Molina E, Librada Flores S, et al. Actividad asistencial y costes en los últimos 3 meses de vida de pacientes fallecidos con cáncer en Euskadi. Gac Sanit. 2017;31(6):524–530. doi: 10.1016/j.gaceta.2016.06.005.

[43] Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17(5):479–500. doi: 10.2165/00019053-200017050-00006.

[44] Sacristán JA, Oliva J, Campillo-Artero C, et al. What is an efficient health intervention in Spain in 2020? Gac Sanit. 2020;34(2):189–193. doi: 10.1016/j.gaceta.2019.06.007.

[45] Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. Health Econ. 2018;27(4):746–761. doi: 10.1002/hec.3633.

[46] Isla D, Lozano MD, Paz-Ares L, et al. New update to the guidelines on testing predictive biomarkers in non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Clin Transl Oncol. 2022;25(5):1252–1267. doi: 10.1007/s12094-022-03046-9.

[47] Bodaghi A, Fattahi N, Ramazani A. Biomarkers: promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases. Heliyon. 2023;9(2):e13323. doi: 10.1016/j.heliyon.2023.e13323.

[48] Simarro J, Pérez-Simó G, Mancheño N, et al. Impact of molecular testing using next-generation sequencing in the clinical management of patients with non-small cell lung cancer in a public healthcare hospital. Cancers (Basel). 2023;15(6):1705. doi: 10.3390/cancers15061705.

[49] Papadopoulou E, Tsoulos N, Tsantikidi K, et al. Clinical feasibility of NGS liquid biopsy analysis in NSCLC patients. PLoS One. 2019;14(12):e0226853. doi: 10.1371/journal.pone.0226853.

[50] Koole SN, Vessies DCL, Schuurbiers MMF, et al. Cell-free DNA at diagnosis for stage IV non-small cell lung cancer: costs, time to diagnosis and clinical relevance. Cancers (Basel). 2022;14(7):1783. doi: 10.3390/cancers14071783.

[51] Malapelle U, Tiseo M, Vivancos A, et al. Liquid biopsy for biomarker testing in non-small cell lung cancer: a European perspective. JMP. 2021;2(3):255–273. doi: 10.3390/jmp2030022.

[52] Englmeier F, Bleckmann A, Brückl W, et al. Clinical benefit and cost-effectiveness analysis of liquid biopsy application in patients with advanced non-small cell lung cancer (NSCLC): a modelling approach. J Cancer Res Clin Oncol. 2023;149(4):1495–1511. doi: 10.1007/s00432-022-04034-w.

[53] Alkhatib NS, McBride A, Bhattacharjee S, et al. Pricing methods in outcome-based contracting: δ5: risk of efficacy failure-based pricing. J Med Econ. 2020;23(11):1246–1255. doi: 10.1080/13696998.2020.1815029.

[54] Weymann D, Pataky R, Regier DA. Economic evaluations of next-generation precision oncology: a critical review. J Clin Oncol Precis Oncol. 2018;2(2):1–23. doi: 10.1200/PO.17.00311.

[55] Zheng Y, Vioix H, Liu FX, et al. Diagnostic and economic value of biomarker testing for targetable mutations in non-small-cell lung cancer: a literature review. Future Oncol. 2022;18(4):505–518. doi: 10.2217/fon-2021-1040.

[56] Fagery M, Khorshidi HA, Wong SQ, et al. Health economic evidence and modeling challenges for liquid biopsy assays in cancer management: a systematic literature review. Pharmacoeconomics. 2023;41(10):1229–1248. doi: 10.1007/s40273-023-01292-5.

[57] Johnston KM, Sheffield BS, Yip S, et al. Comprehensive genomic profiling for non-small-cell lung cancer: health and budget impact. Curr Oncol. 2020;27(6):e569–e577. doi: 10.3747/co.27.5995.

[58] Böckerman P, Ilmakunnas P. Unemployment and self-assessed health: evidence from panel data. Health Econ. 2009;18(2):161–179. doi: 10.1002/hec.1361.