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UNIVERSITAT AUTÒNOMA DE BARCELONA

PROGRAMA DE DOCTORAT EN FARMACOLOGIA

DEPARTAMENT DE FARMACOLOGIA, TERAPEUTICA I TOXICOLOGIA

Analysis of value-based price determinants for innovative oncology and hematology drugs in Spain

Doctoral Thesis

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FAN CONSTAR:

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Summary

Concerns about increasing acquisition costs for oncological and hematologic innovation in Europe are growing as prices of cancer drugs are increasingly high and potentially jeopardizing the financial sustainability of healthcare systems. Adequate models to assess the value of drugs are still an open debate and, even in countries with well-stablished technology assessment processes, apparently prices seem to be unrelated to value and clinical or social benefits.

The general aim of this Doctoral Thesis was to evaluate the relationship between oncology and hematology drug prices and a structured assessment of parameters measuring drug value at the time of reimbursement decision in Spain to identify potential price determinants.

Firstly, due to the heterogeneity in drug-assessment strategies in Europe, an analysis of the uptake and use of multicriteria approaches was conducted to evaluate drug value assessment methodologies of 37 European Health Technology Assessment Bodies (HTAb) by using EVIDEM – multi criteria decision analysis – as the reference framework. As a conclusion, EVIDEM's framework provides contextual value assessment dimensions already used by some HTAb in Europe that can be escalated to other agencies. Most of the 37 European HTAb have room to broaden their contextual assessment tools, especially when social and medical perception of need requires to be explicit to support payer's decision on reimbursement. The full analysis and conclusions can be seen in an article published in August 2021.

Further, all new 22 chemical entities with a first EMA authorization for a single onco-hematologic indication between January 2017 and December 2019 were identified, and price and reimbursement decisions of the Spanish Ministry of Health (MoH), including the notified price and public funding authorization, were tracked based on the publicly available databases and the resolutions published by the MoH until end of October 2022. For standardization and comparison purposes, a daily treatment cost based on notified prices was assigned following the Summary of Product Characteristics recommended posology for the studied indication. When the treatment duration was fixed, cost was annualized and products with a negative decision were assigned a prize of zero. For each product, a set of 56 contextual and non-contextual indicators from the EVIDEM framework was used to explore the relationship between prices and the EVIDEM's value criteria using univariate statistical analyses. The study concludes that the

main drivers for oncology drug prices in the period studied seemed to be when the standard of care was combined treatments, if long-lasting responders were reported, and for several characteristics of the treatment: higher prices for fixed duration as compared to treatment until progression and lower frequencies of administration, and lower prices for oral route as compared to other routes of administration. Price was significantly related to the easiness of use of the drug, the impact of treatment on patient's autonomy, and the existence of recommendations by experts. These findings suggest that criteria other than incremental benefit/risk are important in the reimbursement decision making. The full analysis and conclusions can be seen in an article submitted (under revision) in July 2023.

As general conclusions, the research suggests that the implementation of methodologies based on multiple-criteria decision analysis to set the prices of drugs may help to make robust and sustainable reimbursement decisions for new onco-hematology medicines.

Resum

La preocupació per l'augment dels costos d'adquisició de la innovació oncològica i hematològica a Europa està creixent a mesura que els preus dels medicaments contra el càncer són cada cop més alts i poden posar en perill la sostenibilitat financera dels sistemes sanitaris. Els models adequats per avaluar el valor dels fàrmacs són encara un debat obert i, fins i tot en països amb processos d'avaluació de tecnologies mèdiques i medicaments ben establerts, aparentment els preus semblen no estar relacionats amb el valor i els beneficis clínics o socials d'aquests.

L'objectiu general d'aquesta Tesi Doctoral va ser avaluar els preus dels medicaments en oncologia i hematologia en el marc d'una avaluació estructurada dels paràmetres que mesuren el seu valor en el moment de la decisió de reemborsament a Espanya, per identificar així els possibles determinants del preu.

En primer lloc, a causa de l'heterogeneïtat de les estratègies d'avaluació de fàrmacs a Europa, es va realitzar una anàlisi de l'adopció i l'ús de models multicriteri per avaluar el valor dels fàrmacs de 37 organismes europeus d'avaluació de tecnologies sanitàries (HTAb) mitjançant EVIDEM (anàlisi de decisions multicriteri) com a marc de referència. La principal conclusió de la recerca va ser que el marc EVIDEM proporciona dimensions d'avaluació contextual que ja utilitzen algunes agències a Europa i que es pot escalar a d'altres organismes. La majoria de les 37 agències europees tenen marge per ampliar les

seves eines d'avaluació contextual, especialment quan la percepció de la necessitat clínica i social requereix ser explícita per donar suport a la decisió del pagador sobre el preu i les condicions de reemborsament. L'anàlisi completa i les conclusions es poden veure en un article publicat l'agost de 2021.

Posteriorment, es van identificar les 22 entitats químiques noves amb una primera autorització de l'Agència Europea de Medicaments (EMA) per a una única indicació oncohematològica entre gener de 2017 i desembre de 2019, així com les decisions de preu (notificat) i reemborsament del Ministeri de Sanitat espanyol. Es va fer un seguiment a partir de les bases de dades disponibles públicament i de les resolucions publicades pel Ministeri fins a finals d'octubre de 2022. A efectes d'estandardització i comparació, es va assignar un cost de tractament diari basat en els preus notificats seguint la posologia recomanada pel resum de les característiques del producte per a la posologia de la indicació estudiada. Quan es va fixar la durada del tractament, es va calcular el cost en base anual i als productes amb decisió negativa se'ls va assignar un preu zero. Per a cada producte, es va utilitzar un conjunt de 56 indicadors contextuals i no contextuals del marc EVIDEM per explorar la relació entre els preus i els criteris de valor d'EVIDEM mitjançant anàlisis estadístiques univariants. L'estudi conclou que els principals motors per fixar els preus dels medicaments oncològics a Espanya estan relacionats amb el fet que l'estàndard d'atenció siguin tractaments combinats, si s'informa de l'existència de pacients amb respostes a llarg termini, i per diverses característiques del tractament: preus més elevats per a una durada fixa en comparació amb el tractament fins a la progressió i freqüències d'administració més baixes, i preus més baixos per a la via oral en comparació a altres vies d'administració. El preu es va relacionar significativament amb la facilitat d'ús del fàrmac, l'impacte en l'autonomia del pacient i l'existència de recomanacions d'experts. L'anàlisi completa i les conclusions es poden veure en un article enviat (en revisió) el juliol de 2023.

Com a conclusió general de la recerca, la implementació de metodologies d'anàlisi de decisions amb criteris múltiples per fixar els preus dels medicaments pot ajudar a prendre decisions de reemborsament sòlides i sostenibles per a nous fàrmacs onco-hematològics.

Resumen

La preocupación por el aumento de los costes de adquisición de la innovación oncológica y hematológica en Europa está creciendo a medida que los precios de los medicamentos contra el cáncer son cada vez mayores y pueden poner en peligro la sostenibilidad financiera de los sistemas sanitarios. Los modelos adecuados para evaluar el valor de los fármacos son todavía un debate abierto e, incluso en países con

procesos de evaluación de tecnologías médicas y medicamentos bien establecidos, aparentemente los precios parecen no estar relacionados con el valor y los beneficios clínicos o sociales de éstos.

El objetivo general de esta Tesis Doctoral fue evaluar los precios de los medicamentos oncohematológicos en el marco de una evaluación estructurada de los parámetros que miden su valor en el momento de la decisión de reembolso en España, identificando así los posibles determinantes del precio.
En primer lugar, debido a la heterogeneidad de las estrategias de evaluación de fármacos en Europa, se realizó un análisis sobre la adopción y el uso de enfoques multicriterio para evaluar el valor de los fármacos de 37 agencias europeas de evaluación de tecnologías sanitarias (HTAb) mediante EVIDEM (análisis de decisiones multicriterio) como marco de referencia. La principal conclusión de la investigación fue que el marco EVIDEM proporciona dimensiones de evaluación contextual que ya utilizan algunas agencias en Europa y que puede escalarse a otros organismos. La mayoría de las 37 agencias europeas tienen margen para ampliar sus herramientas de evaluación contextual, especialmente cuando la percepción de la necesidad clínica y social requiere ser explícita para apoyar la decisión del pagador sobre el precio y condiciones de reembolso. El análisis completo y las conclusiones pueden verse en un artículo publicado en agosto de 2021.

Posteriormente, se identificaron las 22 nuevas entidades químicas con una primera autorización de la Agencia Europea de Medicamentos (EMA) para una única indicación oncohematológica entre enero de 2017 y diciembre de 2019, así como las decisiones de precio (notificado) y reembolso del Ministerio de Sanidad español. Se realizó un seguimiento a partir de las bases de datos disponibles públicamente y de las resoluciones publicadas por el Ministerio hasta finales de octubre de 2022. A efectos de estandarización y comparación, se asignó un coste de tratamiento diario basado en los precios notificados siguiendo la posología recomendada por el resumen de las características del producto para la posología de la indicación estudiada. Cuando se fijó la duración del tratamiento, se calculó el coste anualizado y a los productos con decisión negativa se les asignó un precio cero. Para cada producto, se utilizó un conjunto de 56 indicadores contextuales y no contextuales del marco EVIDEM para explorar la relación entre precios y criterios de valor de EVIDEM mediante análisis estadísticos univariantes. El estudio concluye que los principales motores para fijar los precios de los medicamentos oncológicos en España están relacionados con el hecho que el estándar de atención sean tratamientos combinados, si se informa de pacientes que tienen respuestas de larga duración, y para diversas características del tratamiento: precios más elevados para una duración fija en comparación con el tratamiento hasta su progresión y frecuencias

administración más bajas, y precios más bajos para la vía oral en comparación con otras vías de administración. El precio se relacionó significativamente con la facilidad de uso del fármaco, el impacto del tratamiento en la autonomía del paciente y la existencia de recomendaciones de expertos. El análisis completo y las conclusiones pueden verse en un artículo enviado (en revisión) en julio de 2023.

Como conclusión general de la investigación, la implementación de metodologías de análisis de decisiones con criterios múltiples para fijar los precios de los medicamentos puede ayudar a tomar decisiones de reembolso sólidas y sostenibles para nuevos fármacos oncohematológicos.

Acknowledgments

This endeavor would not have been possible without the tireless support of my director and tutor, Caridad Pontes. She has been the northern star along the journey, and I am deeply indebted for her invaluable initial inspiration, her patience, and her continuous and insightful feedback.

I would like to extend my sincere thanks to my co-director, Josep Tabernero, who generously provided me with his deep knowledge and expertise.

I am also grateful to Ferran Torres, Roser Vives, Gemma Puig, Merce Obach, Daniel Gay, Daniel Varon, and Thais de Pando, as co-authors of the published articles related to this research and for their analysis support and continuous feedback.

Lastly, I would be remiss in not mentioning my family, that has kept my spirit, motivation, and commitment high during these last almost 5 years.

Disclosure of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

I am a full-time employee of Sanofi (Paris, France).

List of abbreviations

AEMPS: Spanish Agency of Medicines and Medical Devices

ASCO-VF: American Society of Clinical Oncology Value

ATMPs: Advanced Therapy Medicinal Products

CIPM: Inter-ministerial Committee on Pricing of Medicines and Healthcare Products

CTs: Clinical Trials

DALYs: Disability-Adjusted Life-Years

DGCCSF: General Directorate for Common Portfolio of the NHS and Pharmacy Services

EMA: European Medicines Agency

EPAR: European Public Assessment Report

ESMO-MCBS: European Society of Medical Oncology-Magnitude of Clinical Benefit Scale

EUnetHTA: European Network for Health Technology Assessment

EVIDEM: Evidence and Value Impact on Decision Making

FDA: Food and Drug Administration

HTAb: Health Technology Assessment Bodies

IBP: Indication-based pricing

ICER: Incremental Cost-Effectiveness Ratio

ICER: Institute for Clinical and Economic Review

MCDA: Multi-Criteria Decision Analysis

MEAs: Managed Entry Agreements

MoH: Ministry of Health

MSKCC: Memorial Sloan Kettering Cancer Center

NCCN: National Comprehensive Cancer Network

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NNT: Number Needed to Treat

NNH: Number Needed to Harm

OECD: Organization for Economic Co-operation and Development

OS: Overall Survival

PFS: Progression Free Survival

PRIME: Priority Medicines

QALYS: Quality-Adjusted Life-Years

QoL: Quality of Life

RCTs: Randomized Clinical Trials

REA: Rapid Relative Effectiveness Assessment

TPR: Therapeutic Positioning Report

WHO: World Health Organization

WTP: Willingness to Pay

Chapter 1: Introduction

Context and justification on the project

Cancer and innovative onco-hematology treatments

Cancer is a serious, complex, and heterogeneous disease with multiple potential causes, clinical manifestations, and severity often life-threatening. Cancer is very frequent, with an estimated prevalence (excluding non-melanoma skin cancer) of 260,455 Spanish patients in 2020. The estimates also suggest a sustained growing trend, with an 11% increase expected in 5 years, achieving 289,316 cancer cases in Spain by 2025 [1].

All cancers have in common a process (oncogenesis) by which normal cells transform into cancerous cells, leading to an increased and uncontrolled cellular proliferation that escapes from the endogenous mechanisms for growth regulation. Oncogenesis may be due to a genetic and/or epigenetic alteration, which through sustained or increased proliferative signaling pathways, increased angiogenesis, failure of mechanisms to suppress tissular growth, resistance to mechanisms of programmed cell death, or activated immortal replication and activating invasion, leads to progressive invasion of healthy tissues and distant metastasis in the body [2-3].

The ideal goal for the treatment of cancer is to eradicate neoplastic cells from the body, and thus cure the disease, but this is seldom feasible. Thus, treatments generally intend to reduce as much as possible the tumoral burden, until the natural mechanisms of control can suppress the neoplastic growth [4].

During the last century, in addition to surgery and radiotherapy, approaches to reduce tumors have mostly been based on the use of cytotoxic drugs. Cytotoxic chemotherapy uses products that interfere in the replication cycle, induce toxic effects or attack cells during the replication cycle, taking advantage on the differences in speed of replication between cancer cells and normal cells. Such drugs, however, are also highly toxic on tissues with high turnover, such as blood, skin, and the digestive tract, which limits their application and effectiveness [5].

In the past two decades, improvements in understanding the molecular basis of cancer and huge advances in biotechnology have boosted the development of new successful approaches to treat cancer, such as

targeted therapies and immunotherapy. While the first may mechanistically address specific molecular abnormalities underlying cancerous transformation and induce selective toxicity by recognizing molecular changes in malignant cell surface, the latter are able to cancel some immunological evading mechanisms of cancer cells, thus restoring the susceptibility of cancer to the patient's anticancer mechanisms [5].

The upcoming of innovation has been substantial and provided clinical benefits, but also a shift in the paradigms of therapeutics, with the rise of precision medicine. The availability of new drugs that are both specific and precise has been paralleled by the development of biomarkers and diagnostic tests, aimed to identify the presence of the target for a given drug in the patient's tumor. As a result, the chances of response of guided treatments in the selected population is improved, and so the benefit-risk balance since the test-error approach is reduced [6-7].

Precision medicine is focusing the scope of applicability of new drugs, reducing the target population while increasing the clinical effectiveness. Therefore, the classical approaches to value, that apply a population perspective, are fragmented; individual drugs demonstrate results that were infrequent in the chemotherapy era, are intended to small populations, and in that respect are deemed as orphan medicinal drugs. The increase of innovation and the number of patients with precision approaches increases, becoming a challenge to keep a wide vision of the therapeutic field [6].

Access conditions for new onco-hematology drugs

The pharmaceutical 'innovation' is considered one of the major cost drivers in the European healthcare systems, even more relevant than demographics [8], while also being acknowledged as one of the main contributors to the improvement of the population health status [9].

There is a growing concern in Europe about the cost escalation for oncological and hematologic innovation as prices of new cancer drugs are high and sometimes unrelated to a similar level of improvement on patients' health outcomes. Besides, payers are also concerned about how high prices of new onco-hematologic drugs may jeopardize the financial sustainability of healthcare systems [10].

According to the most recent study from the Organization for Economic Co-operation and Development (OECD) [11], pharmaceutical expenditure accounts for a percentage that ranges between 11.4% (UK) and

19.1% (Spain) of total healthcare expenditure across the five largest European drug markets (France, Germany, Italy, Spain, and the UK). As estimated by a recent study [12-13], the healthcare expenditures on cancer in the European Union's member states represented roughly 6% of total healthcare expenditures. The steady increase of oncology costs is aligned with the disease increasing incidence, the progressive reduction of mortality as well as high prices, in contrast with the less robust evidence data on outcomes [14]. In fact, the increased rate of health spending on cancer in Europe has been faster than the increase in cancer incidence during the last 20 years, representing €199 billion (including EU-27, Iceland, UK, Norway, and Switzerland) in 2018. Similarly, the impact on the loss of productivity in those economies, because of a decrease in working-age population's mortality, has diminished while it is still unknown the potential general productivity loss due to cancer morbidity [15].

The increased budget burden observed in recent decades is mainly the effect of the expansion of multiple new indications for more restricted population to be treated and the increasing trend of regulators to consider new more population-targeted onco-hematologic drugs as orphan-like medicines [16]. In fact, around 40% of the new medicines authorized in Europe as orphan drugs are related to neoplastic disorders. There is also an increasing trend to ease the patients access to products with high potential clinical benefit that explains a rapid authorization process in earlier stages of its clinical development by regulators when compared with non-neoplastic related disorders [12]. Therefore, the provision of more targeted treatments for cancer patients based on precision medicine has been quickly included into regular clinical practice [17-18]. The research and development programs of the industry are shifting to R&D platforms that facilitates the discovery treatments for rare and hard-to-treat illnesses, with unmet medical needs that justify the request for early access to the innovation even when there is a lack of robust evidence [19]. Studies of authorization decisions [20] estimated that 10 years ago only 35% of drugs with oncologic indications showed robust data on survival, and no more than 10% showed improvements on quality of life at the time of market authorization by the European Medicines Agency (EMA). After monitoring post authorization real world evidence for 3,3 years, evidence of benefit on survival of those authorized drugs was only observed in 7% of the cases and improvement on reported quality of life was achieved in only 11% of them. A recent study [21] confirms that the trend has consolidated, and current

research and regulatory practice is biased towards earlier access at the expense of provision of robust evidence to support regulatory decisions.

As seen, high unmet medical needs are a strong driver to promote early access to cancer medicines based only on initial clinical data, that would imply the risk of opportunity costs at the expense of limiting the access to more efficient drugs in other therapeutic areas. An early access to new drugs can qualify for patients with life-threatening or debilitating diseases, with limited or no treatment options, and ominous prognosis. In those situations, early access when basic positive risk-benefit assessment is concluded for drugs requiring long developments can improve the return of investment of developers and serve social demand for access to new treatments for these specific diseases. The social perception, patients' pressure, and appetite from clinicians for early access to treatments for highly unmet needs also creates the general perception of potential unjustified delays in the regulatory authorization and pricing procedures. Recent evidence on access among European countries to 152 innovative medicines also highlights the lack of access equity of new oncology and hematology drugs that become available in each country (152 in Germany compared to 6 in Macedonia) and in availability rates (from 88% to 1%). A significant difference is also seen in the time it took for patients in different countries to access innovative therapies (e.g., 152 days in Germany vs 883 days in Romania) [22].

The (EMA) set up the PRIME (PRIority MEdicines) program to accelerate the regulatory process of medicinal products aimed to treat serious and life-threatening conditions with high unmet medical needs. The program supports the development process of selected medicines that offer a therapeutic alternative with significant advantages over existing treatments or medicines without current treatment options, providing faster authorization pathways [23]. PRIME supports the generation of robust data related to the risk-benefits assessment of the selected drugs, accelerating applications' assessment for medicine approvals through early dialogue between patent holders and regulators. Besides the accelerated regulatory procedures described, the European regulator is also increasing the percentage of authorization of medicines with orphan and advanced therapies designations, as well as conditional and exceptional authorizations [24]. This trend confirms that when the drug can cover clinical unmet needs with poor prognosis, the regulator tends to accept less and poorer evidence and include especial approvals, such as conditional approval related to further assessments of adequate risk benefit rate in

real world, after commercialization, or approval under exceptional circumstances when this may not be achieved, to ensure an earlier access to market [25].

As regulatory pathways also mean additional uncertainty about clinical benefits at the time of approval, there is an open debate in Europe about how to balance optimal speed in access with robustness of evidence on clinical benefits. Recent analysis of oncology medicines approved by the EMA from 2015 to 2020 [22] highlights that most new medicines received marketing authorization based on surrogate outcomes, without evidence of improved overall survival (OS) or quality of life benefits. As a result of the increasing focus on accelerating the access to onco-hematologic medicines, clinical trials in this therapeutic area increasingly allow early interruption based on interim positive results. However, these early trial interruptions overestimate clinical effects, especially when running non-blinded and uncontrolled clinical trials resulting in an underestimation of long treatment effects, especially if the number of events is small [26]. Additionally, a review of pivotal clinical trials (CTs) supporting the approval of recent advanced therapy medicinal products (ATMPs) in the EU, mostly in the oncology area, highlights that marketing authorizations were mainly based on small CTs, with single arm, without control group, eventually compared to historical controls, and using surrogate outcomes as the primary endpoint [27]. Similarly, recent evidence from EMA and FDA shows that ATMPs had fast track or orphan designation, and/or non-standard marketing authorization pathways [28]. Based on this evidence, there is an increasing concern about the magnitude of the clinical benefit and if it compensates the added toxicities of newly authorized products [29].

Recent literature [26] keeps insisting that the potential benefit of patients' early access to new medicines in areas of high unmet medical need, and based on initial data only, have relevant implications in terms of medical and economic costs (opportunity costs of using alternative more efficient treatments available for patients). Several initiatives have been developed in Europe to address these challenges of funding premium priced products related to clear medical unmet needs but with limited evidence [30]. To minimize such opportunity costs derived from funding cancer drugs with very limited evidence at premium prices [31], new access management models have been implemented across Europe during the last decades [31] although the countries and drugs involved in these commercial agreements is still limited and lacking

methodological harmonization to assess the actual clinical outcomes and other benefits on healthcare systems [32].

Price decisions for new onco-hematology drugs

The increase of prices of oncologic products has generated additional concerns from EU governments and multilateral organizations, such as the World Health Organization (WHO) [33], about the above-described disconnection between price and clinical outcomes, as well as the general perception of "value" for the healthcare system and society offered by new cancer products. High prices for medicines with frail evidence may adversely affect the health status and financial wellbeing of patients and their families, the equitable access to care for individuals, and the sustainability of health-care systems of countries. Furthermore, it is widely acknowledged that setting up "fair prices" of new drugs while balancing affordability and achieving the desirable incentives to invest in R&D of innovative oncology treatments is extremely difficult [34].

The therapeutic benefit of a new drug compared to existing alternatives is normally at the center of any value or "fair price" assessment process, and it determines if there is or not a therapeutic improvement based on relevant evidence of superiority and a better risk-benefit profile compared to treatment alternatives. The relative approach is associated to more favorable evaluations than the use of absolute clinical outcomes and it is considered as a starting point for any subsequent multidimensional evaluations [35]. There is a consensus about assessing efficacy and safety based on net effects measured by the magnitude of the clinical effect of the experimental treatment vs the control group to calculate differences in absolute risk, for dichotomous parameters, or measuring the difference of the effects' estimators in each group, for continuous parameters. Measures such as the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) [36], the Standardized Effect Sizes [37], or the Minimally Important Change [38], are commonly used to assess the clinical relevance of the experimental treatment.

Other dimensions to measure outcomes can be used to include subjective values of quality of life associated with the different clinical states (the so-called "utility" measure that ranges from 0 - worst status- to 1 – perfect health status-). Quality-adjusted life years (QALYs) or disability-adjusted life-years (DALYs) are examples of commonly used measures of quality of life [39]. More recently, other methods

including multiple non-clinical dimensions in the evaluation of new drugs have been initially used by regulators and reimbursement authorities in Europe. The Multiple Criteria Decision Analysis (MCDA), for example, uses variables of a different nature (clinical, social, or economic) to synthesize relative weights for each of those dimensions of the value [40].

Methods to set prices are increasingly expanding to the value-based pricing approach which is usually focused on cost-effectiveness analysis [41-42-43]. The WHO identifies [44] the value-based pricing as an approach that has the objective of setting prices for pharmaceutical products based on a measure of "value", that is obtained through a preference elicitation method, quantified using summary metrics such QALYs or DALYs. To determine the price the value-based method usually constrains the value (and price) to a willingness-to-pay threshold or budget that is explicit (e.g., the United Kingdom) or implicit (e.g., Australia); or a frontier for efficiency optimization (e.g., Germany) [40]. Cancer drugs are normally classified as innovation based on implicit clinical value through QALYS (e.g., UK, Australia, Sweden) or using innovation scales (e.g., Canada, Japan, France, Germany, Austria, Italy) [45]. However, the amount, type, and methodology to set the premium price for innovation is not normally veiled by the healthcare authorities, while new cancer drugs are increasingly reimbursed at a higher price than the available alternatives [46].

Beyond the general awareness among healthcare authorities to ensure "value for money", or the link between price and social or clinical value of the pharmaceutical innovation [46], the reimbursement process and value assessment of drugs is still an open debate in Europe [47] and several new methods have been developed to assess the value of drugs and set meaningful prices affordable to health-care systems [48]. However, there is neither a consensus nor a European harmonization related to drug-pricing systems and based on a comparative international policy analysis, and value-based approaches to determine the prices of innovative products are diverse [45].

Recent studies [49] show that even in countries with well-established technology assessment processes (such as UK, Germany, France, and Switzerland), prices may still be considered as disconnected to value. In fact, evidence shows minimal correlation between value assessment and list prices for new cancer medicines in the USA [50], while in countries where average treatment costs are lower than in the US, such as France, Australia, or the UK (on average between 1.2 and 1.9 times lower), prices are only weakly

associated with drug clinical benefits. These findings are consistent with the lack of significant associations between monthly treatment costs and clinical benefit in US, UK, Australia, Germany, and Switzerland (only significant in France), when the American Society of Clinical Oncology Value (ASCO-VF) and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores were used to measure clinical benefit of new cancer drugs for solid tumors with initial adult indication and recently approved by the EMA and the Food and Drug Administration (FDA) [51]. Recent evidence has been published showing significant positive correlation between prices, mortality, and efficacy for cancer drugs, although weaker than for non-cancer medicines [52]. Similar results have been obtained in Italy [53], showing that the only statistically significant predictor of price for oncology products is the incremental progression-free survival in trials, being this association only observed for confidential net prices (included in non-disclosure contracts conditioning international reference pricing [54]).

Besides clear lack of consistency between price and value, the literature remains inconclusive about the factors that Health Technology Assessment Bodies (HTAb) are using to make their decisions on value and how payers are deciding prices even when applying managed entry agreements (MEAs) [55].

Multidimensional assessing models for new onco-hematology drugs

High prices of new oncology and hematology drugs is driving the political and academic debate towards the economic sustainability of healthcare systems. Several countries have systematically included economic evaluations to assess the incremental costs and benefits of new onco-hematology products [60]. This approach requires a clear definition of benefit, as highlighted by the European Commission in its directions for the Horizon Europe contribution to Europe's Beating Cancer Plan, that supports innovative health technology assessment methods to support the better allocation of resources and ensure the suitable access to "innovative, sustainable and high-quality healthcare" [56]. Among those methods the European Commission includes aspects to be included such as clinical effectiveness, cost-effectiveness, ethical, or organizational aspects.

Recent research [60] has been conducted to analyze the pricing processes of cancer medicines across Europe to enhance the healthcare systems sustainability. Among several available tools the authors highlight the use of minimum effectiveness criteria, MEAs, multi criteria decision analysis or

differential/tiered pricing as the most common strategies to better balance the incremental benefits with the incremental costs of new innovative therapies. A recent OECD report [57] recommends the use of MEAs to compensate for the uncertainty regarding the effectiveness and safety of new oncology medicines in routine clinical care due to the immature data available when these new treatments are launched. It also advocates for the use of MCDA as a methodology that provides a suitable ranking of priorities among different treatment alternatives, simplifying complexity in the health policy decision-making process.

New literature [58] shows that MCDA - Evidence and Value Impact on Decision Making (EVIDEM) framework provides a complete and suitable value assessment framework, including contextual dimensions, and it has been progressively adopted by some (Health Technology Assessment Bodies) HTAb in Europe, broadening the scope and approach of the more consolidated European network for Health Technology Assessment (EUnetHTA)'s core model.

In Europe, EUnetHTA was set up to provide strategic guidance and policy orientation on the assessment of health technologies (including drugs), by developing policy papers and discussing areas of potential collaboration. During the last decade the network has focused the efforts on the development of common methodologies, piloting and producing joint early dialogues and HTA joint assessment reports, as well as developing and maintaining common tools [59]. One of the most relevant tools developed by the network is the HTA Core Model for Rapid Relative Effectiveness Assessment (REA) [60]. The Model is a collaborative methodological framework that enables standardized assessment reports across Europe. The framework provides commonly relevant and transferable elements of information that brings a standardized comparison of the drivers that lead pricing and reimbursement decisions among different European countries.

EUnetHTA approach is based on technical aspects, and it is not able to provide directions to align decisions with the ethical and social foundations of healthcare systems [61]. A more holistic approach to assess medicines and vaccines is becoming common among healthcare authorities, especially when it comes to assess the innovation in therapeutic areas such as oncology and rare diseases [62]. EVIDEM [63] was developed based on an analysis of the foundations of healthcare systems, becoming a reference for multicriteria decision approaches in healthcare. It assumes that decision-makers are guided by a

framework of multiple criteria rooted on the foundational bases of healthcare systems, including healthcare ethics, evidenced-based medicine, health economics or health technology assessment approaches. Legitimacy of public decisions can be also highlighted when a multicriteria analysis is in place. EVIDEM reflective multicriteria aims to transform the vision of the value of healthcare interventions to be more relevant and equitable. EVIDEM criteria partially overlap with EUnetHTA [Table 1].

Although multicriteria EVIDEM approach is now applied by several healthcare authorities [64], especially when the social and medical perception of need requires a more holistic assessment framework to support the payer's decision, there is not a formal and systematic comparison of EUnetHTA and EVIDEM methodological frameworks and whether HTAb are aligned with the EVIDEM methodology standards [65]. Since EUnetHTA and EVIDEM frameworks differ in key criteria, it is relevant to investigate the degree of compliance between the two methodological approaches to explore potential avenues of assessment discrepancies. Despite the evidence that 37 European HTAb were using EUnetHTA-core framework criteria to support decision making [20], it is unknown if these HTAb also comply with the wider EVIDEM multicriteria approach [66].

Table 1: EVIDEM and EUnetHTA criteria correspondence

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
NON-CONTEXTUAL CRITERIA		
Disease severity	• Effect of disease on life-expectancy. • Effect of disease on morbidity (includes disability and function). • Effect of disease on patients' quality of life. • Effect of disease on caregivers' quality of life.	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA - SEVERITY DEFINITION.
		Assessments include a description of the health problem and current use of technology.
Size of affected population	• Prevalence.	Methodology requirements for the clinical assessment compared to the

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
	• Incidence.	HTA Core Model for REA – POPULATION.
		Assessments include a description of the health problem and current use of technology.
Unmet needs	• Unmet needs in efficacy. • Unmet needs in safety. • Unmet needs in patient reported outcomes. • Patient demand.	Assessments include a description of the health problem and current use of technology.
		Evidence where systematic search strategies are applied (HEALTH PROBLEM - CURRENT TECHNOLOGY USE).
Comparative effectiveness	• Magnitude of health gain. • Percentage of the target population expected to achieve the anticipated health gain. • Onset and duration of health gain. • Sub-criteria for the measure of efficacy specific to the therapeutic area.	The comparator is supported by evidence on its efficacy profile for the respective clinical indication/population.
		Assessments analyze clinical effectiveness / efficacy (added therapeutic value).
		Evidence where systematic search strategies are applied (EFFICACY-EFFECTIVENESS).
Comparative safety/tolerability	• Adverse events. • Serious adverse events. • Fatal adverse events. • Short-term safety. • Long-term safety. • Tolerability.	The comparator is supported by evidence on its safety profile for the respective clinical indication/population.
		Assessments analyze safety.

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
		Evidence where systematic search strategies are applied (SAFETY).
Comparative patient-perceived health	• Improvement in health-related quality of life. • Impact on autonomy. • Impact on dignity. • Convenience / ease of use / mode & setting of administration.	QALYs applied.
		Assessments analyze patient aspects.
		Assessments include a separate ethical analysis.
		Evidence where systematic search strategies are applied (PATIENT ASPECTS).
Type of preventive benefit	• Eradication, prevention, reduction in disease transmission, reduction in the prevalence of risk factors). Public health perspective.	Not available.
Type of therapeutic benefit	• Symptom relief, prolonging life, cure.	Assessments include a description of the health problem and current use of technology.
Comparative cost consequences – cost of intervention	• Net cost of intervention. • Acquisition cost. • Implementation/ maintenance cost.	Assessments analyze cost, budget impact, or include economic evaluation.
Comparative cost consequences – other medical costs	• Impact on primary care expenditures. • Impact on hospital care expenditures. • Impact on long-term care expenditures.	Assessments analyze cost, budget impact, or include economic evaluation.

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
Comparative cost consequences – non-medical costs	• Impact on productivity. • Financial impact on patients. • Financial impact on caregivers. • Costs to the wider social care system.	Assessments analyze social aspects.
Quality of evidence	• Validity (study design, agreement among studies). • Relevance (population, disease stage, outcomes). • Completeness of reporting (uncertainty, conflicting results across studies, limited number of studies). • Type of evidence.	Sources of evidence included as relevant clinical evidence for the clinical assessment (1- Randomized controlled; 2- Nonrandomized prospective; 3- Other observational; 4- Expert Opinion).
		Methodology requirements for the clinical assessment compared to the HTA Core Model for REA.
		Formal tools or algorithms for evidence grading applied.
		The GRADE approach in routine use.
		Plan for how evidence will be synthesized (e.g., evidence tables, meta-analysis, qualitative synthesis).
		Standard forms or tables available for evidence analysis and synthesis.
		Evidence analysis include surrogate endpoints, composite endpoints, PROs, HRQoL measures, indirect comparisons, meta-analysis, relevant group sub-population, key deficiencies

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
		in available data, transferability issues, summary of findings.
		Sources of evidence on the technology: A. scientific journal publications, B. grey literature (e.g., published reports), C. unpublished data, D. register data, E. administrative data, F. manufacturer data.
		Confidential data from manufacturers accepted.
Expert consensus/clinical practice guidelines	Current consensus of experts on what constitutes state-of-the-art practices (guidelines).	Not available.
CONTEXTUAL CRITERIA		
Mandate and scope of the healthcare system	Alignment with healthcare plans/systems.	Circumstances where HTA reports are provided.
Population priorities and access	• Current priorities of health system (e.g., low socioeconomic status; specific age groups). • Special populations (e.g., ethnicity). • Remote communities. • Rare diseases. • Specific therapeutic areas.	Assessments analyze social aspects.
Common goal and specific interests	• Stakeholder pressures. • Stakeholders' barriers. • Conflict of interest.	Assessments analyze social aspects.

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
Environmental impact	• Environmental impact of production. • Environmental impact of use. • Environmental impact of implementation. • Environmental impact of production. • Environmental impact of use. • Environmental impact of implementation.	Not available.
System capacity and appropriate use of intervention	• Organizational requirements (e.g., process, premises, equipment). • Skill requirements. • Legislative requirements. • Surveillance requirements. • Risk of inappropriate use. • Institutional limitations to uptake.	Assessments include a separate ethical analysis. Assessments analyze legal aspects. Assessments analyze organizational aspects.
Political/historical/cultural context	• Political priorities and context. • Cultural acceptability. • Precedence (congruence with previous and future decisions). • Impact on innovation & research. • Impact on partnership & collaboration among healthcare stakeholders.	Assessments include a separate ethical analysis.

Drug Pricing model in Spain

Over the past few decades Spain has authorized and reimbursed multiple new oncology and hematology drugs with a high level of uncertainty about the clinical, economic, or social benefit that these new

medicines can provide [67]. A recent study [68] establishes that 261 new oncology and hematology drugs were authorized by the Spanish Agency of Medicines and Medical Devices (AEMPS) from January 2010 to September 2022 and half of their indications were reimbursed during this period. These drugs were normally considered innovative, so justifying high prices although their impact assessments were basically based on surrogate endpoints in clinical trials (CTs), such as progression-free survival (PFS) or minimal clinical benefit obtained in some CTs, and a lack of data on quality of life (QoL). The lack of robust evidence to justify the benefits of these new drugs has opened the debate about opportunity costs [69] in Spain of investing excessive resources in therapies with low or uncertain benefits avoiding the investment in alternative health interventions or pharmacotherapies with better outcomes and impacts.

In Spain, detailed information on how healthcare authorities define price and reimbursement conditions of new drugs is not available, and lack of predictability potentially driving to inconsistency between value and price has been described [70-71]. The Royal Legislative Decree 1/2015 (RDL 1/2015) of the Law on Guarantees and Rational Use of Medicines and Health Products [72] lists only a restricted set of criteria to be used by the Spanish National Health System (NHS) to establish prices of public funded medicines, mainly: (1) severity of the disease, (2) the specific needs of certain groups of people, (3) the therapeutic and social value of the medicine and incremental clinical benefit taking into account its cost-effectiveness, (4) the budget impact for a rational use of public resources in the healthcare system, (5) the potential access to lower-priced therapeutic alternatives, and (6) the innovation rate of the new medicine.

The reimbursement decision process starts after the European marketing authorization is formally adopted by the AEMPS [73]. Subsequently, a Therapeutic Positioning Report (TPR) is issued by REvalMed network [74] to inform about the added therapeutic value of the drug as compared to current therapeutic alternatives. The TPR includes a therapeutic evaluation from the AEMPS, including ESMO-MCBS [75] and some of them also adding pharmacoeconomic analysis [76]; although the full economic assessment is run by the General Directorate for Common Portfolio of the NHS and Pharmacy Services (DGCCSF) and a final technical revision is conducted by external experts and scientific societies appointed by the REvalMed network [77]. To note, no formal structures to assess the economic value of new therapies are in place [78], although even the Spanish Constitution states that public resources allocations must be equitable and efficient regarding healthcare related decisions [79].

The TPR, along with the submission dossier filed by the marketing authorization holder and DGCCSF own reports, are supposed to be the main sources for reimbursement decisions. The Inter-ministerial Committee on Pricing of Medicines and Healthcare Products (CIPM) is the body responsible for the final resolution of price and reimbursement conditions [73]. The CIPM decision is published as a listed price (not net price) and it includes a motivation in general terms, which are based on the criteria listed in the RDL 1/2015, but the information provided by the Ministry of Health (MoH) is not detailed enough to know how the value of the drug has been established. Additional reimbursement strategies are added to the price policies to reduce the budget impact of reimbursing new innovative oncology and hematology drugs. In Spain is increasing the use of risk sharing agreements, pay for performance payment schemes or expenditure ceilings for high priced drugs [80].

The historical and current legal and institutional framework in Spain requires the consideration of efficiency and equity criteria when deciding public resources allocations. As described in the literature [84] pharmaceutical related laws and strategic plans have been including broader assessment requirements, although at a slow and incomplete pace. The Medicines Law of 1990 and the National Health Service's Strategic Plan of Pharmaceutical Policy approved in 2004 moved towards the use of the principle of efficiency to decide on selective medicines reimbursement, although the later Law 29/2006 on Guarantees and Rational Use of Medicines and Health Products avoided clear references to the use of economic evaluation procedures in the pricing process. To note, the Order SCO/3422 on 2007 that revised the basket of common services of the Spanish National Health Service (NHS) included a clear reference to the efficiency principle when assessing "health techniques, technologies or procedures" [81]. Under the pressure of the economic crisis in 2010, the Interterritorial Council of the NHS agreed to include measures to strengthen the use of cost-effectiveness criteria in price and reimbursement decisions of new medicines while reinforcing the role of regional and national HTAb as scientific advisors. The Royal Decree-Law 9/2011 amended the Medicines Law to explicitly include therapeutic and social value of assessed drugs as general criteria for public reimbursement. Additionally, the amendments also referred to the need of the CIPM to consider evaluation reports on the Cost-Effectiveness of medicines and health products. These requirements were confirmed by the Royal Decree-Law 16/2012, that also included the need to provide a budget impact analysis for the consideration of the CIPM in the price and

reimbursement decisions. To note, the law also mentioned the creation of an Advisory Committee on the Pharmaceutical Provision of the NHS, created seven years later. As repeatedly highlighted by the Spanish National Commission of Markets and Competition [82-83] and the Court of Auditors [84] there is a lack of transparency in the procedures of price and reimbursement of medicines by the MoH and the CIPM, and little or no extensive value assessment (including efficiency evaluation) has been used so far in the public reimbursement process of medicines.

As seen, and unlike other countries, Spain has not an independent, professionalized, and centralized coordinated assessment agency like NICE in UK, TLV in Sweden, HAS in France, IQWiG in Germany, CADTH in Canada or PBAC in Australia, but multiple actors, such as the Ministry of Health, the AEMPS and the regions are involved in a coordinated network of evaluators.

The European Pharmaceutical Strategy

The upcoming implementation of the new European pharmaceutical strategy proposes a scenario of harmonization in the availability of medicines throughout Europe [85]. The strategy recognises that new medicinal products have high prices, but often also have an increasing uncertainty about their real-life effectiveness. The strategy also expresses concern about the rise in pharmaceutical expending as a growing part of healthcare budgets, and particularly on hospital spending that is increasing to already represent 20-30% of overall hospital expenditure. Considering that costs may condition that medicines are not always available, and the fact that there are still unmet medical needs, the strategy is explicit on the need to monitor and moderate the growth of pharmaceutical expenditure by the European Health Systems. In such context, high prices for innovative drugs and their overhead costs, which are generally expected by companies as a part of the return of investment, may be revisited and questioned, and to that purpose the strategy proposes to open political debates about the price of niche medicines and the "fair return" of industry contributions to research.

About the process for setting prices and deciding reimbursement, the strategy points out that there is a lack of transparency on the actual investment of companies (both for production costs and for R&D costs), but also a high degree of redundance with unjustified divergence in the assessments of added value of innovation by the evaluation bodies designed by the member states. National procedures may lead to

long lasting negotiations with companies, that at the end of the process result in huge differences in access to innovation across Europe. Such differences are particularly wide between countries with high income and partially privatised healthcare models as compared to those with low income and universal public coverage of the entire population. In any case, the result is heterogeneity and lack of consensus across Europe with respect to the access to innovative medicines, and several areas for improvement.

Despite the call for cohesion to avoid inequity in access, the strategy recognises legitimate concerns about the economic impact of innovation and confirms the exclusive competences of the member states regarding price setting. Yet, the strategy proposes and encourages a fluent European coordination and cooperation for the better decision making.

As a reflection, it is important to note that the access scenarios proposed by the strategy are focused on medicines, while ignoring other inequities in health care that do also exist, and likely may have higher impact on health outcomes. The strategy's focus on the procurement of medicines is only understood from an industrial perspective, rather than a health perspective, it does not recognize the differences in health care and financing models, and requires that the member states have to define the concept of affordability and the level of prices we can assume, even though it implicitly forces to set cross-cutting financial minimums intended for the acquisition of the same medicines in all countries. Together, both concepts represent a certain contradiction: while emphasising the need for homogeneous access to medicines throughout Europe, the role of national member states powers in terms of prices and financing is unquestioned. Yet, the European proposal includes centralised access models, in particular joint finalist funds raised between member states for certain situations, such as drugs for cancer, antimicrobials, and rare diseases. Such models may be difficult to fit in the setting of very different health systems, gross domestic product, and heterogeneous drug prices.

The HTA regulation to be deployed in January 2025 [86] captures the strategy’s proposals through a permanent framework for joint work in technology assessment across Europe, with unification of procedures, centralized joint clinical assessments, scientific consultations of access to joint medicines, and tasks to harmonize the identification of emerging health technologies, as well as favouring other voluntary cooperation mechanisms. The new regalement intends to replace the currently voluntary coordination through the network of national authorities (HTA Network) and to collect the learnings form the Joint

Actions EUnetHTA's project, by defining a framework for permanent collaboration. The new framework covers joint clinical assessments, joint scientific consultations, the identification of emerging health technologies, and voluntary cooperation. This will require that every member state sets the structures and mechanisms necessary to be represented in the joint technology assessments, and this likely may favour and accelerate the creation of national HTA bodies in those countries that still do not have formal structures. There is an increasing demand to set up a similar health technology agency in Spain, currently not available, organized as a fully professionalized and independent entity aimed to appraise innovative medicines and to produce health technology reports. Also, the expectation is that reports may be underpinned on a broad assessment concept, that would keep the central pillars of efficacy, safety, and clinical comparability, while adding other key dimensions such as efficiency or equity [87]. In fact, the EUnetHTA Joint Action identified nine reference domains, four clinical (clinical context, characteristics of the intervention, comparative safety, and comparative effectiveness) and five non-clinical (economic, ethical, organizational, social, and legal domains) that should be considered in evaluations. The resulting reports should then be (part of) the basis for national pricing and reimbursement decisions and contribute to the centralized assessments at the European level.

Pricing of cancer drugs in Spain

In the last decade, around half of all pharmaceutical innovation has occurred in onco-haematology, which as a therapeutic area has led globally both the incorporation of new chemical entities into the market, but also has led a substantial part of the pharmaceutical expenditure growth [88].

Based on recent data released by the MoH in 2021 [93], cancer drug costs represented 16,9% of the global pharmaceutical Spanish public budget, and the cost of cancer drugs at hospital level grew by 105,9% since 2016. The huge budget impact of cancer drugs for the Spanish NHS is not accompanied by more clarity about the value provided by innovative cancer drugs, nor using a methodology allowing to know and track how value has been translated into "fair prices". Only partial assessment of the link between clinical benefits and prices has been recently conducted in Spain [68], concluding that anti-cancer agents approved and reimbursed in Spain between 2010 and 2022 demonstrated substantial clinical benefit (according to ESMO-MCBS scores) compared to those that were not reimbursed, but the clinical benefit provided was

often modest in terms of overall survival gain, and a high proportion of the reimbursed indications did not meet a substantial clinical benefit threshold. Besides the lack of analysis of the consistency between the magnitude of benefit on clinical outcomes and price, the evidence available for the Spanish drug reimbursement context confirms the need to add additional dimensions to assess the added drug value, such as the quality of clinical trials, selection of endpoints and comparators, patient reported outcomes, pharmacoeconomic analysis, social value, or impact on the way healthcare is delivered (e.g., efficiency gains) [68].

The context of increasing authorization of new oncology and hematology therapies considered innovative that are reimbursed at exponential high prices, along with the benefit uncertainty in terms of survival gain, improvement of QoL or impact on the efficiency of healthcare delivery, is identified as a high risk for the economic sustainability of the healthcare systems in Spain [84]. While several authors have assessed the link between clinical benefits and reimbursement decisions [68_89_90], there is a general perception that the procedures for pricing and decision making have room to improve transparency, as well as that the criteria applied to quantify the added value and to support pricing and reimbursement decisions may be too narrow, focused on a general clinical positioning and budgetary impact [83]. Thus, there are a lack of information on the current procedures followed by the MoH and on whether the prices are capturing the multidimensional value of new onco-hematologic drugs in Spain.

Hypothesis

- For onco-hematologic drugs authorized in Spain between 2017 and 2019, inclusive, the explicit criteria for the evaluation of pharmacological innovation do not correlate with the price assigned, annual cost of treatment, nor decision to reimburse by the NHS.

Objectives

Primary objective

- For onco-hematologic drugs authorized in Spain between 2017 and 2019, inclusive, to identify the criteria commonly used in estimating the value of pharmacological innovation and in determining the prices of innovative onco-hematologic drugs, in particular those related to safety, efficacy, or efficiency as obtained in pivotal clinical trials, and additional aspects of therapeutic necessity, adequacy of the treatment, or characteristics of the target population, and to apply these criteria to the appraisal of the drugs, in order to analyze their association with the assigned prices and financing decisions.

Secondary objectives

- To describe the pricing and reimbursement decisions made regarding innovative onco-hematologic products authorized in a period of 3 years in Spain.
- To identify the criteria that are determinant of the price and/or the decision and reimbursement conditions among those generally used in estimating the value of the pharmacological innovation.
- To analyze the consistency of price decisions based on the criteria used to estimate the value of pharmacological innovation, in terms of correlation and coherence.
- To propose alternatives to current methodologies for determining the price and financing conditions that reflect the clinical value of the drugs analyzed, which may be applied in a traceable and predictable manner.

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Chapter 2: Concordance of EUnetHTA and MCDA-EVIDEM assessment framework criteria

Abstract

Background

Heterogeneity in drug access throughout Europe may be influenced by differences in drug-assessment strategies. The EUnetHTA's assessment core model (EUnetHTA-core) and the EVIDEM's multicriteria framework are reference methodologies in this context, the latter including a wider compromise between non-contextual and contextual criteria. Compliance of 37 European Health Technology Assessment bodies (HTAb) with EUnetHTA-core has been reported, but the use of EVIDEM by this HTAb is still unknown.

Methods

To describe the uptake and use of multicriteria approaches to evaluate drug value by European HTAb using EVIDEM as reference framework, a multicriteria framework was obtained based on EVIDEM model. The criteria used for drug appraisal by HTAb was extracted from the EUnetHTA report, and completed through search of websites, publications and HTAb reports. Use of EVIDEM assessment model in 37 European HTAb has been described semi-quantitatively and summarized using an alignment heatmap.

Results

Aligned, medium or misaligned profiles were seen for 24,3%, 51,4% and 24,3% of HTAb when matching to EVIDEM dimensions and criteria was considered. HTAb with explicit responsibilities in providing specific advice on reimbursement showed more aligned profiles on contextual and non-contextual dimensions.

Conclusions

EUnetHTA's core model is limited in assessing medicines while EVIDEM's framework provides contextual dimension used by some HTAb in Europe that can be escalated to other agencies. Most of the 37 European HTAb have room to broaden their contextual assessment tools, especially when social and medical perception of need requires to be explicit to support payer's decision on reimbursement.

Key words: Health Technology Assessment, Multicriteria Assessment Methods, Reimbursement Systems

Introduction

One of the major cost drivers in the European healthcare systems is the pharmaceutical 'innovation'; even considered more relevant than demographics [1]. At the same time, it is also recognized as one of the main contributors to the improvement of the population health status [2].

According to the most recent study from the OECD [3], pharmaceutical expenditure accounts for a percentage that range between 11.4% (UK) and 19.1% (Spain) of total healthcare expenditure across the five largest European drug markets (France, Germany, Italy, Spain, and the UK). Specifically, the oncological and hematological drugs are leading the budget impact related to pharmaceutical innovation. The impact is driven by the expansion of multiple new indications normally based on a molecular definition that restricts the population to be treated and the drug ends up being designated as orphan-like medicines [4]. As estimated by a recent study [5-6], the healthcare expenditures on cancer in the European Union member states represented roughly 6% of total healthcare expenditures. The steady increase of oncology costs is aligned with the disease increasing incidence, the progressive reduction of mortality as well as high prices, in contrast with the less robust evidence data on outcomes [7].

A recent study [5] estimated that 40% of the new orphan drugs authorized in Europe are related to rare neoplastic disorders, and compared to non-oncologic indications, the authorization is received at more advance stages of the clinical development and recognizing a higher potential clinical benefit. From 2009 to 2013, only 35% the 68 oncology indications approved by the EMA showed a significant prolongation of survival and only 10% showed an improvement in quality of life at the time of market approval. The magnitude of the benefit on overall survival ranged from 1.0 to 5.8 months (median 2.7 months). In the subsequent post marketing period (3.3 years later) there was evidence for extension of life in 7% of the previous authorizations and reported benefit on quality of life in 11% of the cases [8].

Occasionally, when the drug can cover clinical unmet needs with poor prognosis, the regulators trend to accept less and poorer evidence and include especial approvals, such as conditional approval related to further of adequate risk benefit rate in real world, after commercialization, or approval under exceptional circumstances when this may not be achieved, to ensure an earlier access to market. As described recently [9] the potential benefit of patients' early access to new medicines in areas of high unmet medical need, and based on initial data only, have relevant implications in terms of medical and economic costs (opportunity costs of using alternative more efficient treatments available for patients). Several initiatives have been developed in Europe to address these challenges of funding premium priced products related

to clear medical unmet needs but with limited evidence [10]. New access management models of these drugs have been promoted across Europe recently, especially for advance therapies, orphan drugs and medicines for cancer, and including innovative access schemes as value-based pricing, conditional reimbursement schemes or risk sharing approaches [11]. Despite the smooth increase of these new access schemes, the number of outcome-based solutions is still very limited being the lack of a systematic and harmonized value assessment methodology one of the main limitations [12].

Beyond the general awareness among healthcare authorities to ensure "value for money", or the link between price and social or clinical value of the pharmaceutical innovation [13], the reimbursement process and value assessment of drugs is still an open debate in Europe [14]. Several methods have been developed to assess the value of drugs and set meaningful prices affordable to health-care systems [15]. These methods are normally based on the clinical benefits of the drugs and partially on value-based pricing (e.g., cost-effectiveness analysis). However, there is neither a consensus nor a European harmonization related to drug-pricing systems and, based on a comparative international policy analysis, value-based approaches to determine the prices of innovative products are diverse [16]: including the implicit clinical value of QALYS, mainly used in UK, Sweden or Australia, or the value classification based on innovation scales (used in France, Italy, Germany, Austria, Canada or Japan) [17]. Normally new drugs classified as an innovative medicine are reimbursed at a higher price than the current therapeutic alternatives; although the amount, type, and methodology to set the premium is normally veiled by the healthcare authorities [18].

In Europe, the EUnetHTA was set up in 2006 and includes all EU Member States to provide strategic guidance and policy orientation on the assessment of health technologies (including drugs), by developing policy papers and discussing areas of potential collaboration. During the last decade the network has focused the efforts on the development of common methodologies, piloting and producing joint early dialogues and HTA joint assessment reports, as well as developing and maintaining common tools [19]. One of the most relevant tools developed by the network is the HTA Core Model for Rapid Relative Effectiveness Assessment (REA) [20]. The Model is a methodological framework for the collaborative production and sharing of HTA information that defines the content elements to be considered in an HTA and it enables standardized assessment reporting across Europe. Because of the objective of the framework is to share commonly required elements of information, only information that is considered both important and transferable is collected. The model brings a standardized framework that allows a

common comparison of the drivers that lead pricing and reimbursement decisions among different European authorities.

HTA Network approach is focused on technical aspects while methods to support alignment of decisions with the compassionate impetus of healthcare systems is lacking [21]. In many countries, healthcare authorities are including a broader approach to assess the pharmaceutical products (especially in therapeutic areas like oncology and rare diseases) [22]. EVIDEM [23] was developed based on an analysis of the foundations of healthcare systems, the reasoning underlying decisions and fair processes, and has become a reference for multicriteria decision approaches in this setting. It includes the concept of reflective multicriteria assuming decision-makers are guided by a generic interpretative frame rooted in the baseline values of the healthcare systems, drawing on several domains of knowledge including healthcare ethics, evidenced-based medicine, health economics or health technology assessment approaches. A multicriteria analysis provides an effective approach to increase the legitimacy of decisions. Beyond a tool, reflective multicriteria pioneered by EVIDEM is geared to transform the vision of the value of healthcare interventions and how they might contribute to relevant, equitable and sustainable healthcare systems. EVIDEM can be used to compare various healthcare interventions and prioritize its implementation using a performance matrix underpinned in the several dimensions and criteria defined by the framework [22].

EVIDEM criteria overlap with EUnetHTA-core except for 4 non-contextual and 3 social criteria, which are absent or partially included in the EUnetHTA framework. Inversely, 2 EUnetHTA criteria are absent in the EVIDEM framework [Table 1].

Although multicriteria EVIDEM approach is now applied by several healthcare authorities [24], especially when the social and medical perception of need requires a more holistic assessment framework to support the payer's decision, a formal and systematic comparison of EUnetHTA's and EVIDEM's methodological frameworks and whether European HTAb are aligned with the EVIDEM methodology standards is lacking [25]. Since EUnetHTA and EVIDEM frameworks differ in a substantial number of criteria, it is of interest to know the extent of compliance with EVIDEM framework of HTAs as an additional way to explore potential reasons of assessment discrepancies. Despite the compliance of 37 European HTAb with using the supportive criteria for decision making proposed in the EUnetHTA-core framework has been previously reported [20], whether these HTAb do also comply with the wider EVIDEM multicriteria is unknown.

Thus, the main aim of this study is to describe the uptake and use of multicriteria approaches to appraise drug value by 37 European HTAb, using EUnetHTA and EVIDEM as reference frameworks.

Methods

A quantitative validation of the degree of alignment with the EUnetHTA's standard framework of 37 European HTAb from 28 countries was done, based on a previous qualitative analysis conducted by the European Commission [20] and an additional thorough search of websites, publications and reports of HTAb. The criteria used for appraisal by the different HTAb were identified and classified, and the matching with the criteria described in the EVIDEM methodological framework were described semi-quantitatively using a heatmap of alignment.

The items reported included those criteria in the HTA Core Model, namely: REA of pharmaceuticals, EUnetHTA methodological guidelines [26] and procedure descriptions [27-28]. Also, criteria related to the types of technologies assessed, the administrative level (national, regional, institutional) and the formal background (legislation, formal agreement, internal guideline) of certain methodological requirements were also used.

An updated version of EVIDEM framework (v.10) was analyzed in order to assess how the dimensions and criteria included in the EUnetHTA methodological framework fitted within the EVIDEM's methodological framework.

The EVIDEM framework includes 13 non-contextual dimensions and 6 contextual dimensions [Table 1]. The non-contextual dimensions (EVIDEM core-model) include normative aspects combined with the description of the technical knowledge available. Contextual dimensions tailor the framework to the context of decision-making.

An HTAb heatmap was developed, where heatmap categories were generated for each EVIDEM's dimension using as a source the mentioned criteria in the EUnetHTA's report [20], webs and reports available from the different HTAb analyzed. The contribution (weight) of each mentioned criterion to the final heatmap's score by dimension was equal and proportioned to the number of criteria by dimension described in Table 1. Only when the mentioned criteria were not fully aligned with the EVIDEM's criteria, the mention was weighted by 50% of contribution:

Heat Score = [(∑# criteria mentioned by dimension)/ (∑# total criteria by dimension)] *100

Descriptive statistics (mean, standard deviation, percentiles) were used to summarize the data and 95% confidence interval for each dimension and HTAb, and conditional formatting was used to automatically color code each cell using Microsoft Excel (Windows Office 365) so that graded colors were used with green coding for highest alignment (100) and red for lowest alignment (0). Values outside the interquartile range were used to assess alignment with the EVIDEM's model [29]. HTAbs with and average heat score above the 75th percentile was considered "Aligned" with the EVIDEM model, and those below 25th percentile were considered "Misaligned". The rest were classified as "Medium" in terms of EVIDEM model's alignment.

Results

Most of the non-contextual criteria of EVIDEM are overlapped with the core model of EUnetHTA, except for the type of prevention benefits, non-medical comparative cost consequences, systematic use of expert consensus and use of clinical guidelines to define state-of-the-art, which are not or partially included on the EUnetHTA's framework [Table 2]. Regarding contextual criteria, the assessment of the system capacity and appropriate use of intervention is the most aligned criteria between both frameworks, followed by the political/historical/cultural context assessment, the mandate and scope of the healthcare system, the special population priorities, and equity on access criteria. Other social criteria (stakeholders management, conflict of interest assessment or environmental impact assessment) are not reflected in the EUnetHTA's framework. A systematic general description of the assessed technology and the request of clarification of the assessment process (guidelines and legislation) are key aspects considered by the EUnetHTA analysis that are not explicitly included in the EVIDEM framework.

Most of the non-contextual dimensions (such as disease severity, size of affected population, unmet needs, comparative effectiveness, comparative safety/tolerability or type of therapeutic benefit) show consistently high rates among the HTAb (mean above 85% and standard deviation below 16%); other non-contextual dimensions (type of preventive benefit, comparative non-medical costs, expert consensus) and relevant contextual dimensions (such as population priorities, common goal, environmental impact, system capacity or political/historical/cultural context) are systematically rated low.

All HTAb address consistently the health problem and current use of technology, technical characteristics, clinical effectiveness, and safety criteria, which are included in the EUnetHTA core model. Choices on comparator, methodology of comparison, endpoints and methods of evidence search and synthesis, are

consistently aligned. On the contrary, non-clinical domains, assessment approaches, methodology, modelling algorithms and data are consistently dis-aligned.

None of the local HTAb had high heat scores with regards to the use of contextual criteria [Table 2]. Considering alignment to EVIDEM-driven assessment framework, three patterns of HTAs emerged: "Aligned", "Medium" and "Misaligned" [Table 4].

9 agencies in Bulgary, Hungary, Italy, Malta, Slovakia, Spain, Sweden, and UK showed an "Aligned" profile (average heat score above the 75th percentile) with a consistent alignment on non-contextual dimensions and significantly high alignment scores on political/historical/cultural context, system capacity and appropriate use of the intervention.

Most HTAb (19/37; 51%) showed a "Medium" alignment profile. Alignment rates for non-contextual criteria were mainly high (e.g., patient perceived health and quality of evidence dimensions) in these HTAb, and other contextual dimensions (such as the mandate and scope of the healthcare system, system capacity and appropriate use of the intervention) were rated high. On the contrary, population priorities and access dimension systematically rated below 50%, except for AEMPS.

In 9/37 (24%) HTAb the profile was considered "Misaligned", with low scores on alignment (average score below 25th percentile) in dimensions such as patients perceived health methods, cost-consequence analysis (cost of intervention and other medical costs) and quality of the evidence. Considering the non-contextual perspective, the German G-BA and the NIPH in Norway show high scores focused and limited to the technical comparison of alternatives (effectiveness, safety and quality of evidence assessment). From the contextual perspective, all the HTAb of this group rated low on the mandate and scope of the healthcare system, population priorities on access, system capacity, appropriate use of the interventions and political/historical/cultural context.

HTAb with explicit responsibilities in providing specific advice on pricing and reimbursement (normally regional agencies in countries with more than one HTAb in place, such as Belgian KCE, German IQWIG, Irish HIQA, Italian UCSC, Portuguese INFARMA, Slovakian UHIF, Spanish SESCS or Swedish SBU) showed higher and similar scores on contextual and non-contextual dimensions.

Discussion and conclusions

The alignment between EVIDEM and EUnetHTA methodological frameworks is consistently high, especially when assessing domains related to health problem description, current use of the technology, technical characteristics, clinical effectiveness, and safety. However, non-contextual dimensions of the EVIDEM framework and the EUnetHTA core model are consistently misaligned.

The main EUnetHTA core model criteria, such as clinical effectiveness, safety conditions, health problem description and current use of technology; are consistently addressed by all HTAb. As previously reported [19] the institutions go only partially beyond these criteria, and it is normally dependent on the topic of assessment. For those European HTAb directly advising on price and reimbursement decisions, the reported criteria used to support their decisions show a more balanced alignment between both methodological approaches. That conclusion could explain why in many cases, the subnational HTAb in those countries with multiple agencies, are the ones showing a balanced profile among contextual and non-contextual dimensions.

EVIDEM provides a generic interpretive frame (MCDA – Multi-Criteria Decision Analysis – reflective grid) that can be used to elicit individual values and facilitate deliberations through a common structure that includes interpretive scores (quantitative criteria), qualitative impacts (qualitative criteria) as well as narrative comments (all criteria) [23]. EVIDEM framework was designed to minimize the limitations of the deliberation process by ensuring that: generic assessment criteria (either quantitative or qualitative) are included; evidence relevant to each criterion is made available through an efficient synthesis methodology; and face validity is checked at each step of the process (weights, scores and corresponding narratives, aggregated measures). EVIDEM framework is sufficiently flexible to be adapted to the local assessment context, although it also requires consistency in the identification of a set of criteria, scoring scale and weights when assessing a broad range of competing interventions in a specific local context [31-32].

A holistic approach is required to consistently assess the social and medical needs to support payer's decision on prices and reimbursement conditions of certain drugs, such as disruptive innovations or orphan drugs, broadening the need of using EVIDEM-like contextual assessment tools by European HTAb.

Tables and figures

Table 1: EVIDEM and EUnetHTA criteria correspondence

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
NON-CONTEXTUAL CRITERIA		
Disease severity	• Effect of disease on life-expectancy. • Effect of disease on morbidity (includes disability and function). • Effect of disease on patients' quality of life. • Effect of disease on caregivers' quality of life.	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA - SEVERITY DEFINITION.
		Assessments include a description of the health problem and current use of technology.
Size of affected population	• Prevalence. • Incidence.	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA – POPULATION.
		Assessments include a description of the health problem and current use of technology.
Unmet needs	• Unmet needs in efficacy. • Unmet needs in safety. • Unmet needs in patient reported outcomes. • Patient demand.	Assessments include a description of the health problem and current use of technology.
		Evidence where systematic search strategies are applied (HEALTH PROBLEM - CURRENT TECHNOLOGY USE).
Comparative effectiveness	• Magnitude of health gain. • Percentage of the target population expected to achieve the anticipated health gain. • Onset and duration of health gain. • Sub-criteria for the measure of efficacy specific to the therapeutic area.	The comparator is supported by evidence on its efficacy profile for the respective clinical indication/population.
		Assessments analyze clinical effectiveness / efficacy (added therapeutic value).
		Evidence where systematic search strategies are applied (EFFICACY-EFFECTIVENESS).
	• Adverse events. • Serious adverse events.	The comparator is supported by evidence on its safety profile for

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
Comparative safety/tolerability	• Fatal adverse events. • Short-term safety. • Long-term safety. • Tolerability.	the respective clinical indication/population.
		Assessments analyze safety.
		Evidence where systematic search strategies are applied (SAFETY).
Comparative patient-perceived health	• Improvement in health-related quality of life. • Impact on autonomy. • Impact on dignity. • Convenience / ease of use / mode & setting of administration.	QALYs applied.
		Assessments analyze patient aspects.
		Assessments include a separate ethical analysis.
		Evidence where systematic search strategies are applied (PATIENT ASPECTS).
Type of preventive benefit	• Eradication, prevention, reduction in disease transmission, reduction in the prevalence of risk factors). Public health perspective.	Not available.
Type of therapeutic benefit	• Symptom relief, prolonging life, cure.	Assessments include a description of the health problem and current use of technology.
Comparative cost consequences – cost of intervention	• Net cost of intervention. • Acquisition cost. • Implementation/ maintenance cost.	Assessments analyze cost, budget impact, or include economic evaluation.
Comparative cost consequences – other medical costs	• Impact on primary care expenditures. • Impact on hospital care expenditures. • Impact on long-term care expenditures.	Assessments analyze cost, budget impact, or include economic evaluation.
Comparative cost consequences – non-medical costs	• Impact on productivity. • Financial impact on patients. • Financial impact on caregivers • Costs to the wider social care system.	Assessments analyze social aspects.
Quality of evidence	• Validity (study design, agreement among studies).	Sources of evidence included as relevant clinical evidence for the clinical assessment (1-

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
	• Relevance (population, disease stage, outcomes). • Completeness of reporting (uncertainty, conflicting results across studies, limited number of studies). • Type of evidence.	randomized controlled; 2- Nonrandomized prospective; 3- Other observational; 4- Expert Opinion).
		Methodology requirements for the clinical assessment compared to the HTA Core Model for REA.
		Formal tools or algorithms for evidence grading applied.
		The GRADE approach in routine use.
		Plan for how evidence will be synthesized (e.g., evidence tables, meta-analysis, qualitative synthesis).
		Standard forms or tables available for evidence analysis and synthesis.
		Evidence analysis include surrogate endpoints, composite endpoints, PROs, HRQoL measures, indirect comparisons, meta-analysis, relevant group sub-population, key deficiencies in available data, transferability issues, summary of findings.
		Sources of evidence on the technology: A. scientific journal publications, B. grey literature (e.g., published reports), C. unpublished data, D. register data, E. administrative data, F. manufacturer data.
		Confidential data from manufacturers accepted.
Expert consensus/clinical practice guidelines	Current consensus of experts on what constitutes state-of-the-art practices (guidelines).	Not available.

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
CONTEXTUAL CRITERIA		
Mandate and scope of the healthcare system	Alignment with healthcare plans/systems.	Circumstances where HTA reports are provided.
Population priorities and access.	• Current priorities of health system (e.g., low socioeconomic status; specific age groups). • Special populations (e.g., ethnicity). • Remote communities. • Rare diseases. • Specific therapeutic areas.	Assessments analyze social aspects.
Common goal and specific interests	• Stakeholder pressures. • Stakeholders' barriers. • Conflict of interest.	Assessments analyze social aspects.
Environmental impact	• Environmental impact of production. • Environmental impact of use. • Environmental impact of implementation. • Environmental impact of production. • Environmental impact of use. • Environmental impact of implementation.	Not available.
System capacity and appropriate use of intervention	• Organizational requirements (e.g., process, premises, equipment). • Skill requirements. • Legislative requirements. • Surveillance requirements. • Risk of inappropriate use. • Institutional limitations to uptake.	Assessments include a separate ethical analysis. Assessments analyze legal aspects. Assessments analyze organizational aspects.
Political/historical/cultural context	• Political priorities and context. • Cultural acceptability. • Precedence (congruence with previous and future decisions). • Impact on innovation & research. • Impact on partnership & collaboration among healthcare stakeholders.	Assessments include a separate ethical analysis.

Table 2: HTAb heatmap of coincidence with EVIDEM framework

COUNTRY	Agency	Disease severity	Size of affected population	Unmet needs	Comparative effectiveness	Comparative safety/tolerability	Comparative patient-perceived health / PRO	Type of preventive benefit	Type of therapeutic benefit	Comparative cost consequences – cost of intervention	Comparative cost consequences – other medical costs	Comparative cost consequences – non-medical costs	Quality of evidence	Expert consensus/clinical practice guidelines	Mandate and scope of the healthcare system	Population priorities and access	Common goal and specific interests	Environmental impact	System capacity and appropriate use of intervention	Political/historical/cultural context
Austria	HVB	100	100	100	100	100	25	0	100	50	50	0	100	0	60	30	0	0	13	0
	LBI	75	75	100	100	100	13	0	100	50	50	10	44	0	60	30	10	0	13	30
Belgium	KCE	100	100	100	100	100	50	0	100	50	50	10	89	0	60	30	10	0	40	30
	INAMI	100	75	100	100	83	50	0	100	50	50	10	100	0	60	30	10	0	27	30
Bulgary	NCPHA	100	100	100	100	83	63	0	100	100	100	10	22	0	60	30	10	0	40	30
Croatia	AAZ	100	100	100	100	100	38	0	100	50	50	10	78	0	30	30	10	0	40	30
Czech R.	SUKL	100	100	100	100	100	50	0	100	50	50	0	56	0	60	0	0	0	0	0
Estonia	UoT	100	100	100	100	100	38	0	100	100	100	0	44	0	60	0	0	0	13	0
Finland	FIMEA	75	75	100	100	100	50	0	100	100	100	10	50	0	30	30	10	0	40	30
France	HAS	100	100	100	100	100	50	0	100	50	50	10	56	0	60	30	10	0	40	30
Germany	G-BA	50	50	75	100	100	25	0	50	0	0	0	83	0	60	0	0	0	0	30
	IQWIG	75	75	100	100	100	63	0	100	100	100	0	67	0	60	0	0	0	40	0
Hungary	OGYEI	100	100	100	100	100	63	0	100	100	100	10	89	0	60	30	10	0	27	30
Ireland	HIQA	100	100	100	100	100	63	0	100	50	50	10	89	0	30	30	10	0	40	30
	NCPE	75	75	100	100	100	50	0	100	100	100	0	33	0	60	0	0	0	0	0
Italy	AIFA	75	75	100	100	100	38	0	100	100	100	0	33	0	60	0	0	0	13	0
	RER	100	100	100	100	100	25	0	100	0	0	0	56	0	30	0	0	0	13	0
	UCSC	100	100	100	100	100	50	0	100	100	100	10	67	0	30	30	10	0	40	30
Latvia	NVD	75	100	50	100	83	13	0	50	100	100	0	44	0	60	30	20	0	13	0
Malta	MOH	100	100	100	100	83	75	0	100	100	100	10	33	0	30	30	10	0	40	30
NL	ZIN	100	100	75	100	100	88	0	100	50	50	10	44	0	60	30	10	0	40	30
Poland	AOTMiT	100	100	100	100	100	38	0	100	50	50	10	67	0	60	30	10	0	27	0
Portugal	INFARMED	50	75	50	83	67	50	0	50	100	100	10	100	0	60	30	10	0	40	30
Slovakia	MOH	75	100	100	100	100	25	0	100	0	0	0	28	0	60	0	0	0	0	0
	UHIF	75	75	100	100	100	75	0	100	100	100	10	89	0	30	30	10	0	53	30
Slovenia	JAZMP	50	50	100	100	50	25	0	100	100	100	10	33	0	60	30	10	0	13	30
Spain	AEMPS	50	50	100	100	100	75	0	100	100	100	20	44	0	60	60	20	0	40	30
	AETSA	100	100	100	100	100	63	0	100	50	50	10	44	0	60	30	20	0	40	30
	SESCS	100	100	100	100	100	88	0	100	100	100	10	100	0	60	30	10	0	53	60
	AQUAS	75	75	100	100	100	75	0	100	100	100	0	67	0	60	30	0	0	13	30
Sweden	SBU	100	100	100	100	100	100	0	100	50	50	10	67	0	30	30	10	0	53	60
	TLV	100	100	100	100	50	25	0	100	100	100	0	67	0	60	0	0	0	27	0
UK	NICE	75	75	100	100	100	38	0	100	100	100	10	72	0	60	30	10	0	13	0
	SMC	100	100	100	100	100	75	0	100	100	100	10	50	0	60	30	10	0	13	0
	AWTTC	100	100	100	100	67	63	0	100	100	100	10	89	0	30	30	10	0	13	0
Norway	NIPH	75	75	100	100	100	50	0	50	50	50	0	83	0	30	30	10	0	13	30
	NOMA	100	100	100	100	67	75	0	100	100	100	10	89	0	30	30	10	0	13	0

Table 3: EVIDEM heat score by dimension

Criteria	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	25th Percentile	75th Percentile
Disease severity	87.2	17.3	50.0	100.0	75.0	100.0
Size of affected population	88.5	16.2	50.0	100.0	75.0	100.0
Unmet needs	95.9	12.5	50.0	100.0	100.0	100.0
Comparative effectiveness	99.5	2.7	83.3	100.0	100.0	100.0
Comparative safety/tolerability	92.8	14.5	50.0	100.0	100.0	100.0
Comparative patient-perceived health / PRO	51.7	21.9	12.5	100.0	37.5	62.5
Type of preventive benefit	0.0	0.0	0.0	0.0	0.0	0.0
Type of therapeutic benefit	94.6	15.7	50.0	100.0	100.0	100.0
Comparative– cost of intervention	74.3	32.5	0.0	100.0	50.0	100.0
Comparative – other medical costs	74.3	32.5	0.0	100.0	50.0	100.0
Comparative – non-medical costs	6.8	5.3	0.0	20.0	0.0	10.0
Quality of evidence	64.0	23.4	22.2	100.0	44.4	83.3
Expert consensus/clinical practice guidelines	0.0	0.0	0.0	0.0	0.0	0.0
Contextual criteria	0.0	0.0	0.0	0.0	0.0	0.0
Mandate and scope of the healthcare system	51.1	13.9	30.0	60.0	30.0	60.0

Criteria	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	25th Percentile	75th Percentile
Population priorities and access	23.5	14.4	0.0	60.0	30.0	30.0
Common goal and specific interests	7.8	5.8	0.0	20.0	0.0	10.0
Environmental impact	0.0	0.0	0.0	0.0	0.0	0.0
System capacity & appropriate use of intervention	25.9	16.3	0.0	53.3	13.3	40.0
Political/historical/cultural context	19.5	17.6	0.0	60.0	0.0	30.0
GLOBAL	47.9	5.8	31.2	60.5	44.7	51.25

Table 4: EVIDEM heat score by HTAb

HTAb	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	Degree of Alignment with EVIDEM model
HVB	46.4	44.3	26.5	66.3	Medium
LBI	43.0	37.8	26.0	60.0	Misaligned
KCE	50.9	40.2	32.9	69.0	Medium
INAMI	48.8	39.0	31.2	66.3	Medium
NCPHA	52.4	42.1	33.5	71.3	Aligned
AAZ	48.3	40.0	30.3	66.2	Medium
SUKL	43.3	44.0	23.5	63.0	Misaligned
UoT	47.8	46.8	26.7	68.8	Medium
FIMEA	50.0	40.2	31.9	68.1	Medium
HAS	49.3	39.2	31.6	66.9	Medium
G-BA	31.2	36.8	14.6	47.7	Misaligned
IQWIG	49.0	44.0	29.2	68.8	Medium
OGYEI	55.9	43.3	36.4	75.4	Aligned
HIQA	50.1	40.5	31.9	68.3	Medium
NCPE	44.7	45.0	24.4	64.9	Misaligned
AIFA	44.7	44.5	24.7	64.7	Medium
RER	36.2	45.1	15.9	56.5	Misaligned
UCSC	53.3	42.6	34.2	72.5	Aligned
NVD	41.9	39.5	24.2	59.7	Misaligned

HTAb	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	Degree of Alignment with EVIDEM model
MOH	52.1	42.3	33.1	71.1	Misaligned
ZIN	49.3	38.9	31.9	66.8	Medium
AOTMiT	47.0	41.0	28.6	65.5	Medium
INFARMED	45.3	35.0	29.5	61.0	Medium
MOH	34.4	44.1	14.6	54.2	Aligned
UHIF	53.9	41.4	35.3	72.5	Aligned
JAZMP	43.1	38.3	25.9	60.3	Misaligned
AEMPS	52.5	38.4	35.2	69.7	Aligned
AETSA	49.8	38.9	32.4	67.3	Medium
SESCS	60.5	43.2	41.1	80.0	Aligned
AQUAS	51.3	42.5	32.1	70.4	Medium
SBU	53.0	40.9	34.6	71.4	Aligned
TLV	46.4	45.2	26.1	66.7	Medium
NICE	49.2	42.6	30.0	68.3	Medium
SMC	52.4	44.8	32.3	72.5	Aligned
AWTTC	50.6	44.3	30.7	70.5	Medium
NIPH	42.3	36.5	25.9	58.8	Misaligned
NOMA	51.2	44.6	31.2	71.2	Medium
GLOBAL	47.9	5.8	46.0	49.7	Medium

Figure 1: EVIDEM alignment score by dimension

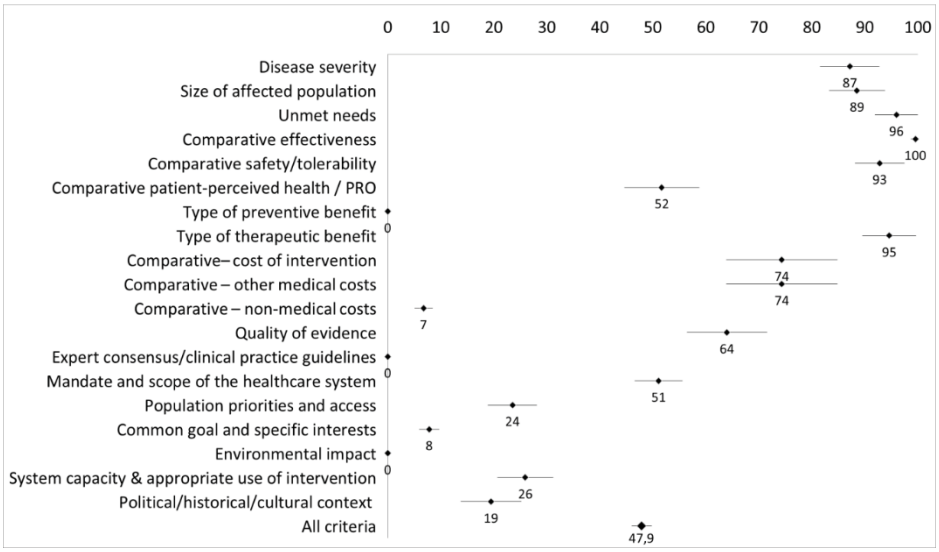
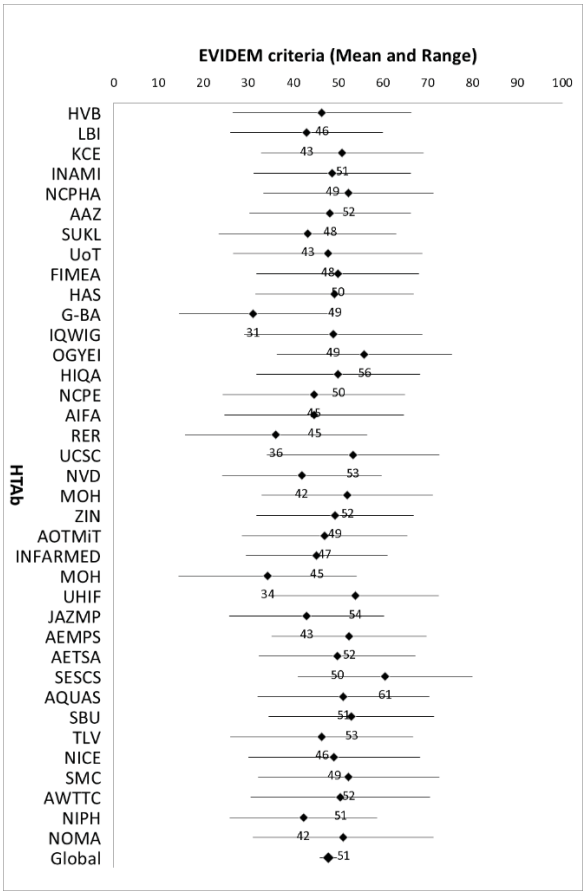


Figure 2: EVIDEM alignment score by HTAb



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Chapter 3: Onco-hematologic products price analysis

Abstract

Background

Even using well-stablished technology assessment processes, the basis of the decisions on drug price and reimbursement are sometimes perceived as poorly informed, and sometimes may be seen as disconnected to value. The literature remains inconclusive about how HTAb should report the determinants of their decisions. This study evaluates the relationship between oncology and hematology drug list prices and structured value parameters at the time of reimbursement decision in Spain.

Methods

The study included all new onco-hematological products (22) with a first indication authorized between January 2017 and December 2019 in Spain, and pricing decisions published until October 2022. For each product 56 contextual and non-contextual indicators reflecting the structured multiple criteria decision analysis (MCDA) - EVIDEM framework were measured. The relationship between prices and the MCDA-EVIDEM framework was explored using univariate statistical analyses.

Results

Higher prices were observed when the standard of care included combinations, if there were references to long-lasting responses, for fixed duration of treatment as compared to treatment until progression and for lower frequencies of administration; lower prices for oral route as compared to other routes of administration. Statistically significant associations were observed between prices and the median duration of treatment, the impact on patient's autonomy, the easiness to use the drug, as well as the recommendation of experts.

Conclusions

The study suggests that indicators related to the type of standard of care, references to long-lasting responders, the convenience in the use of the drug and the impact of treatment on patient's autonomy as well as contextual indicators such as the existence of previous clinical consensus are drivers to set oncology drug prices in Spain. The implementation of MCDA-EVIDEM methodologies may be useful to capture the influence on pricing decisions of additional factors not included in legislation or consolidated assessment frameworks such as European Network for Health Technology Assessment (EunetHTA) core model. It may be opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and pricing and reimbursement procedures.

Keywords

Health Technology Assessment, Multicriteria Assessment Methods, Price and Reimbursement Systems, Onco-Hematologic Prices, Value Assessment.

Background

Concerns about the increasing cost for oncological and hematologic innovation in Europe are growing as prices of cancer drugs are high but not always related to a proportional improvement on patients' health status [1]. In Europe, the increase rate of health spending on cancer has been faster than the increase in cancer incidence during the last 20 years. Similarly, the loss of productivity related to premature cancer mortality has decreased, while productivity loss related to morbidity is still uncertain [2].

Progressively flexible regulatory criteria for authorization in the setting of precision medicine points the focus of market access decision to the pricing and reimbursement process. Studies of authorization decisions in Europe estimated that after monitoring post authorization real world evidence for 3,3 years, benefits on survival of those authorized drugs were only observed in 7% of the cases, and improvement on reported quality of life was achieved in only 11% of them [3]. A recent study [4] confirms that this trend is consolidated, and regulatory practice is biased towards earlier access at the expense of production of post-authorization robust evidence, especially when the drug covers clinical unmet needs in diseases with poor prognosis [5]. Pricing and reimbursement decisions are tough when evidence is scarce and lacking comparative data, risking opportunity costs [6]. In order to minimize those, new access management models have been implemented across Europe during the last decades [7] although in a limited amount

and with a lack of methodological harmonization [8]. The increase of prices of oncologic products has generated additional international concerns [9] about the disconnection between price and value.

There is still an open debate in Europe about which are the adequate methods to assess the value of drugs [10]. Methods to set "fair prices" are generally focused on clinical benefits or expanded to the so-called value-based pricing which is usually focused on cost-effectiveness analysis [11-12-13]. Cancer drugs are normally classified as innovation based on implicit clinical value through QALYS (e.g., UK, Australia, Sweden) or using innovation scales (e.g., Canada, Japan, France, Germany, Austria, Italy) [14]. However, healthcare authorities do not normally unveil the details of the methodology applied to assess value, while new cancer drugs are increasingly reimbursed at a higher price than the available alternatives [15].

Recent studies [16] show that even in countries with well-stablished technology assessment processes (such as UK, Germany, France, and Switzerland), prices may still be considered as disconnected to value. In fact, in countries such as France, Australia, or UK, prices are only weakly associated with drug clinical benefits [17-18-19].

Besides lack of elements to check consistency between price and value, the literature remains inconclusive about the factors that HTAb are using to make their decisions on value and how the payers are deciding and reporting price decisions, especially when applying managed entry agreements [20]. Recent studies [21] show that EVIDEM's framework provides a complete and suitable value assessment framework, including contextual dimensions, and it has been progressively adopted by some HTAb in Europe. Additionally, differences may exist in the concept of value between payers and patients: while payers are generally focused on objective clinical outcomes to determine reimbursement conditions, the importance of patient's preferences is not clear [22-23].

In Spain, the pricing and decision process starts after the European marketing authorization is formally adopted by the AEMPS [24]. Subsequently, a Therapeutic Positioning Report (TPR) is issued by REvalMed network [25] to inform about the added therapeutic value of the drug as compared to current therapeutic alternatives. The TPR includes a therapeutic evaluation from the AEMPS; an economic assessment from the General Directorate for Common Portfolio of the NHS and Pharmacy Services (DGCCSF); and a final technical revision by external experts and scientific societies appointed by the REvalMed network. The TPR, together with the application dossier filed by the marketing authorization holder and DGCCSF own reports, are supposed to be the main driver for reimbursement decisions. The Inter-ministerial Committee on Pricing of Medicines and Healthcare Products (CIPM) is the body responsible for the final resolution of price and reimbursement conditions [26]. The CIPM decision is published as a listed price (not net price)

and motivation in general terms, which are based on the criteria listed in the RDL 1/2015, but the information provided by the Ministry of Health (MoH) is not detailed enough to know how the value of the drug has been stablished. It has been questioned whether the Spanish pricing model is based only in budgetary impact and lower European nominal price, without accounting contextual criteria and societal needs.

In fact, detailed information on how Spanish healthcare authorities define price and reimbursement conditions of new drugs is not available, and lack of predictability, potentially driving to inconsistency between value and price has been alleged [27-28]. The Royal Legislative Decree 1/2015 (RDL 1/2015) of the Law on Guarantees and Rational Use of Medicines and Health Products [29] lists only a restricted set of criteria to be used by the Spanish NHS to stablish prices of public funded medicines.

Based on recent data released by MoH [30], 90% of assessed oncologic medicines in Spain are publicly funded with a listed price 15 times higher than the average price of new non-cancer related drugs. By 2021, cancer drug costs represented 16,9% of the global pharmaceutical Spanish public budget, and the cost of cancer drugs at hospital level grew by 105,9% since 2016. The main objective of this study was to externally evaluate whether there is a relationship between the prices of oncology and hematology drugs and the evidentiary and contextual information available at the time of reimbursement decision in Spain, by applying a structured assessment of parameters measuring drug value, and to identify the most relevant criteria related to price decisions made by health authorities.

Methods

All new chemical entities with a first EMA authorization for a single onco-hematologic indication between January 2017 and December 2019 were identified, and price and reimbursement decisions of the Spanish MoH, including the notified price and public funding authorization, were tracked based on the publicly available database Bifimed [31] and the resolutions published by the MoH until end of October 2022 (Appendix).

For standardization and comparison purposes, a daily treatment cost based on notified prices was assigned following the Summary of Product Characteristics recommended posology for the studied indication. When the treatment duration was fixed, cost was annualized. Products with a negative decision were assigned a prize of zero; no other data imputation was applied.

For each product, a set of indicators from the MCDA-EVIDEM framework was used. A literature review was carried out to identify the indicators [32-33-34-35-36] for each MCDA-EVIDEM dimension (Table 2). The inclusion criteria for the review were articles published from January 2017 to December 2021 that included MCDA-EVIDEM related indicators to assess onco-hematologic drugs as well as country legislation and HTAb official documents available in English or Spanish. The review did not include outdated documents. The indicators for each product were extracted from available European Public Assessment Report (EPAR), TPR [37], European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) evaluations [38], National Institute for Health and Care Excellence (NICE) economic assessments [39] and freely available information from national and regional healthcare authorities [40]. The indicators were informed by a stepwise approach including two independent reviewers for each product and discrepancies were resolved through discussion. Public notified reimbursed prices per product (expressed as annual cost per treatment) were also included.

Continuous variables for each MCDA-EVIDEM dimensions' indicators were expressed as mean ± standard deviation, and categorical variables were expressed as percentage.

To evaluate the relation between oncology and hematology treatment prices and MCDA-EVIDEM indicators at the time of reimbursement decision, univariate analyses were performed. For correlation analyses, categories were normalized, and summaries calculated by dimension; prices were categorized by terciles where required. To compare variables, the non-parametric Mann-Whitney test was used for continuous variables and the Fisher exact test for categorical variables. Spearman's coefficients and 95% confidence intervals were calculated to assess correlations. The statistical significance was set at 5% two-tailed. The analysis was deemed exploratory, and thus no measures to account for multiplicity were applied.

Results

From January 2017 to December 2019, 24 oncological new chemical entities were granted a first indication marketing authorization in Europe. One product was excluded due to conflict of interest of the team, and an adjuvant product for photodynamic therapy was deemed as not suitable for the exercise [41] (Figure1). Eventually, 22 products were analyzed, aimed to treat 11 different tumors. By October 2022, pricing and reimbursement had been granted for 18 products and denied to 4 products (Table 1). Most frequent indications were breast and lung cancer and 9 drugs had orphan designation (Table 1). Only 2 products had no therapeutic alternatives (in lung and agnostic indications) and roughly half of the products had

targeted therapies as alternative options. Likewise, half of the treatments had impact on patients' autonomy (long intravenous administration, daycare admission), mostly in acute leukemia, lymphomas, melanoma, and neuroblastoma. Products for the treatment of melanoma, breast, neuroblastoma, and agnostic indications showed longer Progression Free Survival - PFS (observed and compared to control) over the median (14 months) and better Overall Survival (OS) versus control was seen for products to treat leukemia and neuroblastoma. Most of the products were aimed to non-curative settings (19/22), with a moderate MCBS score (13/22 products under the score of 4) and low quality of evidence (17/22 products under a JADAD score of 3). Most did not require new healthcare service delivery routes (14/22) and were administered orally (15/22). Many had an Incremental Cost-Effectiveness Ratio (ICER) over the NICE threshold and were included in the NICE Cancer Drugs Fund (16/22), and most were related to cancers included in a National or Regional Health Plans (18/22). More than half of the products (12/22) were explicitly recommended by experts' consensus or included in clinical practice guidelines while 4/22 products were explicitly not recommended (Table 2).

The univariate analysis (Table 3 and Table 4) showed significantly higher listed prices when the standard of care was combined treatments, if long-lasting responders were reported, and for several characteristics of the treatment: higher prices for fixed duration as compared to treatment until progression and lower frequencies of administration, and lower prices for oral route as compared to other routes of administration. There were significant correlations between price and the easiness of use of the drug, the impact of treatment on patient's autonomy, and the existence of recommendations by experts. Regarding summaries by dimensions, the only association to price values was observed for the "expert consensus/clinical practice guidelines recommendations" dimension, that contained a single item.

Discussion

Our findings suggest that the initial price of oncology and hematology products tends to be influenced (higher prices) only by few variables: the type of standard of care, the reporting of long-lasting responders, the convenience of use of drugs, the impact on patient's autonomy, a limited duration of the treatment, as well as contextual indicators such as the existence of previous clinical consensus. None of the individual items for comparative efficacy, safety or quality of life reached significance for price correlation. Attempts to summarize values by dimensions, as compared to description of individual items, did not improve explanation of price differences. However, the lack of standardized metrics and harmonized interpretation of contextual indicators limits the interpretation of the results.

The limitations to move forward with more transparent and standardized drug pricing processes is mainly the lack of shared convention about the definition of "price" as an expression of "value" [42]. For example, concepts such as quality-adjusted life-years (to standardize health gains) are not capturing the social perception of health benefit when life expectancy of diseases differ [43]. Additionally, price setting processes are conditioned by available and previous therapeutic alternatives, influencing prices of pharmaceutical innovation based on historical inertias and baseline costs of the disease for the system [44]. Additionally, dose, posology, or treatment duration, add complexity to direct comparison of value-based prices of new drugs.

There is a diversity of standardized clinical outcomes (overall survival, progression free survival, quality of life, and safety) that medical societies and European healthcare authorities [38] are using to guide or define reimbursement conditions of oncology drugs [45]. Other reports [18_19_20_21_22_46] suggest that perceived additional therapeutic benefits based on weak variables (such as response rates) or perception of severity (when this is measured) may be driving oncology drug prices. In our data, these clinical variables as well as "hard" variables such as overall survival were not good pricing predictors. However, we observed higher prices for products reporting references to long-lasting responders. Furthermore, our research also shows that other intermediate indicators such PFS, generally accepted as indicators of the capacity of a drug to cure or alter the natural history of the disease [47], were not strong predictors of prices either. The lack of consistent evidence based on long-term efficacy data, or on relative efficacy data of new drugs versus frequently used drugs at the time of price negotiations, does not seem to penalty the price and reimbursement decisions in Spain. The study also suggests the influence of contextual indicators, such as the existence of expert consensus and the impact of the route of administration to patients, in setting prices.

Several limitations of the study should be considered. Firstly, only few new oncology drugs authorized for a first indication were analyzed. The influence that multiple indications may have in price negotiations requires further analysis. Secondly, the value assessment was made by evaluators working in a context of payers of healthcare services, so that may not fully reflect the perspectives of pricing and reimbursement decision making. Third, we did not calculate summary indicators or overall scores for MCDA-EVIDEM, as suggested by others[44], since the exercise was aimed to check whether a more transparent reporting of the criteria used for decisions may help all stakeholders to predict the key determinants of value, to

support both the expectations of manufacturers, the information to lay public and the consistency in decision making by authorities. Finally, we did not do a systematic search of the literature using diversity of databases to identify all potential studies analyzing the relationship between prices and the MCDA-EVIDEM framework, and there is scarcity of references available on methods and definitions for data extraction and analysis; we cannot exclude that our work may be influenced by publication biases.

Our work may provide a basis for some proposals in the context of upcoming regulations and changes in the setting of Health Technology Assessments. The new European regulation [48] states that inclusive joint clinical assessments able to respond to all Member States' requirements must be produced at the EU level, ideally through consensus, and become part of multi-step national procedures. This new regulation enhances in this way the relevance of multiple domains (clinical, social, or economic) of assessment in the process of decision making by national price and reimbursement organisms, being EVIDEM a solid starting point. In this view, further research is needed to standardize measures and determine the socially acceptable weights among EVIDEM dimensions, as well as a set of financial factors by dimension. So far, only very limited experiences [49] have been tested with this broader approach aimed to more transparent and fair pricing, but still lacking solutions to tackle additional limitations such as a potential disincentive effect on R&D efficiency discouraging future disruptive innovation.

Conclusions

Our exercise shows that, regardless the paucity of explicative criteria on the decisions, the use of an standardized multidimensional framework allowed to identify that the listed prices of new cancer products with a single first reimbursed indication in Spain are related to the type of standard of care, references to long-lasting responses, the convenience of use of the drug and its impact on patient's autonomy, as well as contextual indicators such as the existence of previous clinical consensus. While individual items are quite explanatory, grouping by the synthetic MCDA-EVIDEM dimensions does not improve explicative value or information.

Based on our results and the lack of detailed information on how Spanish healthcare authorities define price and reimbursement conditions of new onco-hematologic drugs, we propose that the implementation of MCDA-EVIDEM methodologies may help to capture and report additional factors generally not included in consolidated assessment frameworks, such as EunetHTA core model. It may be

opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and pricing and reimbursement procedures [50].

Tables and figures

Table 1: *Price and funding decisions by October 2022 for oncological products with first regulatory authorization* from January 2017 to December 2019.*

Active principle	*Indication*	*Date authorization*	*Date final P&R decision*	*Public funding*	*Time# to final P&R decision (days)*	*Yearly treatment cost~ (public listing price)*
Inotuzumab ozogamicin	*Acute lymphoblastic leukemia*	*21/07/2017*	*1/7/2019*	*yes*	*710*	*189,431.35 €*
Dinutuximab beta	*Neuroblastoma*	*06/09/2018*	*1/6/2022*	*yes*	*1,364*	*171,998.95 €*
Mogamulizumab	*Squamous cell carcinoma*	*05/06/2019*	*1/7/2021*	*yes*	*757*	*160,158.35 €*
Polatuzumab vedotin	*Acute myeloid leukemia*	*18/02/2020*	*1/9/2021*	*yes*	*561*	*139,200.05 €*
Brigatinib	*Lung cancer*	*28/11/2019*	*1/5/2021*	*yes*	*520*	*109,781.05 €*
Durvalumab	*Lung cancer*	*31/10/2018*	*1/1/2020*	*yes*	*427*	*98,550.00 €*
Rucaparib	*Breast cancer*	*10/05/2019*	*1/1/2020*	*yes*	*236*	*91,129.55 €*
Midostaurin	*Chronic myelogenous leukemia*	*30/10/2017*	*1/4/2019*	*yes*	*518*	*86,997.75 €*
Encorafenib	*Melanoma*	*04/10/2018*	*1/9/2019*	*yes*	*332*	*86,844.45 €*
Binimetinib	*Melanoma*	*19/10/2018*	*1/9/2019*	*yes*	*317*	*86,844.45 €*
Niraparib	*Ovarian cancer*	*08/03/2018*	*1/8/2019*	*yes*	*511*	*64,918.90 €*
Lorlatinib	*Lung cancer*	*20/06/2019*	*1/2/2021*	*yes*	*592*	*63,630.45 €*
Neratinib	*Breast cancer*	*07/01/2020*	*1/7/2022*	*no*	*906*	*61,320.00 €*

Active principle	*Indication*	*Date authorization*	*Date final P&R decision*	*Public funding*	*Time# to final P&R decision (days)*	*Yearly treatment cost~ (public listing price)*
Ribociclib	*Breast cancer*	*04/09/2017*	*1/11/2017*	*yes*	*58*	*57,936.45 €*
Tivozanib	*Renal cancer*	*09/04/2018*	*1/3/2019*	*yes*	*326*	*47,650.75 €*
Abemaciclib	*Breast cancer*	*26/10/2018*	*1/5/2019*	*yes*	*187*	*46,668.90 €*
Citarabine/ daunorubicin	*Acute myeloid leukemia*	*19/12/2018*	*1/3/2022*	*yes*	*1.168*	*42,639.30 €*
Gemtuzumab ozogamicin	*Acute myeloid leukemia*	*25/05/2018*	*1/7/2019*	*yes*	*402*	*35,999.95 €*
Dacomitinib	*Lung cancer*	*23/05/2019*	*1/8/2020*	*yes*	*436*	*32,850.00 €*
Talazoparib	*Breast cancer*	*24/07/2019*	*1/8/2021*	*no*	*739*	*0.00 €*
Gilteritinib	*Acute myeloid leukemia*	*05/12/2019*	*1/6/2021*	*no*	*544*	*0.00 €*
Larotrectinib	*Agnostic indication*	*21/11/2019*	*1/4/2022*	*no*	*862*	*0.00 €*

** Cemiplimab was excluded because of conflict of interest; padeliporfin was excluded because the indication was as an adjuvant for photodynamic therapy. ~ Cost calculated according to posology in the product information for the studied indication and annualized where required if fixed maximum length of treatment. Costs of 0.00 € reflect negative price and reimbursement decisions by October 2022.*

 # Time from the date of European Marketing Authorization until inclusion in the national reimbursement listing; since negative decisions and successive resubmissions may occur until reimbursement is granted, it does not reflect the length of pricing and reimbursement procedure.

Table 2: Description of MCDA-EVIDEM dimensions and metrics.

Dimensions and indicators	Metrics	Mean (SD) or %	(N)
Non contextual			
Disease severity			
Speed tumor growth	*Time of duplication (months)*	*13.64 (19.61)*	*20*
% Metastasized	*Percentage of patients with metastasis at diagnosis*	*50% (40%)*	*22*
Expected survival 5-years	*Percentage of patients with expected survival ≥ 5 years*	*29% (25%)*	*22*
Physical function and general health	*Normalized Score of SF36 - EQ5D – EORTC QLC or C30*	*62.41 (21.72)*	*12*
Size of affected population			
Prevalence	*Cases per 10.000 inhabitants*	*23.83 (219.32)*	*22*
Incidence	*New cases per 10.000 inhabitants and year*	*27.06 (29.57)*	*22*
Unmet needs			
Treatment options	*Percentage with/without alternative treatment options*	*With: 90%* *Without: 9%*	*22*
Type of standard of care	*Percentage of chemotherapy / immunotherapy / directed agents /surgery / radio/ combined /others / none*	*Chemotherapy:21%* *Directed agents: 47%* *Combined:17%* *Others: 4%* *None: 9%*	*22*
Comparative effectiveness			
Progression free survival	*Months (median) during which patients have not experienced disease progression*	*13.69 (7.83)*	*22*
Progression free survival vs control	*Difference in months (median) during which patients have not experienced disease progression vs control*	*6.73 (4.59)*	*22*
Objective response rate (RECIST/MRD)	*Percentage of patients that experience complete response and partial response*	*0.55 (0.17)*	*19*

Dimensions and indicators	Metrics	Mean (SD) or %	(N)
Objective response rate (RECIST/MRD) vs Control	*Difference in percentage of patients that experience complete response and partial response vs control*	*20% (14%)*	*14*
Complete response (RECIST/MRD)	*Percentage of patients that experience complete response*	*23% (27%)*	*20*
Complete response (RECIST/MRD) vs control	*Difference in percentage of patients that experience complete response vs control*	*9% (13%)*	*15*
Partial response (RECIST /MRD)	*Percentage of patients that experience partial response*	*33% (18%)*	*18*
Partial response (RECIST /MRD) vs control	*Difference in percentage of patients that experience partial response vs control*	*10% (7%)*	*13*
Long responders	*Percentage of patients mentioned as long responders*	*Yes: 9%* *No: 91%*	*22*
Overall survival	*Months (median) of treatment randomized to death*	*25.61 (16.43)*	*15*
Overall survival vs control	*Difference in months (median) of treatment randomized to death vs control*	*9.23 (13.25)*	*12*
Comparative safety and tolerability			
Any adverse event	*Percentage of patients experiencing an adverse event*	*97% (6%)*	*22*
Any adverse event vs control	*difference in percentage of patients experiencing an adverse event vs control*	*5% (10%)*	*16*
Non-fatal serious adverse events (>3)	*Percentage of patients experiencing an adverse event of grade 3 to 5*	*57% (26%)*	*16*
Non-fatal serious adverse events (>3) vs control	*Difference in percentage of patients experiencing an adverse event of grade 3 to 5 vs control*	*15% (19%)*	*16*
Fatal adverse events (Grade 5)	*Percentage of patients experiencing an adverse event of grade 5*	*7% (7%)*	*21*
Fatal adverse events (Grade 5)	*Difference in percentage of patients experiencing an adverse event of grade 5 vs control*	*1% (5%)*	*16*
Dosage adjustment due to adverse events	*Mention (yes/no) of dosage adjustment due to adverse effects*	*Yes: 73%* *No: 14%*	*22*

Dimensions and indicators	Metrics	Mean (SD) or %	(N)
		Not relevant: 13%	
Treatment discontinuation due to adverse events	*Percentage of patients discontinuing treatment due to adverse events*	*14% (10%)*	*22*
Treatment discontinuation due to adverse events vs control	*Difference in percentage of patients discontinuing treatment due to adverse events vs control*	*8% (7%)*	*22*
Median duration of treatment	*Months (median) of duration of treatment*	*21.27 (24.54)*	*17*
Other Indications (patients exposed)	*Number of potential patients for all indications (exposed population as reported in EPAR)*	*920.95 (665.65)*	*22*
Comparative patient-perceived health and patient-reported outcomes			
Quality of Life	*Normalized score of quality-of-life scale*	*0.06 (0.22)*	*14*
Impact on autonomy	*Mentioned (yes/no) disruption of daily activities due to delivering of treatment*	*Yes: 41%* *No: 59%*	*22*
Frequency of treatment (administration)	*Dose administration by unit of time*	*Once month: 4%* *Twice month: 4%* *Once week: 4%* *Twice week: 0%* *>Twice week: 9%* *Once day: 48%* *Twice day: 17%*	*22*
Variable treatment guideline	*Mentioned (yes/no) treatment guideline's changes*	*Yes: 13%* *No: 68%*	*22*
Time of treatment	*Mentioned (fixed/up to progression/variable) time of treatment*	*Fixed: 17%* *Up to progress: 50%* *Other: 36.4%*	*22*
Easy to use, mode and set of administration	*Mentioned (oral/injection/intrathecal) way of administration*	*Oral: 68%* *Injection: 27%* *Intrathecal: 4%*	*22*
Combined chemotherapy	*Mentioned (with/without) combination with chemotherapy*	*With: 18%* *Without: 81%*	*22*

Dimensions and indicators	Metrics	Mean (SD) or %	(N)
Magnitude of therapeutic benefit (*)			
Magnitude of clinical benefits MCBS	*Scale of MCBS*	*3.14 (0.77)*	*22*
Type of benefit			
Curative/Non-Curative	*Mentioned (curative/non curative) clinical benefit*	*Curative:18.2%* *Non-Curative:81.8%*	*22*
Comparative cost consequences – cost of intervention			
NICE ICER > threshold	*Mentioned (yes/no) NICE ICER > threshold before any patient access scheme in place.*	*NA:4.5%* *Yes: 72.7%* *No: 22.7%*	*21*
NICE cancer fund	*Mentioned (yes/no) inclusion as a NICE Cancer Fund's Drug*	*Yes: 36.4%* *No: 63.6.7%*	*22*
ICER (NICE value)	*Δ monthly target therapy cost / Δ time to disease progression as per NICE information*	*52,363.9 (28,859.4)*	*18*
Comparative cost consequences – other medical costs			
Cost treatment (procedures and tests-physician visits-hospitalizations…)	*Yearly direct medical costs (€) excluding purchasing costs of the technology (i) concomitant medications, ii) outpatient visits, diagnostic/laboratory tests, hospitalizations, and other monitoring costs (including management AEs), and iii) terminal care.*	*NA: 50%* *0: 45.5%* *>0: 4.5%*	*11*
Comparative cost consequences – non-medical costs			
Cost treatment	*Yearly cost of (€) treatment (based on notified prices)*	*NA: 100%*	*0*
Quality of evidence (**)			
JADAD scale	*JADAD scale*	*2.50 (1.40)*	*22*
Expert consensus and clinical practice guidelines			
Recommendation by experts	*Mentioned (yes/no) recommendation included in consensus available at the time of pricing*	*Recommended: 24.0%* *Not recommended: 76.4%*	*17*
Contextual			

Dimensions and indicators	Metrics	Mean (SD) or %	(N)
Mandate and scope of the healthcare system			
Included in National/Sub-National Health Plan	*Type of cancer mentioned (yes/no) in healthcare plans*	*Included:81.8%* *Not included: 18.2%*	*22*
Population priorities and access			
Preferences of the population as a need	*Type of cancer mentioned (yes/no) in official positions or documents from NGO's and Patient Advocacy Groups*	*Identified: 18.2%* *Not identified: 81,8%*	*22*
Common goal and specific interests			
Stakeholders' expression of interest and alignment	*Type of cancer mentioned (yes/no) in societal sources (mass or digital media)*	*Identified: 22.7%* *Not identified: 77.3%*	*22*
Environmental impact			
Impact of the intervention on environment - packaging, production	*Relevant environmental impact mentioned (yes/no) in EPAR*	*Yes:21.1%* *No: 78.9%*	*19*
System capacity and appropriate use of intervention			
Healthcare services delivery change	*Mentioned (yes/no) change in healthcare service delivery or inversion (e.g., new biomarkers) to deliver care*	*Yes: 36.4%* *No: 63.6%*	*22*
Political, historical, or cultural context			
Societal acceptability of the decisions	*Type of cancer mentioned (yes/no) at legal level or included in political statements*	*Identified:9.1%* *Not identified: 90.9%*	*22*

(*) Non-curative indications range from 1 (lowest) to 5 (highest) benefit. Curative indications range from A to C [A equalized to 5 and C to 1].

(**) JADAD scores range from 0 (lowest) to 5 (highest) quality of trials.

Table 3: Description of the mean (SD) listed yearly prices of oncology drugs according to the values of MCDA categorical items.

Variables and values	Mean	SD	Lower limit 95% CI	Upper limit 95% CI
Alternative treatment options				
with	78,800.06 €	52,983.23 €	55,308.61 €	131,783.30 €
without	49,275.00 €	69,685.37 €	18,378.24 €	80,171.76 €
Type of standard of care				
Chemotherapy	68,353.67 €	66,410.51 €	38,908.90 €	97,798.44 €
Combined	143,946.84 €	43,194.75 €	124,795.36 €	163,098.32 €
Directed agents	59,858.69 €	29,376.64 €	46,833.81 €	72,883.56 €
None	49,275.00 €	69,685.37 €	18,378.24 €	80,171.76 €
Long responders				
Not mentioned	60,764.84 €	29,538.65 €	47,668.13 €	73,861.54 €
Yes	98,389.07 €	16,110.32 €	91,246.16 €	105,531.99 €
NA	89,928.88 €	75,408.73 €	56,494.52 €	123,363.23 €
Dosage adjustment due to AEs active				
No	86,236.67 €	80,786.88 €	50,417.77 €	122,055.56 €
Not Relevant	83,546.67 €	76,674.75 €	49,550.99 €	117,542.34 €
Yes	72,825.08 €	47,833.71 €	51,616.80 €	94,033.36 €
Impact of treatment on Autonomy				
No	50,990.95 €	35,392.51 €	35,298.79 €	86,289.74 €
Yes	112,407.66 €	55,550.03 €	87,778.15 €	137,037.16 €
Interval of treatment administration				
Daily	55,771.42 €	35,111.77 €	40,203.73 €	71,339.10 €
Weekly or less frequent	104,747.50 €	71,259.64 €	73,152.75 €	136,342.25 €
Variable treatment guideline				
No	76,789.96 €	54,409.58 €	52,666.11 €	100,913.81 €

Variables and values	Mean	SD	Lower limit 95% CI	Upper limit 95% CI
Yes	74,671.70 €	55,243.71 €	50,178.01 €	99,165.38 €
Duration of treatment				
Fixed schedule	110,623.33 €	56,319.09 €	85,652.85 €	135,593.82 €
Other	89,918.15 €	66,683.08 €	60,352.53 €	119,483.78 €
Up to progression	56,666.91 €	36,126.07 €	40,649.51 €	72,684.32 €
Easy to Use / Mode & Set of Administration				
Injection	108,091.67 €	58.881.72 €	81.984.97 €	134.198.36 €
Intrathecal	189,430.00 €	- €	- €	- €
Oral	55,771.42 €	35,111.77 €	40,203.73 €	71,339.10 €
Combined chemotherapy				
With	108,549.34 €	59,703.00 €	82,078.51 €	135,020.17 €
Without	68,908.55 €	50,841.26 €	46,366.80 €	91,450.30 €
ESMO -MCBS setting Curative/Non-Curative				
Curative	89,079.34 €	59,071.05 €	62,888.70 €	115,269.98 €
Non-Curative	73,235.22 €	53,406.60 €	49,556.06 €	96,914.38 €
ICER (> NICE threshold)				
No	71,603.22 €	14,199.42 €	64,542.02 €	78,664.43 €
yes	82,283.45 €	59,142.59 €	52,872.53 €	111,694.36 €
ICER (NICE cancer fund)				
no	81,547.28 €	62,812.10 €	53,697.95 €	109,396.60 €
yes	66,611.17 €	32,409.99 €	52,241.39 €	80,980.96 €
Recommendation by experts				
NA	63,000.00 €	69,753.90 €	28,821.22 €	97,178.78 €
Not Recommended	35,209.46 €	26,193.69 €	22,374.79 €	48,044.14 €
Recommended	88,901.03 €	49,442.76 €	64,674.53 €	113,127.54 €
Included in National/Sub-National Health Plan				

Variables and values	Mean	SD	Lower limit 95% CI	Upper limit 95% CI
Included	73,752.18 €	49,723.26 €	51,706.12 €	95,798.24 €
Not Included	86,753.01 €	75,706.10 €	53,186.81 €	120,319.22 €
Preferences of the population as a need?				
Identified	110,990.61 €	45,170.96 €	90,962.93 €	201,953.55 €
Not identified	68,366.05 €	52,976.65 €	44,877.51 €	91,854.58 €
Stakeholders' expression of interest & alignment				
Identified	98,322.90 €	48,297.69 €	76,908.91 €	119,736.90 €
Not identified	69,584.52 €	54,346.47 €	45,488.64 €	93,680.39 €
Impact of the intervention on environment - packaging, production				
NA	108,149.44 €	57,269.58 €	80,546.39 €	135,752.50 €
No	77,689.18 €	54,898.41 €	51,228.99 €	104,149.37 €
Yes	46,191.30 €	37,980.02 €	27,885.52 €	64,497.09 €
Healthcare services delivery change				
No	69,930.29 €	48,388.88 €	48,475.86 €	91,384.71 €
Yes	86,940.90 €	63,093.87 €	58,966.65 €	114,915.16 €
Societal acceptability of the decisions				
Identified	102,425.00 €	98,393.91 €	58,799.58 €	146,050.42 €
Not identified	73,485.06 €	50,562.17 €	51,067.05 €	95,903.07 €
All products				
Yearly price	76,115.97 €	53,353.38 €	52,460.40 €	99,771.53 €

SD: standard deviation; 95% CI: 95% Confidence interval; AEs: Adverse events; ESMO-MCBS: European Society of Medical Oncology – Magnitude of Clinical Benefit Score; ICER: Incremental Cost- effectiveness ratio; NICE: National Institute for Health and Care Excellence

Table 4: Univariate analysis of the association between listed prices of oncology drugs and the dimensions of MCDA and subitems within each dimension.

Dimensions and individual items	N	Correlation Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p Value for H0: Rho=0
1. Disease severity	**22**	**-0,29**	**-0,63**	**0,15**	**0,18**
Speed tumor growth	20	-0.26	-0.61	0.18	0.23
% Metastasized	22	-0.23	-0.60	0.21	0.29
Expected survival 5-years	22	-0.37	-0.68	0.06	0.08
Overall Survival	20	0.09	-0.34	0.49	0.68
Physical function and general health (SF36 - EQ5D - EORTC QLQ-C30)	12	-0.11	-0.50	0.33	0.63
2. Size of affected population	**22**	**0,17**	**-0,27**	**0,55**	**0,44**
Prevalence	22	0.23	-0.21	0.59	0.30
Incidence	22	0.16	-0.28	0.54	0.47
3. Unmet needs	**22**	**0,05**	**-0,38**	**0,46**	**0,81**
Treatment options	22	-0.07	-0.48	0.36	0.74
Type of standard of care	22	0.05	-0.38	0.46	0.81
4. Comparative effectiveness	**22**	**0,15**	**-0,29**	**0,54**	**0,50**
Progression Free Survival observed observed	22	-0.14	-0.53	0.30	0.53
Progression Free Survival difference to control	18	0.14	-0.30	0.53	0.52
Objective Response Rate (RECIST/MRD) observed	19	-0.35	-0.67	0.09	0.10
Objective Response Rate (RECIST/MRD) difference to control	14	0.20	-0.24	0.57	0.37

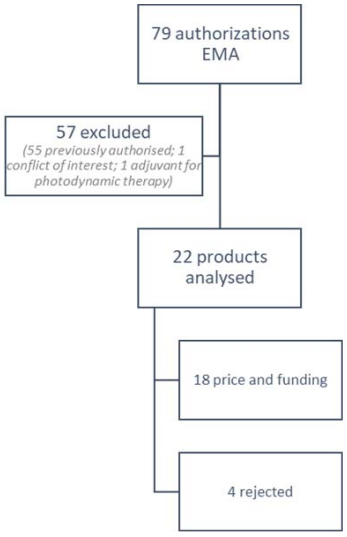
Dimensions and individual items	N	Correlation Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p Value for H0: Rho=0
Complete response (RECIST/MRD) observed	20	-0.01	-0.43	0.41	0.96
Complete response (RECIST/MRD) difference to control	15	0.38	-0.04	0.69	0.07
Partial response (RECIST /MRD) observed	18	-0.15	-0.54	0.29	0.49
Partial response (RECIST /MRD) difference to control	13	0.27	-0.17	0.62	0.22
Long responders (Yes/no)	11	0.17	-0.27	0.55	0.44
Overall Survival observed	15	0.21	-0.23	0.58	0.33
Overall Survival difference to control	12	0.29	-0.15	0.63	0.18
5. Comparative safety/tolerability	**22**	**-0,13**	**-0,53**	**0,30**	**0,55**
Any Adverse Events observed	22	-0.18	-0.56	0.26	0.42
Any Adverse Events difference to control	16	0.04	-0.39	0.45	0.87
Non-Fatal Serious Adverse Events (>3) observed	22	0.15	-0.29	0.54	0.50
Non-Fatal Serious Adverse Events (>3) difference to control	16	-0.02	-0.44	0.40	0.91
Fatal Adverse Events (Grade 5 AEs) observed	21	-0.06	-0.47	0.37	0.78
Fatal Adverse Events (Grade 5 AEs) difference to control	16	0.08	-0.35	0.48	0.72
Dosage adjustment due to adverse effects	22	0.06	-0.37	0.47	0.78
Treatment discontinuation (due to AEs) active	22	-0.25	-0.61	0.19	0.25

Dimensions and individual items	N	Correlation Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p Value for H0: Rho=0
Treatment discontinuation (due to AEs) difference to control	17	-0.07	-0.48	0.35	0.74
Median duration of treatment	22	-0.49	-0.75	-0.09	***0.01***
Extent of exposure: Other indications, number of indications	22	-0.22	-0.58	0.22	0.31
6. Comparative patient-perceived health / PRO	**22**	**-0,14**	**-0,53**	**0,30**	**0,54**
HRQoL	14	0.37	-0.06	0.68	0.08
Impact on Autonomy	22	-0.45	-0.73	-0.04	***0.03***
Frequency of treatment (how often is administered)	22	0.40	-0.03	0.70	0.06
Variable treatment schedule	22	0.02	-0.40	0.44	0.92
Time of treatment	22	0.41	-0.01	0.71	0.05
Easy to Use / Mode & Set of Administration	22	-0.48	-0.75	-0.08	***0.02***
Combined chemotherapy	22	-0.27	-0.62	0.17	0.21
7.a. Magnitude of preventive benefit	**18**	**0.16**	**-0.28**	**0.55**	**0.47**
Magnitude of preventive benefit	18	0.16	-0.28	0.55	0.47
7.b. Magnitude of therapeutic benefit	**22**	**0.13**	**-0.31**	**0.52**	**0.57**
Magnitude of therapeutic benefit	22	0.13	-0.31	0.52	0.57
8. Comparative cost consequences – cost of intervention	**22**	**-0,03**	**-0,45**	**0,39**	**0,87**
Incremental Cost-effectiveness ratio (ICER) over NICE threshold (yes/no)	21	-0.09	-0.49	0.34	0.69
ICER: NICE assigns cancer fund (Yes / no)	22	-0.01	-0.43	0.41	0.95

Dimensions and individual items	N	Correlation Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p Value for H0: Rho=0
ICER: NICE value (€ or pounds – with 95% CI)	18	-0.08	-0.49	0.35	0.70
11. Quality of evidence:	**22**	**-0,02**	**-0,44**	**0,40**	**0,91**
JADAD/ESMO assessment of quality (from 1 to 5 where 5 maximum)	22	-0.02	-0.44	0.40	0.91
12. Expert consensus/clinical practice guidelines	**17**	**0,56**	**0,17**	**0,79**	**0,00**
Availability of guidance for use and recommendation in guidance/by experts	17	0.56	0.17	0.79	*0.00*
13. Contextual criteria	**22**	**0,03**	**-0,40**	**0,44**	**0,90**
Mandate and scope of the healthcare system	22	-0.05	-0.46	0.38	0.81
Population priorities and access	22	0.35	-0.09	0.67	0.11
Common goal and specific interests	22	0.26	-0.18	0.61	0.24
Environmental impact	19	0.01	-0.41	0.43	0.97
System capacity and appropriate use of intervention	22	-0.17	-0.55	0.26	0.43
Political/historical/cultural context	22	0.05	-0.38	0.46	0.83

Dimension 7 was analyzed separately for preventive and therapeutic benefits since these used different scoring. Dimensions 9 to 12 had a single item each so that the estimate for the dimension is the same than that of the item. Due to lack of data the dimensions number 9" comparative cost consequences – other medical costs" and the corresponding item "Cost treatment (procedures and tests-physician visits-hospitalizations) / Year" and number 10 "comparative cost consequences –non-medical costs" and the corresponding item "Cost/ Year" were not analyzed for correlation.

Figure 1. Product selection



Annex 1: Description of MCDA-EVIDEM items and dimensions.

Dimensions and indicators	Metrics
Non contextual	
Disease severity	
Speed tumor growth	Time of duplication (months)
% Metastasized	Percentage of patients with metastasis at diagnosis
Expected survival 5-years	Percentage of patients with expected survival ≥ 5 years
Physical function and general health	Normalized Score of SF36 - EQ5D – EORTC QLC or C30
Size of affected population	
Prevalence	Cases per 10.000 inhabitants
Incidence	New cases per 10.000 inhabitants and year
Unmet needs	
Treatment options	Percentage with/without alternative treatment options
Type of standard of care	Percentage of chemotherapy / immunotherapy / directed agents /surgery / radio/ combined /others / none

Dimensions and indicators	Metrics
Comparative effectiveness	
Progression free survival	Months (median) during which patients have not experienced disease progression
Progression free survival vs control	Difference in months (median) during which patients have not experienced disease progression vs control
Objective response rate (RECIST/MRD)	Percentage of patients that experience complete response and partial response
Objective response rate (RECIST/MRD) vs Control	Difference in percentage of patients that experience complete response and partial response vs control
Complete response (RECIST/MRD)	Percentage of patients that experience complete response
Complete response (RECIST/MRD) vs control	Difference in percentage of patients that experience complete response vs control
Partial response (RECIST /MRD)	Percentage of patients that experience partial response
Partial response (RECIST /MRD) vs control	Difference in percentage of patients that experience partial response vs control
Long responders	Percentage of patients mentioned as long responders
Overall survival	Months (median) of treatment randomized to death
Overall survival vs control	Difference in months (median) of treatment randomized to death vs control
Comparative safety and tolerability	
Any adverse event	Percentage of patients experiencing an adverse event
Any adverse event vs control	difference in percentage of patients experiencing an adverse event vs control
Non-fatal serious adverse events (>3)	Percentage of patients experiencing an adverse event of grade 3 to 5
Non-fatal serious adverse events (>3) vs control	Difference in percentage of patients experiencing an adverse event of grade 3 to 5 vs control
Fatal adverse events (Grade 5)	Percentage of patients experiencing an adverse event of grade 5
Fatal adverse events (Grade 5)	Difference in percentage of patients experiencing an adverse event of grade 5 vs control

Dimensions and indicators	Metrics
Dosage adjustment due to adverse events	Mention (yes/no) of dosage adjustment due to adverse effects
Treatment discontinuation due to adverse events	Percentage of patients discontinuing treatment due to adverse events
Treatment discontinuation due to adverse events vs control	Difference in percentage of patients discontinuing treatment due to adverse events vs control
Median duration of treatment	Months (median) of duration of treatment
Other Indications (patients exposed)	Number of potential patients for all indications (exposed population as reported in EPAR)
Comparative patient-perceived health and patient-reported outcomes	
Quality of Life	Normalized score of quality-of-life scale
Impact on autonomy	Mentioned (yes/no) disruption of daily activities due to delivering of treatment
Frequency of treatment (administration)	Dose administration by unit of time
Variable treatment guideline	Mentioned (yes/no) treatment guideline's changes
Time of treatment	Mentioned (fixed/up to progression/variable) time of treatment
Easy to use, mode and set of administration	Mentioned (oral/injection/intrathecal) way of administration
Combined chemotherapy	Mentioned (with/without) combination with chemotherapy
Magnitude of therapeutic benefit (*)	
Magnitude of clinical benefits MCBS	Scale of MCBS
Type of benefit	
Curative/Non-Curative	Mentioned (curative/non curative) clinical benefit
Comparative cost consequences – cost of intervention	
NICE ICER > threshold	Mentioned (yes/no) NICE ICER > threshold before any patient access scheme in place.
NICE cancer fund	Mentioned (yes/no) inclusion as a NICE Cancer Fund's Drug

Dimensions and indicators	Metrics
ICER (NICE value)	Δ monthly target therapy cost / Δ time to disease progression as per NICE information
Comparative cost consequences – other medical costs	
Cost treatment (procedures and tests-physician visits-hospitalizations…)	Yearly direct medical costs (€) excluding purchasing costs of the technology (i) concomitant medications, ii) outpatient visits, diagnostic/laboratory tests, hospitalizations, and other monitoring costs (including management AEs), and iii) terminal care.
Comparative cost consequences – non-medical costs	
Cost treatment	Yearly cost of (€) treatment (based on notified prices)
Quality of evidence (**)	
JADAD scale	JADAD scale
Expert consensus and clinical practice guidelines	
Recommendation by experts	Mentioned (yes/no) recommendation included in consensus available at the time of pricing
Contextual	
Mandate and scope of the healthcare system	
Included in National/Sub-National Health Plan	Type of cancer mentioned (yes/no) in healthcare plans
Population priorities and access	
Preferences of the population as a need	Type of cancer mentioned (yes/no) in official positions or documents from NGO's and Patient Advocacy Groups
Common goal and specific interests	
Stakeholders' expression of interest and alignment	Type of cancer mentioned (yes/no) in societal sources (mass or digital media)
Environmental impact	
Impact of the intervention on environment - packaging, production	Relevant environmental impact mentioned (yes/no) in EPAR
System capacity and appropriate use of intervention	
Healthcare services delivery change	Mentioned (yes/no) change in healthcare service delivery or inversion (e.g., new biomarkers) to deliver care

Dimensions and indicators	Metrics
Political, historical, or cultural context	
Societal acceptability of the decisions	Type of cancer mentioned (yes/no) at legal level or included in political statements

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Chapter 4: Discussion

Although several authors [1–2–3] have assessed the link between expected clinical outcomes of new onco-hematologic drugs and their price, this research is the first ever comprehensive published analysis about the consistency of new drugs' price decision and its value defined by multiple dimensions (clinical, economic, political, and social) in the Spanish context. The results of our research confirmed a limited relationship between the prices of new onco-hematologic drugs and the parameters of value of these drugs, mainly related to the type of standard of care, references to long-lasting responders, the convenience in the use of the drug and the impact of treatment on patient's autonomy as well as contextual indicators such as the existence of previous clinical consensus are drivers to set oncology drug prices in Spain.

Holistic definition of "value" for new onco-hematologic drugs

The provision of sustained access to new onco-hematologic medicines is a global raising concern even for high income countries that are facing a continuous increase in prices and rapid scientific advancements in oncology. In this regard, several challenges [4] are faced by payer to tackle the access to new onco-hematologic drugs:

Precision approaches

- The collective additional better understanding of the biology and pathophysiology underlying cancer diseases is driving substantive significant scientific advances that are impacting healthcare in this therapeutic area. The more profound knowledge of the genomic characteristics of tumors is enabling the identification of targeted pharmacotherapeutic alternatives for individual patients and sub-groups of population who are more likely to have successful responses to treatments with specific new medicines. Drug development is progressively based on targeting molecular pathways, identifying treatments that can inhibit growth of tumor tissues, with a much better toxicity profile when compared with conventional chemotherapeutic regimens. Major progress has been extensively developed in immunotherapies to fight against types of cancer for which there were previously few effective therapeutic alternatives.
- Such an evolving scenario has led substantial changes in the classical paradigms of price setting, since innovation is incremental, rapidly growing, and targeted, because high rates of response are observed in few highly selected individuals based on new biomarkers or clinical parameters

for whose no information is yet available. As opposite, the classical scenario considers a population perspective where the global impact is assessed assuming that relatively poor results will be obtained due to a substantial number of failures due to lack of specificity of the interventions. There is a growing strain that emphasizes the need to be more proficient in making decisions, by improving the transparency and traceability of the process for consistency and continuous improvement, since applying old criteria to new settings may result in a potential overpricing.

Thus, these rapid developments have added financial pressure to healthcare budgets, jeopardizing the sustainability of affordable access to oncology care, even when sound evidence of effectiveness, cost-effectiveness, and efficiency are available at the time of reimbursement decisions by national or regional payers.

In addition, a related financial sustainability issue is the growing uncertainty in clinical benefit (that impacts cost-effectivity analysis) and budget impact, as result of non-conventional developments and fast-track authorization (and reimbursement) processes in onco-hematology. These are needed to promote early and rapid access for new medications in areas with a perception of clear clinical unmet need but are often based on clinical trials not designed to provide solid evidence to make quick decisions on price and reimbursement.

Multiple indications

- Another major challenge is that many of the new onco-hematologic products have (or potentially will have) multiple indications, with a wide variety of degrees of clinical benefit by indication. The so-called “cascade’’ of indications indicates the tendency for oncology medicines patent holders to obtain marketing authorization (and reimbursement) for multiple indications, implying different levels of cost-effectiveness ratios at a given single price.
- This generates a relevant debate about how appropriate is setting prices by indication to reflect differences in “value”. Indication-based pricing (IBP) could provide better access conditions (if compared to a single “high” price with coverage restrictions), allowing companies to capture a larger share of the surplus generated (if compared to a single “low” price), thus sending “appropriate” signals to innovators.

- On the other hand, many payers disagree with IBP principles, especially because of feasibility limitations in its implementation. Among those who apply IBP models (normally through confidential agreements) a minority can track the use of drugs by indication [5]. The coverage of each additional indication of a product often leads to a price reduction to reflect the anticipated volume increase, even in countries willing to consider differential values across indications.

Combinations

- Similarly, schemes combining old and/or innovative products increment the number of drugs in a single prescription for the same disease and increases the complexity of assessing the added value of innovations that come on top of treatments already commercialized. Thus, determining the appropriate place in therapy for a new medication is also a relevant challenge, as treatment regimens are being notably complexified by using combined or close sequences of medicines with different but complementary mechanisms of action, making it difficult to determine the contribution of each combined drug to the overall clinical impact, and the subsequent price negotiation. The lack of a systemic, robust, and transparent way to assess such combinations raises heterogeneous decisions that are often based on budgetary allowance, rather than on prospective efficiency appraisals, and thus risks an inequity "postcode prescription" access effect conditioned by differences among coverage policies or specific purchasing mechanisms.
- Recent evidence [6] shows 16 "combination" therapies approved in Europe at the end of 2019, while the ongoing clinical trials that combine novel immunotherapies with other targeted therapies would add the need to tackle better ways to assess the value of these combinations. So far, the HTAb assess the value of a new product ('add-on' therapy) in combination with an existing product ('backbone' therapy) using normally as comparator backbone therapy and determining if the overall effect at the incremental cost is aligned with their willingness to pay (WTP) for the combination.
- Negotiations are more easily conducted when the combined products are marketed by the same patent holder, as a reduction of the backbone therapy when the overall incremental cost exceeds the payers' WTP. Ideally, new prices reflect the respective benefit contributions of each medicine in the combination, but there is no consensus in defining a suitable assessment mechanism to define separately the specific contributions of each medicine and adjust prices accordingly. This challenge is even more difficult to solve, almost impossible to manage, when the products in

combination are sold by different companies as competition law avoids any alignment among companies to set prices of individual prices (under the risk of being considered collusion by competition laws).

- Furthermore, when price setting processes are based on cost-effectiveness explicit or implicit thresholds (being the case a large list of European countries, where Spain is not an exception) the "value" assessment can be highly inconsistent with the social and commonwealth, as the incremental cost effectiveness rate (ICER) of the combination, even if the add-on drug is priced zero, can be above the threshold just because of the marginal extension of live when the ICER of the backbone therapy is very close to such threshold [7]. The limited list of countries that have in place pricing methods for combinations (e.g., United Kingdom – England -, France or Switzerland), after having determined their ICER for a combined therapy, negotiate individually with each company involved in the combination of drugs, reaching price adjustments generally as confidential rebates on list prices.

Uncertainty on clinical benefit

- But one of the most relevant challenges to be tackled when assessing the innovation in the onco-hematologic area is the often-significant uncertainty about the clinical benefit of a new medicine at the time of market reimbursement. More frequently onco-hematologic new drugs and indications are approved in early phases of development, based on surrogate endpoint data, or on evidence from non-randomized trials that can drive conclusions towards an overestimation of clinical benefits [8].

The main rationale to justify an acceleration of the authorization and reimbursement process, despite the lack of evidence robustness, is underpinned on the legitimate desire to provide rapid access to promising therapies in areas where there are clear unmet or inadequately met clinical needs. On the other hand, this acceleration positions HTAb and payers is a very struggling position to determine the real "value" of these products and decide related "fair prices".

The use of surrogate endpoints or biomarkers quite early after the intervention, rather than final clinical outcomes measured, are less susceptible to be biased or influenced by other factors (such as co-interventions or death from unrelated causes) before reaching the final clinical endpoint. Additionally, in some cases, the measurement of a final clinical outcome may be excessively invasive or risky for patients,

apart from the fact that patient survival may require lengthy follow-up as well as a large number of patients to reach the evidence of benefit, especially in early stages of the disease. However, the surrogate endpoints normally used have not always been well validated, meaning that a change in the surrogate that can predict a subsequent change in the clinically more relevant endpoints may be unclear [9].

Thus, a common approach to addressing uncertainty in the "value" assessment of these new drugs has been the use of managed entry agreements, with the key explicit goal of managing financial risks for the payers [8]. As suggested by some authors [10], very frequently these agreements have not helped reduce uncertainties related to "hard" clinical outcomes of the treatments under assessment, limiting as well its cost-effectiveness interpretation.

Although final clinical endpoints from randomized clinical trials (RCTs), such as the overall survival, are considered the reference for robust evidence to inform reimbursement and price decisions, in some cases these requirements would be neither ethical nor feasible in specific cancers, such as rare tumor types or those with long survival times. In those cases, there are issues related to running RCTs with a limited understanding of the natural history and epidemiology of rare tumors; the absence of standard supporting diagnostic tests; patients recruitment limitations; or population heterogeneity [11].

Furthermore, regulatory agencies increasingly accept single-arm studies as the basis for "fast track" approvals, weakening the baseline of available evidence for subsequent comparative studies. As a reminder, although these studies cannot be used to generate comparative evidence on cancer progression in the absence of the new medicine, in some cases comparisons can be made using historical controls. In this regard, recent literature [7] highlights the overestimation of the effects of drugs approved using duration of response in non-randomized trials as it represents a poor proxy for overall survival.

All the preceding challenges described above contribute to the limitations of achieving patient expectations of timely access to new oncology medicines while adequately assessing the "value" provided by such innovation to the healthcare system. Due to the exponential budget burden and increasing prices of new onco-hematologic drugs [12], as well as the emerging challenges described, there is an interest to design and implement adequate pricing methodologies for oncology drugs. Among these approaches, the use of clinical effectiveness thresholds, tier pricing schemes, value-based "fair pricing" models, as well as amortization models, in addition to managed entry agreements [13] are the most extended. The limitations to move forward with more transparent and standardized pricing processes are mainly related to

establishing a shared understanding and convention about the definition of "price" as an expression of "value". For example, concepts such as quality-adjusted life-years to standardize health gains, although being broadly used by several payers in Europe, and besides having clear methodological limitations when assessing end-of-life treatments, are also not systematically capturing the social perception of health benefit when life expectancy of diseases differ [14]. Additionally, criteria included in price setting processes are deeply conditioned by available and previous therapeutic alternatives, that can influence the range of prices of pharmaceutical innovation based on historical inertias and baseline costs of the disease for the system [15], and not assessing properly the added value of the appraised innovation. Similarly, limitations on the "value" assessment are reinforced when new add-on treatments based on incremental health benefits over standard of care therapies necessarily increase the price of innovation to the overall treatment burden, but without revising prices of backbone therapies according to the benefit contribution of each combined medicines, thus driving to growing unsustainable costs to manage diseases such as multiple myeloma [11]. Furthermore, depending on the therapeutic area, or the decision-making context, prices may be dependent on dose, posology, or treatment duration, adding complexity to direct comparison of value-based prices of new drugs.

There is a wide academic consensus [16] that the current consolidated and traditional assessment process to decide drug prices are based on a purely economic perspective often failing to reflect a broader social scope of potential benefits of a drug such as equity improvement, achievement of social or patients' expectations, or efficiency gains in the way healthcare is delivered. As previously highlighted in other studies [17] economic rationale is not the only dimension considered by healthcare authorities and payers when deciding drug prices. As the concern to correctly match "price" and "value" in oncology is significantly increasing [18], there is a clear need to assess the value of the reimbursement of new drugs in the light of a more comprehensive decision criteria including as well the perspective of key group of stakeholders (e.g., patients and clinicians) to secure a consistent and transparent rationale for policymakers to prioritize and maximize the social welfare of any healthcare innovation [19].

Based on these traditional health economic concepts that drive policy decision-making, manufacturers also adjust the value proposition of their new drugs to exclusively use health economic tools and to assess their research and development investments [20]. The basic health economic approach compares the incremental potential clinical benefit with the incremental cost. The most prominent measure of benefit is limited to the QALY that estimates the gain of quantity and quality of years of life provided by the new

drug compared to its associated costs. The clear advantage of a single estimate of benefit is its capacity to compare benefits and costs of different drugs and technologies among different therapeutic areas, as shown by the extensive literature published and based on QALYs [21]. This economic approach is extensively used by HTA agencies worldwide, but several studies are repeatedly and regularly identifying key limitations on the use the QALY concept as a unique approach to assess the benefits on new technologies [22-23], showing that the theoretical assumptions of QALY are based on inconsistent preferences [24]. Additionally, several authors conclude that QALY estimates are conditioned by different utility assessment methods [25] and that evidence suggests that the QALY concept is strongly distanced from the social preferences to allocate health care resources [26]. As pointed out by other authors [26] the simple trade of QALY-Cost has additional limitations related to not including information about the severity of disease as well as not capturing the divergent perspective of several stakeholders impacted by the reimbursement of new drugs.

When it comes to analyzing the benefits of new onco-hematologic drugs, other specific limitations should be considered in the currently used "value" assessment methods. Specific frameworks for onco-hematologic products have been launched recently, being the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the Institute for Clinical and Economic Review (ICER), the Memorial Sloan Kettering Cancer Center (MSKCC) and the National Comprehensive Cancer Network (NCCN) the most prominent [27-28-29-30-31]. As previously highlighted by other authors [32] although these frameworks are extremely useful to improve the clinical assessment, they are limited in the inclusion of additional relevant value criteria and normally minimize the impact of uncertainty on potential benefits of the innovation. Additionally, few methodological issues related to the use of omitted or arbitrary weighting criteria to elicit stakeholders' preferences or the lack of economic considerations included in these cancer specific assessment frameworks are among the main limitations recently highlighted by many authors [33-34]. Even when these methodological frameworks are combined with traditional health economic assessments, additional issues arise. Available evidence [35] suggests that QALYs gained at the end of life receive a greater socially weight than QALYs gained from alleviating temporary health problems, and even palliative care receives greater weight than (short) life extensions at the end of life. Based on these results, patients and social preferences seem to be related to the proximity to death, so giving an extra value to whatever therapeutic solution that can be implemented (extending life or not) for patients in the last stages of their lives. These conclusions can have relevant

implications for the "value" assessment of cancer drugs, especially with patients with limited life expectancy or late lines of treatment. Based on the available evidence [32] cancer drugs for patients at the end of life should receive an extra weight if they reduce toxicity and therefore undesirable side effects or significant QoL improve, even if they do not extend life. This approach would systematically improve the perceived benefits of palliative treatments that are often not considered cost-effective given the benefits they provide are of very short duration. Therefore, current exclusively QALY-based assessment models are not sensitive to the relative tradeoff between quantity of life vs life expectancy (known this as the failure of the constant proportional trade-off assumption), systematically underestimating the "value" of end-of-life related therapies.

Alternatively, MCDA frameworks provide a more holistic approach that considers preferences of several stakeholders impacted my new technologies (e.g., patients, providers, clinicians, healthcare authorities or payers), and are especially well suited to solve complex decision-making problems, such as the emerging sophisticated onco-hematologic drug innovation [36]. As highlighted in recent studies [37], although MCDA (and specially EVIDEM) provides a clear wide range of opportunities to support reimbursement decisions (including price setting) [38], it is an assessment framework relatively new in oncology and mainly used for HTA processes, such as reimbursement decisions. MCDA has clear advantages for the value assessment processes [39] as it provides exhaustivity (including multiplicity of outcomes), flexibility (as the scores can be ordinal or numerical), and inclusivity (as it involves the preferences of multiple stakeholders) [1]; therefore, broadening the scope of cancer drugs' benefits assessment and supporting the usual HTA approaches (basically based on cost-effectiveness analysis), by including additional relevant dimensions of "value". This wider approach includes new relevant criteria such as the social value of the new drug, its "innovation level" (combination of unmet need and contribution to improve this need), or its safety profile. The combination of the positive impact of the new drug on these additional dimensions of "value" sometimes can partially offset the "excessive" cost based on traditional clinical outcomes [40]. Furthermore, the evaluation of a wider scope of items follows the rationale that differences may exist in the concept of value between payers and patients: while payers are generally focused on objective clinical outcomes to determine reimbursement conditions, the importance of patient's preferences is not clear. Evidence suggests [41] that for melanoma, for example, regardless of adverse reactions, only 30% of patients prefer any therapeutic alternative that even marginally prolongs life, while physicians are strongly prioritizing combination immunotherapy with improved survival, driving not only to higher

frequency of severe adverse events (59%) as compared to other alternatives (17%-21%), but also to higher costs. Similarly, discrepancies among stakeholders have been also recently highlighted by evidence in England [42], where four of the most relevant outcomes declared by cancer patients and caregivers were survival; progression or relapse; post-treatment side effects; and return to daily life activities; while commissioners of cancer care services were following only mortality data, and no systematic tracking was done on progression or morbidity evidence after setting prices and reimbursement conditions. These discrepancies confirm the need for a more consistent, coherent, and holistic value assessment process by payers and healthcare providers.

Use of explicit Multi Criteria Decision Analysis (EVIDEM) in the European HTA context

Although HTAb do not always explicitly use the MCDA terminology, many assessment agencies apply multiple decision-making rules in their assessment process. Especially for those HTAb without explicit cost-effectiveness thresholds to be applied (as the one used by NICE), the implementation of a MCDA framework can perfectly complement cost-effectiveness and budget impact analysis to enhance the transparency and consistency of the reimbursement and pricing decision making. Even if a clear cost-effectiveness threshold is used by a HTAb, adjustments related to specific social context or disease characteristics (e.g., orphan drugs or end-of-life treatments), should be defined. In that regard, EVIDEM can ease deliberations and elicit preferences or values (MCDA reflective grid) through a common framework that includes interpretive scores (quantitative criteria), qualitatively impacts (qualitative criteria) as well as narratively comments (all criteria) [22]. EVIDEM was designed to reduce the limitations of the process of deliberation by a methodology that ensures a) all relevant generic criteria are included (whether they are considered qualitatively or quantitatively); b) evidence relevant to each criterion is made available through an efficient synthesis methodology; and c) validity is checked at each step of the process (weights, scores and corresponding narratives, aggregated measures) [22].

In the European context, the EUnetHTA, that includes all EU Member States and was set up in 2013, provides policy orientation on the assessment of health technologies (including drugs) based on common methodologies and tools [43] such as the HTA Core Model for Rapid Relative Effectiveness Assessment (REA) [44]. The REA model is a methodological framework that enables standardized technology assessment in the EU, bringing a harmonized framework that allows the comparison of pricing and

reimbursement dimensions considered among different European authorities. EUnetHTA approach is focused on technical aspects that not necessarily assess the degree of alignment with healthcare compassionate principles [45]. As discussed above, European healthcare authorities are among those that progressively including a broader approach to assess the pharmaceutical products, especially in therapeutic areas such as oncology, to reduce the limitations of the current EUnetHTA assessment framework [46]. EVIDEM is the most extended MCDA model used by European HTAb [47] and it includes the concept of reflective multicriteria assuming decision-makers are guided by the values of the healthcare systems: ethically, clinically, socially, and economically. As seen previously, a multicriteria analysis increases the legitimacy of public decisions.

Based on the analysis of 37 European HTAb of 28 EU member states, our research shows that there is a high alignment between the EUnetHTA and EVIDEM methodological frameworks, with consistent approach to domains related to the health problem, current use of the technology, technical characteristics, clinical effectiveness, and safety. On the contrary, there is a clear misalignment on the contextual dimensions included in the EVIDEM framework when compared with EUnetHTA core model. In that regard, the assessment of the system's capacity and appropriate use of intervention is the most aligned criteria between both frameworks, followed by the political/historical/cultural context assessment, the mandate and scope of the healthcare system, the priorities of targeted populations and the equity on access criteria. The EUnetHTA's framework also does not include other social criteria (environmental impact assessment, stakeholders' management, or the assessment of conflict of interests). EUnetHTA analysis includes a general description of the assessed technology and a description of assessment process (guidelines and legislation) in a systematic way, while these criteria are absent in the EVIDEM framework. As previously suggested [20], HTAb do not normally go beyond non-contextual criteria, and it is normally dependent on the specific topic of assessment (e.g., orphan drugs), including or not social, political or cultural perspectives in the value assessment process of new drugs. Additionally, our research concludes that the reported criteria used to support decisions on price and reimbursement of those European HTAb that have the joint responsibility of advising on price and implementing reimbursement final decisions show a more balanced alignment between both methodological frameworks. Thus, the subnational HTAb (where regional authorities are full budget owners) seems to have a more balanced profile among contextual and non-contextual dimensions. The results of our research on the partial concordance of EUnetHTA's REA and EVIDEM frameworks allow us to suggest that

an extension and systematic implementation of the EVIDEM framework in the reimbursement and price decision-making process with a wider value-based approach is not only desirable but technically feasible in a mid-term time horizon in some healthcare systems (such as the Spanish) if there is the adequate political will.

Price of onco-hematologic drugs in Spain and use of MCDA-EVIDEM indicators

In Spain, detailed information about how healthcare authorities define price and reimbursement conditions of new drugs is not available, and lack of predictability potentially driving to inconsistency between value and price has been alleged [48-49] as the information provided by the MoH is not detailed enough to know how the value of the drug has been set. Based on recent data released by MoH [50] 90% of assessed oncologic medicines in Spain are publicly funded with a listed price 15 times higher than the average price of new non-cancer related drugs.

Similarly, there is a lack of available evidence about the relationship between the prices of onco-hematologic drugs and the evidentiary and contextual information available at the time of reimbursement decision in Spain. As our research also suggests, there is room and opportunity to broaden the use of EVIDEM-like contextual assessment tools by European HTAb to support the payer's decision on prices of certain drugs. This approach would allow a structured assessment of parameters measuring drug value by identifying the most relevant EVIDEM criteria related to price decisions made by health authorities and providing relevant information for the feasible implementation of a more systematic Multi Criteria Decision Analysis along the price and reimbursement process in Spain.

There are previous experiences trying to identify and weight MCDA criteria that best reflect the value of medicines in the reimbursement decision-making process, mainly in the orphan drugs' space [51], and showing that clinical efficacy and therapeutic benefit, severity of the disease, along with perception of unmet need were the most important factors in the reimbursement decisions. Some of these international experiences were based on applying a disaggregation process of historic preferences of health–technology assessment, allowing the reconstruction of the preference criteria of the health-technology assessment agencies [52]. A similar approach was taken by Kolasa [53] based on previous assessments by the Polish HTA agency. The authors identified previously determined criteria of 57 assessments run by the agency, concluding that the five more relevant ones were: clinical evidence, cost of the therapy, benefits

and safety aspects, therapeutic alternatives, and cost-effectiveness analysis. The conclusions of that study also highlighted that the economic criteria, although having a relevant weight, were not among the most relevant decision drivers. Similarly, Schey et al. [54] found a relationship between greater treatment costs and higher MCDA scores for several orphan drugs and when comparing the different weighting settings, they found only slight differences between the scores.

A different approach was used by Gothenburg [55] comparing the assessment processes of HTAb in Belgium, UK, Colombia, Norway, Italy, Canada, Spain, and the Netherlands using the dimensions and criteria proposed by EVIDEM and running a consensus among these HTAb representatives to weight the EVIDEM criteria and domains. The final alignment ordered by priority the 'decrease or prevent suffering', 'service the population in an equal manner', 'sustainability of the health system', and 'make informed decisions based on context and evidence', as the most relevant dimensions in the appraisal process of new drugs. The most relevant individual criteria were evidence quality, intervention cost, and comparative efficacy. Similarly, when different stakeholders are asked about the prioritization criteria using a MCDA-EVIDEM frameworks, results are inconsistent, as showed by Sussex et al. [56]. They selected a group of criteria based on a review of the literature that was assessed by physicians, HTA specialists, and patient representatives in Europe and the United States. Clinical and economic experts gave greater weight to clinical impact evidence, availability of treatments and disease prognosis as compared with current standard of care (no weight was assigned to technological innovation). Patient representatives assigned the weights more homogeneously, giving the largest individual weight to treatment clinical and social impact.

As the therapeutic options in the onco-hematologic space are increasing, there is a need for a clarification about how the existing multi-criteria assessment frameworks should be applied [57]. Several studies that used existing multi-criteria assessment frameworks in oncology have shown they can support HTAb by comparing treatments' benefits and their costs [58] in cancer immunotherapies [59], prostate cancer [60] and thyroid cancer [61].

The use of multidimensional assessment frameworks in Spain is gaining traction, especially in health authorities and HTAb involved in the final reimbursement and access conditions of new drugs (regional agencies) [62]. Three main reasons justify such interest in the use of multi criteria approaches by these agencies [60]. Firstly, it is extensively alleged [63] that the current methodological scope to appraise new drugs can be considered narrow if compared to the possibility of simultaneous evaluation of multiple

factors impacting the value of drugs along the price and reimbursement process. Regional assessment bodies increasingly highlight the need for methodological approaches with a better trade-off between economic and noneconomic aspects [61]. Secondly, the need for additional engagement of multiple stakeholders in the reimbursement decision-making process in the healthcare sector is becoming a technical and political emerging request [64], with special attention in the capacity to gather objectivity and legitimacy of the reimbursement decisions, especially regarding patients' experiences as well as social preferences. Finally, there is a clear political and academic pressure, especially in the Spanish context, to gain transparency about the reimbursement and price decision-making process [62], as payers are under increasing public scrutiny not only when rejecting reimbursement (or limited access) of new onco-hematologic drugs, but also for the public resources' allocation decisions in healthcare [65].

Early experiences in implementing MCDA approaches in the reimbursement decisions in Spain started in Catalonia. The Catalan Health Care System (Servei Català de la Salut, CatSalut), the regional health care body responsible for ensuring public access and rights for health delivery, chose the reflective MCDA-EVIDEM framework in 2017 [66] to help to contextualize the relevant data of new drugs and support the decision-making process on the effective reimbursement conditions. Specific adaptation to orphan drug therapies was also conducted later [64]. The experiences in Catalonia showed that MCDA is a suitable method to visualizing the non-explicit criteria during the price and reimbursement decisions reached in medicines evaluation committees, such as disease severity, clinical unmet needs, or quality of live, as well as other so-called contextual variables which can capture the social and policy complexity environment, the size, and the preferences of the potentially treated population [64]. Additional experiences have been also implemented in Spanish regional pharmacy and therapeutic committee settings with similar conclusions [67]. Recently, a limited pilot experience [68] has been developed to validate a reflective MCDA framework for the assessment and positioning of oncologic therapies in Spain, concluding that only 8 of the EVIDEM dimensions are relevant for oncologists: disease severity, unmet needs, comparative efficacy, comparative safety/tolerability, treatment intent, comparative treatment cost, comparative other medical costs, and quality of evidence.

Based on the increasing use of multi criteria approaches to define reimbursement conditions in Spain, our first-ever exercise to analyze how prices of drugs concord with multi criteria value dimension shows that the listed prices of new cancer products with a single first reimbursed indication in Spain are related to the type of standard of care, references to long-lasting responders, the convenience in the use of the drug

and the impact of treatment on patient's autonomy as well as contextual indicators such as the existence of previous clinical consensus.

These findings suggest that none of the individual items for comparative efficacy, safety or quality of life reached significance for price correlation why contextual synthetic dimensions MCDA-EVIDEM scores [48] (expert consensus), seem to drive to higher perceived value and subsequently higher prices of new onco-hematologic drugs. The lack of standardized metrics and harmonized definition of contextual indicators limits the interpretation of our results, which may be considered only as a proxy of the actual assessment at the time of decision by the Spanish health authorities.

There is a diversity of standardized clinical outcomes (OS, PFS, quality of life, and safety) that medical societies and experts propose to guide pricing decisions [69], and that European healthcare authorities are using to define the public reimbursement conditions of oncology drugs [70]. Other reports [71_72_73_74_75_76] suggest that perceived additional therapeutic benefits based on weak variables (such as response rates) or perception of severity (in the few circumstances where this is measured) may not be driving exclusively onco-hematologic drug prices. In our research, clinical variables, or clinical "hard" variables such as overall survival were not good pricing predictors and it is worthy to note that even other intermediate indicators such PFS, generally accepted as indicators of the capacity of a drug to cure or alter the natural history of the disease [77], were not predicting prices either. The lack of consistent evidence based on long-term efficacy data, or on relative efficacy data of new drugs vs frequently used drugs at the time of price negotiations, does not seem to penalize the price and reimbursement decisions in Spain. As the decision analyzed during this research is focused on defining the price, and not the reimbursement decision, the lack of significant impact of well stablished clinical indicators on price can be explained by the fact that the clinical value has been already taken in consideration during the authorization and reimbursement decision process.

The current research also confirms how relevant can be for Spanish reimbursement authorities the impact on the patient's perception (easiness of use and autonomy), that our data confirmed as statistically significant in the association with prices. The evidence presented in this research also suggests the influence of other contextual indicators, such as the existence of expert consensus and the impact of the route of administration to patients, in the new drugs' pricing decision-making process in Spain. These results highlight that contextual dimensions influence the current Spanish reimbursing processes and support the more systematic implementation of MCDA-EVIDEM methodologies, which capture additional

factors as compared to other frameworks such as EunetHTA core model, to improve the traceability and consistency of successive reimbursement decisions for new drugs. It may be opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and pricing and reimbursement procedures [78].

Several limitations of the study should be considered. Firstly, only few new oncology drugs authorized for a first indication were analyzed. The influence that multiple indications may have in price negotiations requires further analysis. Secondly, the value assessment was made by evaluators working in a context of payers of healthcare services, so that may not fully reflect the perspectives of all stakeholders impacted by pricing and reimbursement decision making. Thirdly, the indicators to explain how MCDA-EVIDEM dimensions are correlated with listed prices, were based on previous literature of an exercise that applied to the hospital perspective and did not include indicators of contextual dimensions, and thus may not be appropriate to summarize actual weights that could be decided by pricing and reimbursement decision makers [48].

Our work may provide a basis for some proposals, that should be set in the context of upcoming regulations and changes in the setting of HTA.

The new European regulation [79] states that inclusive joint clinical assessments able to respond to all Member States' requirements must be produced at the EU level, ideally through consensus, and become part of multi-step national procedures. When, how and by whom the joint clinical assessment reports are used in national decisions must be defined, but since added value of new drugs will depend on the healthcare context and relevant comparisons in each country, yet the final responsibility of the assessments and final decisions remain fully on the remit of the Member States in national procedures, so that, despite non-binding, the joint EU reports will already ensure a degree of consensus on the minimum set of evidentiary data across Europe. The joint EU reports would include relative effects of the intervention on outcomes, critical analysis of validity of the evidence and identification of scientific uncertainty, but must expressely avoid therapeutic positioning judgements. Together with the requirement of transparency and sharing of national basis for decision, the new reglament enhances in this way the relevance of other domains of assessment in the process of decision making by national price and reimbursement organisms. Based on our research, several recommendations can be proposed to improve onco-hematologic (and beyond) drugs price decision-making process in Spain:

- Extension of value-based pricing would allow to set prices for pharmaceutical products based on the measured and quantified multidimensional "value", not limited to QALY based cost-effectiveness analysis and encompassing budget impact analysis with opportunity cost of funding decisions (considering "value" from a systemic and social perspective, assessing clinical benefits, medical unmet needs, degree of innovativeness, safety profile or social expectations and/or preferences).
- Improvement of MCDA-EVIDEM frameworks to ensure an adequate adaptation to the Spanish institutional, social and health context. That requires deciding criteria weighting in any multidimensional assessment approach, as this is key in determining the importance of each criterion among different stakeholders, and because weighting can affect final scoring of assessment dimensions and the value perception of medicines and vaccines. Participation processes to determine acceptable scores and decision processes in the Spanish context are critical to ensuring that social preferences and values are adequately embedded in the technical process. Additionally, providing perspectives from key stakeholders may lead to more acceptable systems and better transparency on how public decisions are made. As there is the risk of diluting the expertise knowledge of certain stakeholders, mainly clinicians that provide solid and scientific arguments that cannot be ignored, lessons from setting clinical practice guidelines could help identifying methods to solve these issues [80].
- Design and implementation of additional operational requirements to extend a holistic value-based pricing process in Spain:
    - Harmonizing and systematizing the collection of benefit measures based on the EVIDEM dimensions, as per the indicators included in this research (Annex 1). As proposed in our study, criteria descriptors must be simple, providing the same understanding by different stakeholders and easing the evaluation of the same characteristics by each specific criterion. Additionally, the definition of the set of criteria must be concise, independent and nonredundant.
    - Enabling the tracking of use of drugs by indication through routinely collected data, registries, or post marketing studies to inform ex-post price adjustments based on monitored expenditures and performance linked to specific indications.

- Limiting the performance-based managed entry agreements to support the generation and collection evidence directly and exclusively related to clinical outcomes uncertainty.

- Implementation of a refined, holistic, simple, and transparent cost-plus methodology ("cost-plus-value" method), adding the monetization of the added value of the innovation to the cost of discovery, manufacturing, and supply of a drug, based on a more robust holistic (MCDA-EVIDEM) definition and assessment of value, as per the description above. This approach goes beyond the basic discussion on antithetic cost-plus [81] vs value-based approaches of pricing [82]. That requires reliable cost information from market authorization holders (direct material costs, direct labor costs, overhead costs associated with R&D, manufacturing costs, regulatory processes, other costs related to business operations and agreed profit margins) and a systematic translation of "value" into "money". As previously discussed, further research will be required to determine the socially acceptable weights among EVIDEM dimensions as well as a set of financial factors by dimension. So far, only very limited experiences [83] has been tested with this broader approach and still lacking solutions to tackle relevant limitations such as the disincentivizing of R&D efficiency (R&D failures discourage disruptive innovation). The proposed model requires to discount 'push' models (e.g., grants for research projects in advance) but secure 'pull' mechanisms that reward for research accomplishments agreed all along the stages of the drug development.

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Chapter 5: Conclusions

1. Structured frameworks to support decision and deliberation processes, such as EUnetHTA and EVIDEM, are widely recommended to improve traceability, transparency and consistency of pricing and reimbursement procedures. Similarly, to EUnetHTA core model, EVIDEM provides a generic interpretive frame (MCDA reflective grid) that can facilitate deliberations and be used to elicit individual values through a common structure. EVIDEM, by including not only non-contextual, but also contextual quantified measures of the value of new drugs, may better respond to the social and medical claim for a more holistic assessment framework to support the payer's decision on prices of certain drugs, such as disruptive cancer diseases.
2. Structured frameworks are barely, or only partially, implemented by current pricing and reimbursement decision bodies across Europe. Those bodies more closely related to pricing and reimbursement decision-making are the ones with wider implementation of multidimensional assessments. There is room and opportunity to broaden the use of contextual assessment tools, such as EVIDEM, to provide a more systematic and transparent price and reimbursement decision-making process.
3. 24 onco-hematologic products were included (first indication) in the Common Portfolio of the Spanish NHS Pharmacy Services (January 2017 – December 2019). All products included but 4 had received a positive decision of pricing and reimbursement in Spain by October 2022. One product was excluded of the analysis due to conflict of interest of the team, and an adjuvant product for photodynamic therapy was deemed as not suitable for the exercise. Eventually, 22 products were analyzed, aimed to treat 11 different tumors. Most frequent indications were breast and lung cancer and 9 drugs had orphan designation. Only 2 products had no therapeutic alternatives (in lung and agnostic indications) and roughly half of the products had targeted therapies as alternative options.
4. The products obtaining a positive reimbursement decision were mainly oral treatments aimed for a non-curative setting, with moderate ESMO MCBS, low quality of evidence, not requiring significant changes in the way the healthcare was delivered, had relevant impact on patients' autonomy (mainly in acute leukemia, lymphomas, melanoma, and neuroblastoma) and their ICER

was normally over the NICE threshold. More than half of the products were also explicitly recommended by experts' consensus or included in the available clinical practice guidelines.

5. The main drivers for oncology drug prices in the period studied seemed to be when the standard of care was combined treatments, if long-lasting responders were reported, and for several characteristics of the treatment: higher prices for fixed duration as compared to treatment until progression and lower frequencies of administration, and lower prices for oral route as compared to other routes of administration.
6. Price was significantly related to the easiness of use of the drug, the impact of treatment on patient's autonomy, and the existence of recommendations by experts. These findings suggest that criteria other than incremental benefit/risk are important in the reimbursement decision making.
7. The implementation of MCDA-EVIDEM methodologies as a standardized framework to assess drugs' innovation has been useful in our exercise to explain the elements that may drive reimbursement decisions for new onco-hematology drugs. Thus, it may represent opportunities to achieve a more consistent and transparent methodology to set prices for new onco-hematologic drugs.
8. Further, the implementation of a more robust and holistic (MCDA-EVIDEM) definition, as well as a value assessment framework as per the definitions included in our research, may be useful to advance into new models for fair pricing through refined, holistic, simple, and transparent cost-plus methodology ("cost-plus-value" method), adding the monetization of the added value of the innovation to the cost of discovery, manufacturing, and supply of a drug.

Annexes

Annex 1. Description of MCDA-EVIDEM items and dimensions.

Dimensions and indicators	Metrics
Non contextual	
Disease severity	
Speed tumor growth	Time of duplication (months)
% Metastasized	Percentage of patients with metastasis at diagnosis
Expected survival 5-years	Percentage of patients with expected survival ≥ 5 years
Physical function and general health	Normalized Score of SF36 - EQ5D – EORTC QLC or C30
Size of affected population	
Prevalence	Cases per 10.000 inhabitants
Incidence	New cases per 10.000 inhabitants and year
Unmet needs	
Treatment options	Percentage with/without alternative treatment options
Type of standard of care	Percentage of chemotherapy / immunotherapy / directed agents /surgery / radio/ combined /others / none
Comparative effectiveness	
Progression free survival	Months (median) during which patients have not experienced disease progression
Progression free survival vs control	Difference in months (median) during which patients have not experienced disease progression vs control
Objective response rate (RECIST/MRD)	Percentage of patients that experience complete response and partial response

Dimensions and indicators	Metrics
Objective response rate (RECIST/MRD) vs Control	Difference in percentage of patients that experience complete response and partial response vs control
Complete response (RECIST/MRD)	Percentage of patients that experience complete response
Complete response (RECIST/MRD) vs control	Difference in percentage of patients that experience complete response vs control
Partial response (RECIST /MRD)	Percentage of patients that experience partial response
Partial response (RECIST /MRD) vs control	Difference in percentage of patients that experience partial response vs control
Long responders	Percentage of patients mentioned as long responders
Overall survival	Months (median) of treatment randomized to death
Overall survival vs control	Difference in months (median) of treatment randomized to death vs control
Comparative safety and tolerability	
Any adverse event	Percentage of patients experiencing an adverse event
Any adverse event vs control	difference in percentage of patients experiencing an adverse event vs control
Non-fatal serious adverse events (>3)	Percentage of patients experiencing an adverse event of grade 3 to 5
Non-fatal serious adverse events (>3) vs control	Difference in percentage of patients experiencing an adverse event of grade 3 to 5 vs control
Fatal adverse events (Grade 5)	Percentage of patients experiencing an adverse event of grade 5
Fatal adverse events (Grade 5)	Difference in percentage of patients experiencing an adverse event of grade 5 vs control

Dimensions and indicators	Metrics
Dosage adjustment due to adverse events	Mention (yes/no) of dosage adjustment due to adverse effects
Treatment discontinuation due to adverse events	Percentage of patients discontinuing treatment due to adverse events
Treatment discontinuation due to adverse events vs control	Difference in percentage of patients discontinuing treatment due to adverse events vs control
Median duration of treatment	Months (median) of duration of treatment
Other Indications (patients exposed)	Number of potential patients for all indications (exposed population as reported in EPAR)
Comparative patient-perceived health and patient-reported outcomes	
Quality of Life	Normalized score of quality-of-life scale
Impact on autonomy	Mentioned (yes/no) disruption of daily activities due to delivering of treatment
Frequency of treatment (administration)	Dose administration by unit of time
Variable treatment guideline	Mentioned (yes/no) treatment guideline's changes
Time of treatment	Mentioned (fixed/up to progression/variable) time of treatment
Easy to use, mode and set of administration	Mentioned (oral/injection/intrathecal) way of administration
Combined chemotherapy	Mentioned (with/without) combination with chemotherapy
Magnitude of therapeutic benefit (*)	
Magnitude of clinical benefits MCBS	Scale of MCBS

Dimensions and indicators	Metrics
Type of benefit	
Curative/Non-Curative	Mentioned (curative/non curative) clinical benefit
Comparative cost consequences – cost of intervention	
NICE ICER > threshold	Mentioned (yes/no) NICE ICER > threshold before any patient access scheme in place.
NICE cancer fund	Mentioned (yes/no) inclusion as a NICE Cancer Fund's Drug
ICER (NICE value)	Δ monthly target therapy cost / Δ time to disease progression as per NICE information
Comparative cost consequences – other medical costs	
Cost treatment (procedures and tests-physician visits-hospitalizations…)	Yearly direct medical costs (€) excluding purchasing costs of the technology (i) concomitant medications, ii) outpatient visits, diagnostic/laboratory tests, hospitalizations, and other monitoring costs (including management AEs), and iii) terminal care.
Comparative cost consequences – non-medical costs	
Cost treatment	Yearly cost of (€) treatment (based on notified prices)
Quality of evidence (**)	
JADAD scale	JADAD scale
Expert consensus and clinical practice guidelines	
Recommendation by experts	Mentioned (yes/no) recommendation included in consensus available at the time of pricing
Contextual	
Mandate and scope of the healthcare system	

Dimensions and indicators	Metrics
Included in National/Sub-National Health Plan	Type of cancer mentioned (yes/no) in healthcare plans
Population priorities and access	
Preferences of the population as a need	Type of cancer mentioned (yes/no) in official positions or documents from NGO's and Patient Advocacy Groups
Common goal and specific interests	
Stakeholders' expression of interest and alignment	Type of cancer mentioned (yes/no) in societal sources (mass or digital media)
Environmental impact	
Impact of the intervention on environment - packaging, production	Relevant environmental impact mentioned (yes/no) in EPAR
System capacity and appropriate use of intervention	
Healthcare services delivery change	Mentioned (yes/no) change in healthcare service delivery or inversion (e.g., new biomarkers) to deliver care
Political, historical, or cultural context	
Societal acceptability of the decisions	Type of cancer mentioned (yes/no) at legal level or included in political statements

Annex 2. Article published on the description of the use of multicriteria to support pricing and reimbursement decisions by European health technology assessment bodies.

Elvira et al. BMC Health Services Research (2021) 21:814
https://doi.org/10.1186/s12913-021-06784-8

BMC Health Services Research

RESEARCH ARTICLE Open Access

Description of the use of multicriteria to support pricing and reimbursement decisions by European health technology assessment bodies

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Abstract

Background: Heterogeneity in drug access throughout Europe may be influenced by differences in drug-assessment strategies. The EUnetHTA's assessment core model (EUnetHTA-core) and the EVIDEM's multicriteria framework are reference methodologies in this context, the latter including a wider compromise between non-contextual and contextual criteria. Compliance of 37 European Health Technology Assessment bodies (HTAb) with EUnetHTA-core has been reported, but the use of EVIDEM by this HTAb is still unknown.

Methods: To describe the uptake and use of multicriteria approaches to evaluate drug value by European HTAb using EVIDEM as reference framework, a multicriteria framework was obtained based on EVIDEM model. The criteria used for drug appraisal by HTAb was extracted from the EUnetHTA report, and completed through search of websites, publications and HTAb reports. Use of EVIDEM assessment model in 37 European HTAb has been described semi-quantitatively and summarized using an alignment heatmap.

Results: Aligned, medium or misaligned profiles were seen for 24,3%, 51,4% and 24,3% of HTAb when matching to EVIDEM dimensions and criteria was considered. HTAb with explicit responsibilities in providing specific advice on reimbursement showed more aligned profiles on contextual and non-contextual dimensions.

Conclusions: EUnetHTA's core model is limited in assessing medicines while EVIDEM's framework provides contextual dimension used by some HTAb in Europe that can be escalated to other agencies. Most of the 37 European HTAb have room to broaden their contextual assessment tools, especially when social and medical perception of need requires to be explicit to support payer's decision on reimbursement.

Keywords: Health technology assessment, Multicriteria assessment methods, Reimbursement systems

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Introduction

One of the major cost drivers in the European healthcare systems is the pharmaceutical 'innovation'; even considered more relevant than demographics [1]. At the same time, it is also recognized as one of the main contributors to the improvement of the population health status [2].

According to the most recent study from the Organization for Economic Co-operation and Development (OECD) [3], pharmaceutical expenditure accounts for a percentage that range between 11.4% (UK) and 19.1% (Spain) of total healthcare expenditure across the five largest European drug markets (France, Germany, Italy, Spain, and the UK). Specifically, the oncological and hematological drugs are leading the budget impact related to pharmaceutical innovation. The impact is driven by the expansion of multiple new indications normally based on a molecular definition that restricts the population to be treated and the drug ends up being designated as orphan-like medicines [4]. As estimated by a recent study [5, 6], the healthcare expenditures on cancer in the European Union member states represented roughly 6% of total healthcare expenditures. The steady increase of oncology costs is aligned with the disease increasing incidence, the progressive reduction of mortality as well as high prices, in contrast with the less robust evidence data on outcomes [7].

A recent study [5] estimated that 40% of the new orphan drugs authorized in Europe are related to rare neoplastic disorders, and compare to non-oncologic indications, the authorization is received at more advance stages of the clinical development and recognizing a higher potential clinical benefit. From 2009 to 2013, only 35% the 68 oncology indications approved by the European Medicines Agency (EMA) showed a significant prolongation of survival and only 10% showed an improvement in quality of life at the time of market approval. The magnitude of the benefit on overall survival ranged from 1.0 to 5.8 months (median 2.7 months). In the subsequent post marketing period (3,3 years later) there was evidence for extension of life in 7% of the previous authorizations and reported benefit on quality of life in 11% of the cases [8].

Occasionally, when the drug can cover clinical unmet needs with poor prognosis, the regulators trend to accept less and poorer evidence and include especial approvals, such as conditional approval related to further of adequate risk benefit rate in real world, after commercialization, or approval under exceptional circumstances when this may not be achieved, in order to ensure an earlier access to market. As described recently [9] the potential benefit of patients' early access to new medicines in areas of high unmet medical need, and based on initial data only, have relevant implications in terms of medical and economic costs (opportunity costs of using alternative more efficient treatments available for patients). Several initiatives have been developed in Europe to address these challenges of funding premium priced products related to clear medical unmet needs but with limited evidence [10]. New access management models of these drugs have been promoted across Europe recently, especially for advance therapies, orphan drugs and medicines for cancer, and including innovative access schemes as value-based pricing, conditional reimbursement schemes or risk sharing approaches [11]. Despite the smooth increase of these new access schemes, the number of outcome-based solutions is still very limited being the lack of a systematic and harmonized value assessment methodology one of the main limitations [12].

Beyond the general awareness among healthcare authorities to ensure "value for money", or the link between price and social or clinical value of the pharmaceutical innovation [13], the reimbursement process and value assessment of drugs is still an open debate in Europe [14]. Several methods have been developed to assess the value of drugs and set meaningful prices affordable to healthcare systems [15]. These methods are normally based on the clinical benefits of the drugs and partially on value-based pricing (e.g. cost-effectiveness analysis). However, there is neither a consensus nor a European harmonization related to drug-pricing systems and, based on a comparative international policy analysis, value-based approaches to determine the prices of innovative products are diverse [16]: including the implicit clinical value of the quality-adjusted life-years (QALYS), mainly used in UK, Sweden or Australia, or the value classification based on innovation scales (used in France, Italy, Germany, Austria, Canada or Japan) [17]. Normally new drugs classified as an innovative medicine are reimbursed at a higher price than the current therapeutic alternatives; although the amount, type and methodology to set the premium is normally veiled by the healthcare authorities [7].

In Europe, the European Network for Health Technology Assessment (EUnetHTA) was set up in 2006 and includes all EU Member States to provide strategic guidance and policy orientation on the assessment of health technologies (including drugs), by developing policy papers and discussing areas of potential collaboration. During the last decade the network has focused the efforts on the development of common methodologies, piloting and producing joint early dialogues and Health Technology Assessment (HTA) joint assessment reports, as well as developing and maintaining common tools [18]. One of the most relevant tools developed by the network is the HTA Core Model for Rapid Relative Effectiveness Assessment (REA) [19]. The Model is a methodological framework for the collaborative production and sharing of

HTA information that defines the content elements to be considered in an HTA and it enables standardized assessment reporting across Europe. Because of the objective of the framework is to share commonly required elements of information, only information that is considered both important and transferable is collected. The model brings a standardized framework that allows a common comparison of the drivers that lead pricing and reimbursement decisions among different European authorities.

HTA Network approach is focused on technical aspects while methods to support alignment of decisions with the compassionate impetus of healthcare systems is lacking [20]. In many countries, healthcare authorities are including a broader approach to assess the pharmaceutical products (especially in therapeutic areas like oncology and rare diseases) [21]. EVIDEM [22] (Evidence and Value Impact on Decision Making) was developed based on an analysis of the foundations of healthcare systems, the reasoning underlying decisions and fair processes, and has become a reference for multicriteria decision approaches in this setting. It includes the concept of reflective multicriteria assuming decision-makers are guided by a generic interpretative frame rooted in the baseline values of the healthcare systems, drawing on several domains of knowledge including healthcare ethics, evidenced-based medicine, health economics or health technology assessment approaches. A multicriteria analysis provides an effective approach to increase the legitimacy of decisions. Beyond a tool, reflective multicriteria pioneered by EVIDEM is geared to transform the vision of the value of healthcare interventions and how they might contribute to relevant, equitable and sustainable healthcare systems. EVIDEM can be used to compare various healthcare interventions and prioritize its implementation using a performance matrix underpinned in the several dimensions and criteria defined by the framework [20].

EVIDEM criteria overlap with EUnetHTA-core except for 4 non-contextual and 3 social criteria, which are absent or partially included in the EUnetHTA framework. Inversely, 2 EUnetHTA criteria are absent in the EVIDEM framework (Table 1).

Although multicriteria EVIDEM approach is now applied by several healthcare authorities [23], especially when the social and medical perception of need requires a more holistic assessment framework to support the payer's decision, a formal and systematic comparison of EUnetHTA's and EVIDEM's methodological frameworks and whether European health technology assessment bodies (HTAb) are aligned with the EVIDEM methodology standards is lacking [24]. Since EUnetHTA and EVIDEM frameworks differ in a substantial number of criteria, it is of interest to know the extent of compliance with EVIDEM framework of HTAs as an additional way to explore potential reasons of assessment discrepancies. Despite the compliance of 37 European HTAb with using the supportive criteria for decision making proposed in the EUnetHTA-core framework has been previously reported [18], whether these HTAb do also comply with the wider EVIDEM multicriteria is unknown.

Thus, the main aim of this study is to describe the uptake and use of multicriteria approaches to appraise drug value by 37 European HTAb, using EUnetHTA and EVIDEM as reference frameworks.

Methods

A quantitative validation of the degree of alignment with the EUnetHTA's standard framework of 37 European HTAb from 28 countries was done, based on a previous qualitative analysis conducted by the European Commission [18] and an additional thorough search of websites, publications and reports of HTAb. The criteria used for appraisal by the different HTAb were identified and classified, and the matching with the criteria described in the EVIDEM methodological framework were described semi-quantitatively using a heatmap of alignment.

The items reported included those criteria in the HTA Core Model, namely: Relative Effectiveness Assessment (REA) of pharmaceuticals, EUnetHTA methodological guidelines [25] and procedure descriptions [26, 27]. Also, criteria related to the types of technologies assessed, the administrative level (national, regional, institutional) and the formal background (legislation, formal agreement, internal guideline) of certain methodological requirements were also used.

An updated version of EVIDEM framework (v.10) was analyzed in order to assess how the dimensions and criteria included in the EUnetHTA methodological framework fitted within the EVIDEM's methodological framework.

The EVIDEM framework includes 13 non-contextual dimensions and 6 contextual dimensions (Table 1). The non-contextual dimensions (EVIDEM core-model) include normative aspects combined with the description of the technical knowledge available. Contextual dimensions tailor the framework to the context of decision-making.

An HTAb heatmap was developed, where heatmap categories were generated for each EVIDEM's dimension using as a source the mentioned criteria in the EUnetHTA's report [18], webs and reports available from the different HTAb analyzed (supplementary file). The contribution (weight) of each mentioned criterion to the final heatmap's score by dimension was equal and proportioned to the number of criteria by dimension described in Table 1. Only when the mentioned criteria

Table 1 EVIDEM and EUnetHTA criteria correspondence

	EVIDEM CRITERIA	EUnetHTA CRITERIA
NON-CONTEXTUAL CRITERIA		
Disease severity	• Effect of disease on life-expectancy • Effect of disease on morbidity (includes disability and function) • Effect of disease on patients' quality of life • Effect of disease on caregivers' quality of life	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA - SEVERITY DEFINITION A description of the health problem and current use of technology are included in assessments
Size of affected population	• Prevalence • Incidence	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA - POPULATION A description of the health problem and current use of technology are included in assessments
Unmet needs	• Unmet needs in efficacy • Unmet needs in safety • Unmet needs in patient reported outcomes • Patient demand	A description of the health problem and current use of technology are included in assessments Systematic search strategies applied to evidences (HEALTH PROBLEM - CURRENT TECHNOLOGY USE)
Comparative effectiveness	• Magnitude of health gain • Percentage of the target population expected to achieve the anticipated health gain • Onset and duration of health gain • Sub-criteria for the measure of efficacy specific to the therapeutic area	The comparator is supported by evidence on its efficacy profile for the respective clinical indication/population Assessments analyze clinical effectiveness / efficacy (added therapeutic value) Systematic search strategies applied to evidences (EFFICACY-EFFECTIVENESS)
Comparative safety/ tolerability	• Adverse events • Serious adverse events • Fatal adverse events • Short-term safety • Long-term safety • Tolerability	The comparator is supported by evidence on its safety profile for the respective clinical indication/population Assessments analyze safety Systematic search strategies applied to evidences (SAFETY)
Comparative patient-perceived health	• Improvement in health-related quality of life • Impact on autonomy • Impact on dignity • Convenience / ease of use / mode & setting of administration	QALYs applied Assessments analyze patient aspects Assessments include a separate ethical analysis Systematic search strategies applied to evidences (PATIENT ASPECTS)
Type of preventive benefit	• Eradication, prevention, reduction in disease transmission, reduction in the prevalence of risk factors). Public health perspective.	Not available
Type of therapeutic benefit	• Symptom relief, prolonging life, cure	Assessments include a description of the health problem and current use of technology
Comparative cost consequences – cost of intervention	• Net cost of intervention • Acquisition cost • Implementation/ maintenance cost	Assessments analyze cost, budget impact or include economic evaluation
Comparative cost consequences – other medical costs	• Impact on primary care expenditures • Impact on hospital care expenditures • Impact on long-term care expenditures	Assessments analyze cost, budget impact or include economic evaluation
Comparative cost consequences – non-medical costs	• Impact on productivity • Financial impact on patients • Financial impact on caregivers • Costs to the wider social care system	Assessments analyze social aspects
Quality of evidence	• Validity (study design, agreement among studies) • Relevance (population, disease stage, outcomes) • Completeness of reporting (uncertainty, conflicting results across studies, limited number of studies) • Type of evidence	Sources of evidence included as relevant clinical evidence for the clinical assessment (1- randomized controlled; 2- Nonrandomized prospective; 3- Other observational; 4- Expert Opinion). Methodology requirements for the clinical assessment compared to the HTA Core Model for REA Formal tools or algorithms for evidence grading applied The GRADE approach in routine use Plan for how evidence will be synthesized (e.g. evidence tables,

Table 1 EVIDEM and EUnetHTA criteria correspondence *(Continued)*

	EVIDEM CRITERIA	EUnetHTA CRITERIA
		meta-analysis, qualitative synthesis)
		Tables and forms are standardized for evidence synthesis and analysis
		Evidence analysis include surrogate endpoints, composite endpoints, PROs, HRQoL measures, indirect comparisons, meta-analysis, relevant group sub-population, key deficiencies in available data, transferability issues, summary of findings
		Sources of evidence on the technology: A. scientific journal publications, B. grey literature (e.g. published reports), C. unpublished data, D. register data, E. administrative data, F. manufacturer data
		Confidential data from manufacturers accepted
Expert consensus/ clinical practice guidelines	Current consensus of experts on what constitutes state-of-the-art practices (guidelines	Not available
CONTEXTUAL CRITERIA		
Mandate and scope of the healthcare system	Alignment with healthcare plans/systems	Circumstances where HTA reports are provided
Population priorities and access	• Current priorities of health system (e.g. low socioeconomic status; specific age groups) • Special populations (e.g. ethnicity) • Remote communities • Rare diseases • Specific therapeutic areas	Assessments analyze social aspects
Common goal and specific interests	• Stakeholder pressures • Stakeholders barriers • Conflict of interest	Assessments analyze social aspects
Environmental impact	• Environmental impact of production • Environmental impact of use • Environmental impact of implementation • Environmental impact of production • Environmental impact of use • Environmental impact of implementation	Not available
System capacity and appropriate use of intervention	• Organizational requirements (e.g., process, premises, equipment) • Skill requirements • Legislative requirements • Surveillance requirements • Risk of inappropriate use • Institutional limitations to uptake	Assessments include a separate ethical analysis Assessments analyze legal aspects Assessments analyze organizational aspects
Political/historical/ cultural context	• Political priorities and context • Cultural acceptability • Precedence (congruence with previous and future decisions) • Impact on innovation & research • Impact on partnership & collaboration among healthcare stakeholders	Assessments include a separate ethical analysis

Source: reference [20]. *GRADE* Grading of Recommendations, Assessment, Development and Evaluations, *HTA* Health Technology Assessment, *HRQoL* Health Related Quality of Life, *PROs* Patient Reported Outcomes, *QALY* Quality Adjusted Life Years, *REA* Relative Effectiveness Assessment

were not fully aligned with the EVIDEM's criteria, the mention was weighted by 50% of contribution:

$$Heat\ Score = \left[\left(\sum \#criteria\ mentioned\ by\ dimension\right)/\left(\sum \#total\ criteria\ by\ dimension\right)\right]*100$$

Descriptive statistics (mean, standard deviation, percentiles) were used to summarize the data and 95% confidence interval for each dimension and HTAb Figs. 1 and 2, and conditional formatting was used to automatically color code each cell using Microsoft Excel (Windows Office 365) so that graded colors were used with green coding for highest alignment (100) and red for lowest alignment (0). Values outside the interquartile range were used to assess alignment with the EVIDEM's model [28]. HTAbs with and average heat score above the 75th percentile were considered "Aligned" with the

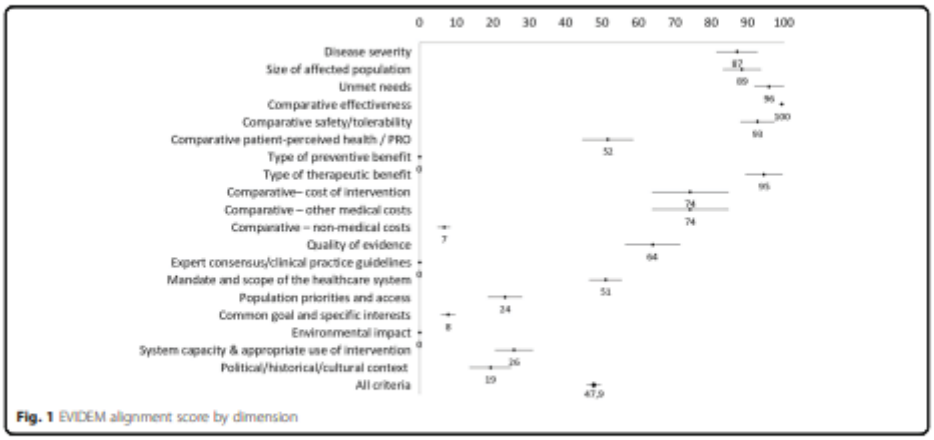

Fig. 1 EVIDEM alignment score by dimension

EVIDEM model, and those below 25th percentile were considered "Misaligned". The rest were classified as "Medium" in terms of EVIDEM model's alignment.

Results

Most of the non-contextual criteria of EVIDEM are overlapped with the core model of EUnetHTA, except for the type of prevention benefits, non-medical comparative cost consequences, systematic use of expert consensus and use of clinical guidelines to define state-of-the-art, which are not or partially included on the EUnetHTA's framework (Table 1). Regarding contextual criteria, the assessment of the system capacity and appropriate use of intervention is the most aligned criteria between both frameworks, followed by the political/historical/cultural context assessment, the mandate and scope of the healthcare system, the special population priorities and equity on access criteria. Other social criteria (stakeholders management, conflict of interest assessment or environmental impact assessment) are not reflected in the EUnetHTA's framework. A systematic general description of the assessed technology and the request of clarification of the assessment process (guidelines and legislation) are key aspects considered by the EUnetHTA analysis that are not explicitly included in the EVIDEM framework.

Most of the non-contextual dimensions (such as disease severity, size of affected population, unmet needs, comparative effectiveness, comparative safety/tolerability or type of therapeutic benefit) show consistently high rates among the HTAb (mean above 85% and standard deviation below 16%); other non-contextual dimensions (type of preventive benefit, comparative non-medical costs, expert consensus) and relevant contextual dimensions (such as population priorities, common goal, environmental impact, system capacity or political/historical/cultural context) are systematically rated low (Table 2).

All HTAb address consistently the health problem and current use of technology, technical characteristics, clinical effectiveness and safety criteria, which are included in the EUnetHTA core model. Choices on comparator, methodology of comparison, endpoints and methods of evidence search and synthesis, are consistently aligned. On the contrary, non-clinical domains, assessment approaches, methodology, modelling algorithms and data are consistently dis-aligned (Table 3).

None of the local HTAb had high heat scores with regards to the use of contextual criteria (Table 2). Considering alignment to EVIDEM-driven assessment framework, three patterns of HTAs emerged: "Aligned", "Medium" and "Misaligned" (Table 4).

Nine agencies in Bulgary, Hungary, Italy, Malta, Slovakia, Spain, Sweden and UK showed an "Aligned" profile (average heat score above the 75th percentile) with a consistent alignment on non-contextual dimensions and significantly high alignment scores on political/historical/cultural context, system capacity and appropriate use of the intervention.

Most HTAb (19/37; 51%) showed a "Medium" alignment profile. Alignment rates for non-contextual criteria were mainly high (e.g. patient perceived health and quality of evidence dimensions) in these HTAb, and also other contextual dimensions (such as the mandate and scope of the healthcare system, system capacity and appropriate use of the intervention) were rated high. On the contrary, population priorities and access dimension systematically rated below 50%, except for AEMPS.

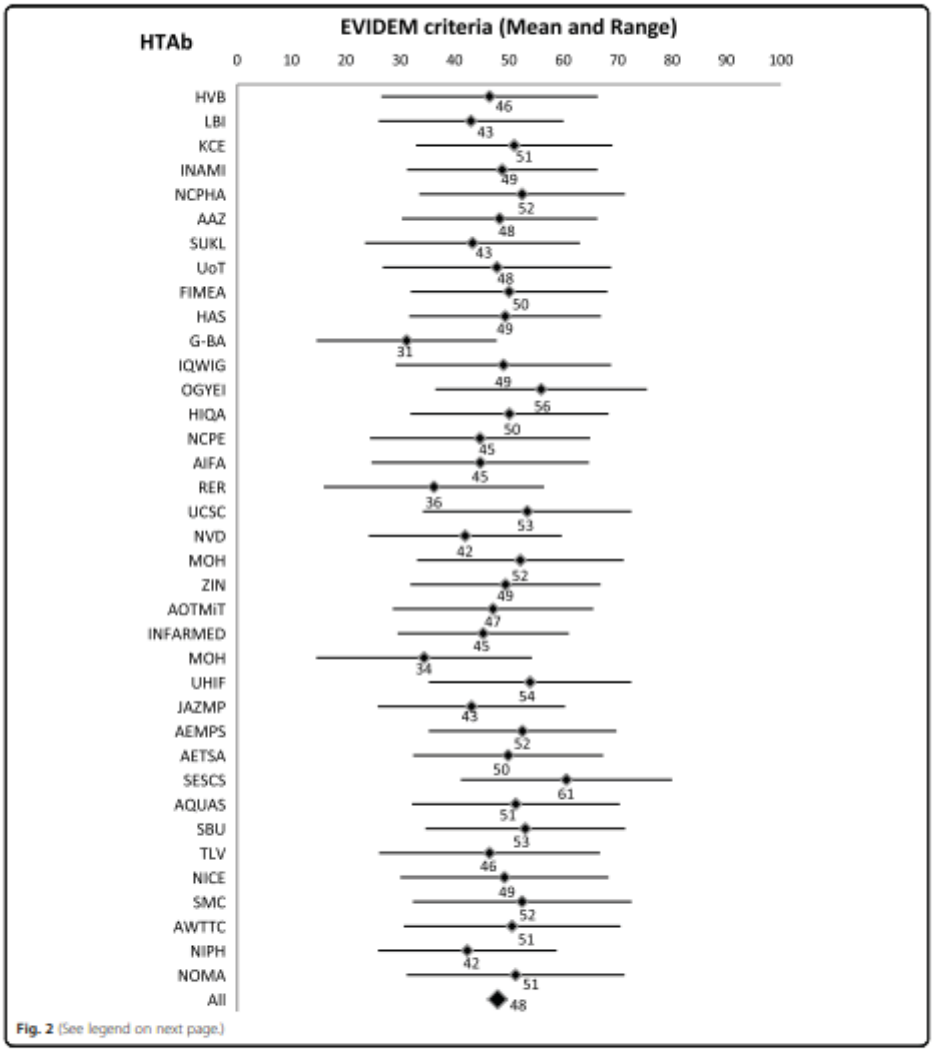

Fig. 2 (See legend on next page.)

(See figure on previous page.)
Fig. 2 EVIDEM alignment score by HTAb. HTAb: Health Technology Assessment body. SESCS: Servicio de Evaluación del Servicio Canario de Salud; SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services; HVB: Hauptverband der Österreichischen Sozialversicherungsträger; KCE: Belgian Health Care Knowledge Centre; INAMI-RIZIV: National Institute for Health and Disability Insurance; NCPHA: National Center of Public Health and Analyses; SUKL: State Institute for Drug Control; FIMEA: Finnish Medicines Agency; HAS: Haute Autorité de Santé; IQWiG: Institute for Quality and Efficiency in Health Care; OGYÉI: National Institute of Pharmacy and Nutrition; HIQA: Health Information and Quality Authority; NCPE: National Centre for Pharmacoeconomics; AIFA: Italian Medicines Agency; UCSC: Università Cattolica del Sacro Cuore; ZIN: Zorginstituut Nederland; AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji; INFARMED: National Authority of Medicines and Health Products; UHIF: Union Health Insurance Fund; AEMPS: Agencia Española de Medicamentos y Productos Sanitarios; AETSA: Agencia de Evaluación de Tecnologías Sanitarias de Andalucía; AQUAS: Agència de Qualitat i Avaluació Sanitàries de Catalunya; TLV: Dental and Pharmaceutical Benefits Agency; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; AWTTC: All Wales Therapeutics and Toxicology Centre; NIPH: Norwegian Institute of Public Health; NoMA: Norwegian Medicines Agency; LBI-HTA: Ludwig Boltzmann Institute of Health Technology Assessment; AAZ: Agency for Quality and Accreditation in Health Care and Social Welfare; UoT: University of Tartu; G-BA: Gemeinsamer Bundesausschuss; RER: Regione Emilia-Romagna; NVD: The National Health Service; MOH: Ministry of Health Malta; MOH: Ministry of Health Slovakia; JAZMP: Agency for Medicinal Products and Medical Devices

In 9/37 (24%) HTAb the profile was considered "Misaligned", with low scores on alignment (average score below 25th percentile) in dimensions such as patients perceived health methods, cost-consequence analysis (cost of intervention and other medical costs) and quality of the evidence. Considering the non-contextual perspective, the German G-BA and the NIPH in Norway show high scores focused and limited to the technical comparison of alternatives (effectiveness, safety and quality of evidence assessment). From the

Table 2 HTAb heatmap of coincidence with EVIDEM framework

COUNTRY	Agency	Disease severity	Size of affected population	Unmet needs	Comparative effectiveness	Comparative safety/tolerability	Comparative patient-perceived health / HRQ	Type of preventive benefit	Type of therapeutic benefit	Comparative cost consequences – cost of intervention	Comparative cost consequences – other medical costs	Comparative cost consequences – non-medical costs	Quality of evidence	Expert consensus/clinical practice guidelines	Mandate and scope of the healthcare system	Population priorities and access	Common goal and specific interests	Environmental impact	System capacity and appropriate use of intervention	Public value/relevance/cultural context
Austria	HVB	100	100	100	100	100	25	0	100	50	50	0	100	0	60	80	0	0	13	0
	LBI	75	75	100	100	100	13	0	100	50	50	30	44	0	60	80	80	0	13	80
Belgium	KCE	100	100	100	100	100	50	0	100	50	50	30	89	0	60	80	80	0	48	80
	INAMI	100	75	100	100	80	50	0	100	50	50	30	100	0	60	80	80	0	27	80
Bulgary	NCPHA	100	100	100	100	80	63	0	100	100	100	30	22	0	60	80	80	0	48	80
Croatia	AAZ	100	100	100	100	100	38	0	100	50	50	30	78	0	60	80	80	0	48	80
Czech R.	SUKL	100	100	100	100	100	50	0	100	50	50	0	56	0	60	0	0	0	0	0
Estonia	UoT	100	100	100	100	100	38	0	100	100	100	0	44	0	60	0	0	0	13	0
Finland	FIMEA	75	75	100	100	100	50	0	100	100	100	30	90	0	60	80	80	0	48	80
France	HAS	100	100	100	100	100	50	0	100	50	50	30	56	0	60	80	80	0	48	80
Germany	G-BA	50	50	75	100	100	25	0	50	0	0	0	83	0	60	0	0	0	0	80
	IQWiG	75	75	100	100	100	63	0	100	100	100	0	67	0	60	0	0	0	48	0
Hungary	OGYÉI	100	100	100	100	100	63	0	100	100	100	30	89	0	60	80	80	0	27	80
Ireland	HIQA	100	100	100	100	100	63	0	100	50	50	30	89	0	60	80	80	0	48	80
Italy	NCPE	75	75	100	100	100	50	0	100	100	100	0	33	0	60	0	0	0	0	0
	AIFA	75	75	100	100	100	38	0	100	100	100	0	33	0	60	0	0	0	13	0
	IRFI	100	100	100	100	100	25	0	100	0	0	0	56	0	60	0	0	0	13	0
	UCSC	100	100	100	100	100	50	0	100	100	100	30	67	0	60	80	80	0	48	80
Latvia	NVD	75	100	50	100	80	13	0	50	100	100	0	44	0	60	80	20	0	13	0
Malta	MOH	100	100	100	100	80	25	0	100	100	100	30	33	0	60	80	80	0	48	80
NL	ZIN	100	100	75	100	100	88	0	100	50	50	30	44	0	60	80	80	0	48	80
Poland	AOTMiT	100	100	100	100	100	38	0	100	50	50	30	67	0	60	80	80	0	27	0
Portugal	INFARMED	50	75	50	80	67	50	0	50	100	100	30	100	0	60	80	80	0	48	80
Slovakia	MOH	75	100	100	100	100	25	0	100	0	0	0	28	0	60	0	0	0	0	0
	UHIF	75	75	100	100	100	75	0	100	100	100	30	89	0	60	80	80	0	53	80
Slovenia	JAZMP	50	50	100	100	50	25	0	100	100	100	30	33	0	60	80	80	0	13	80
Spain	AEMPS	50	50	100	100	100	75	0	100	100	100	20	44	0	60	60	20	0	48	80
	AETSA	100	100	100	100	100	63	0	100	50	50	30	44	0	60	80	80	0	48	80
	MSCS	100	100	100	100	100	88	0	100	100	100	30	100	0	60	80	80	0	53	80
	AQUAS	75	75	100	100	100	75	0	100	100	100	0	67	0	60	80	0	0	13	80
Sweden	SBU	100	100	100	100	100	100	0	100	50	50	30	67	0	60	80	80	0	53	80
	TLV	100	100	100	100	50	25	0	100	100	100	0	67	0	60	0	0	0	27	0
UK	NICE	75	75	100	100	100	38	0	100	100	100	30	72	0	60	80	80	0	13	0
	SMC	100	100	100	100	100	75	0	100	100	100	30	90	0	60	80	80	0	13	0
	AWTTC	100	100	100	100	67	63	0	100	100	100	30	89	0	60	80	80	0	13	0
Norway	NIPH	75	75	100	100	100	50	0	50	50	50	0	83	0	60	80	80	0	13	80
	NOMA	100	100	100	100	67	75	0	100	100	100	30	89	0	60	80	80	0	13	0

HTA Health Technology Assessment, *HRQoL* Health Related Quality of Life, *PROs* Patient Reported Outcomes, *QALY* Quality Adjusted Life Years, *REA* Relative Effectiveness Assessment
Color code using Microsoft Excel (Windows Office 365). Graded colors were used with green coding for highest alignment (100) and red for lowest alignment (0)

Table 3 EVIDEM heat score by dimension

Criteria	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	25th Percentile	75th Percentile
Disease severity	87.2	17.3	50.0	100.0	75.0	100.0
Size of affected population	88.5	16.2	50.0	100.0	75.0	100.0
Unmet needs	95.9	12.5	50.0	100.0	100.0	100.0
Comparative effectiveness	99.5	2.7	83.3	100.0	100.0	100.0
Comparative safety/tolerability	92.8	14.5	50.0	100.0	100.0	100.0
Comparative patient-perceived health / PRO	51.7	21.9	12.5	100.0	37.5	62.5
Type of preventive benefit	0.0	0.0	0.0	0.0	0.0	0.0
Type of therapeutic benefit	94.6	15.7	50.0	100.0	100.0	100.0
Comparative– cost of intervention	74.3	32.5	0.0	100.0	50.0	100.0
Comparative – other medical costs	74.3	32.5	0.0	100.0	50.0	100.0
Comparative – non-medical costs	6.8	5.3	0.0	20.0	0.0	10.0
Quality of evidence	64.0	23.4	22.2	100.0	44.4	83.3
Expert consensus/clinical practice guidelines	0.0	0.0	0.0	0.0	0.0	0.0
Contextual criteria	0.0	0.0	0.0	0.0	0.0	0.0
Mandate and scope of the healthcare system	51.1	13.9	30.0	60.0	30.0	60.0
Population priorities and access	23.5	14.4	0.0	60.0	30.0	30.0
Common goal and specific interests	7.8	5.8	0.0	20.0	0.0	10.0
Environmental impact	0.0	0.0	0.0	0.0	0.0	0.0
System capacity & appropriate use of intervention	25.9	16.3	0.0	53.3	13.3	40.0
Political/historical/cultural context	19.5	17.6	0.0	60.0	0.0	30.0
GLOBAL	47.9	5.8	31.2	60.5	44.7	51.25

contextual perspective, all the HTAb of this group rated low on the mandate and scope of the healthcare system, population priorities on access, system capacity, appropriate use of the interventions and political/historical/cultural context.

HTAb with explicit responsibilities in providing specific advice on pricing and reimbursement (normally regional agencies in countries with more than one HTAb in place, such as Belgian KCE, German IQWIG, Irish HIQA, Italian UCSC, Portuguese INFARMA, Slovakian UHIF, Spanish SESCS or Swedish SBU) showed higher and similar scores on contextual and non-contextual dimensions.

Discussion and conclusions

The alignment between EVIDEM and EUnetHTA methodological frameworks is consistently high, especially when assessing domains related to health problem description, current use of the technology, technical characteristics, clinical effectiveness, and safety. However, other non-contextual dimensions of the EVIDEM framework and the EUnetHTA core model are consistently misaligned.

The main EUnetHTA core model criteria, such as clinical effectiveness, safety conditions, health problem description and current use of technology; are consistently addressed by all HTAb. As previously reported [18] the institutions go only partially beyond these criteria and it is normally dependent on the topic of assessment. For those European HTAb directly advising on price and reimbursement decisions, the reported criteria used to support their decisions show a more balanced alignment between both methodological approaches. That conclusion could explain why in many cases, the subnational HTAb in those countries with multiple agencies, are the ones showing a balanced profile among contextual and non-contextual dimensions.

EVIDEM provides a generic interpretive frame (MCDA – Multi-Criteria Decision Analysis – reflective grid) that can be used to elicit individual values and facilitate deliberations through a common structure that includes interpretive scores (quantitative criteria), qualitative impacts (qualitative criteria) as well as narrative comments (all criteria) [21]. EVIDEM framework was designed to minimize the limitations of the deliberation process by ensuring that: generic assessment criteria (either quantitative or qualitative) are included; evidence relevant to each criterion is made available through an efficient synthesis methodology; and face validity is checked at each step of the process (weights, scores and corresponding narratives,

Table 4 EVIDEM heat score by HTAb

HTAb	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	Degree of Alignment with EVIDEM model
HVB	46.4	44.3	26.5	66.3	Medium
LBI	43.0	37.8	26.0	60.0	Misaligned
KCE	50.9	40.2	32.9	69.0	Medium
INAMI	48.8	39.0	31.2	66.3	Medium
NCPHA	52.4	42.1	33.5	71.3	Aligned
AAZ	48.3	40.0	30.3	66.2	Medium
SUKL	43.3	44.0	23.5	63.0	Misaligned
UoT	47.8	46.8	26.7	68.8	Medium
FIMEA	50.0	40.2	31.9	68.1	Medium
HAS	49.3	39.2	31.6	66.9	Medium
G-BA	31.2	36.8	14.6	47.7	Misaligned
IQWIG	49.0	44.0	29.2	68.8	Medium
OGYEI	55.9	43.3	36.4	75.4	Aligned
HIQA	50.1	40.5	31.9	68.3	Medium
NCPE	44.7	45.0	24.4	64.9	Misaligned
AIFA	44.7	44.5	24.7	64.7	Medium
RER	36.2	45.1	15.9	56.5	Misaligned
UCSC	53.3	42.6	34.2	72.5	Aligned
NVD	41.9	39.5	24.2	59.7	Misaligned
MOH	52.1	42.3	33.1	71.1	Misaligned
ZIN	49.3	38.9	31.9	66.8	Medium
AOTMiT	47.0	41.0	28.6	65.5	Medium
INFARMED	45.3	35.0	29.5	61.0	Medium
MOH	34.4	44.1	14.6	54.2	Aligned
UHIF	53.9	41.4	35.3	72.5	Aligned
JAZMP	43.1	38.3	25.9	60.3	Misaligned
AEMPS	52.5	38.4	35.2	69.7	Aligned
AETSA	49.8	38.9	32.4	67.3	Medium
SESCS	60.5	43.2	41.1	80.0	Aligned
AQUAS	51.3	42.5	32.1	70.4	Medium
SBU	53.0	40.9	34.6	71.4	Aligned
TLV	46.4	45.2	26.1	66.7	Medium
NICE	49.2	42.6	30.0	68.3	Medium
SMC	52.4	44.8	32.3	72.5	Aligned
AWTTC	50.6	44.3	30.7	70.5	Medium
NIPH	42.3	36.5	25.9	58.8	Misaligned
NOMA	51.2	44.6	31.2	71.2	Medium
GLOBAL	47.9	5.8	46.0	49.7	Medium

HTAb Health Technology Assessment body, *SESCS* Servicio de Evaluación del Servicio Canario de Salud, *SBU* Swedish Agency for Health Technology Assessment and Assessment of Social Services, *HVB* Hauptverband der Österreichischen Sozialversicherungsträger, *KCE* Belgian Health Care Knowledge Centre, *INAMI-RIZIV* National Institute for Health and Disability Insurance, *NCPHA* National Center of Public Health and Analyses, *SUKL* State Institute for Drug Control, *FIMEA* Finnish Medicines Agency, *HAS* Haute Autorité de Santé, *IQWIG* Institute for Quality and Efficiency in Health Care, *OGYÉI* National Institute of Pharmacy and Nutrition, *HIQA* Health Information and Quality Authority, *NCPE* National Centre for Pharmacoeconomics, *AIFA* Italian Medicines Agency, *UCSC* Università Cattolica del Sacro Cuore, *ZIN* Zorginstituut Nederland, *AOTMiT* Agencja Oceny Technologii Medycznych i Taryfikacji, *INFARMED* National Authority of Medicines and Health Products, *UHIF* Union Health Insurance Fund, *AEMPS* Agencia Española de Medicamentos y Productos Sanitarios, *AETSA* Agencia de Evaluación de Tecnologías Sanitarias de Andalucía, *AQUAS* Agència de Qualitat i Avaluació Sanitàries de Catalunya, *TLV* Dental and Pharmaceutical Benefits Agency, *NICE* National Institute for Health and Care Excellence, *SMC* Scottish Medicines Consortium, *AWTTC* All Wales Therapeutics and Toxicology Centre, *NIPH* Norwegian Institute of Public Health, *NoMA* Norwegian Medicines Agency, *LBI-HTA* Ludwig Boltzmann Institute of Health Technology Assessment, *AAZ* Agency for Quality and Accreditation in Health Care and Social Welfare, *UoT* University of Tartu, *G-BA* Gemeinsamer Bundesausschuss, *RER* Regione Emilia-Romagna, *NVD* The National Health Service, *MOH* Ministry of Health Malta, *MOH* Ministry of Health Slovakia, *JAZMP* Agency for Medicinal Products and Medical Devices

aggregated measures). EVIDEM framework is sufficiently flexible to be adapted to the local assessment context, although it also requires consistency in the identification of a set of criteria, scoring scale and weights when assessing a broad range of competing interventions in a specific local context [29, 30].

A holistic approach is required to consistently assess the social and medical needs to support payer's decision on prices and reimbursement conditions of certain drugs, such as disruptive innovations or orphan drugs, broadening the need of using EVIDEM-like contextual assessment tools by European HTAb.

Abbreviations

EMA: European Medicines Agency; EUnetHTA: European Network for Health Technology Assessment; EVIDEM: Evidence and Value: Impact on DEcision Making; HTA: Health Technology Assessment; HTAb: Health Technology Assessment Bodies; MCDA: Multi-Criteria Decision Analysis; OECD: Organization for Economic Co-operation and Development; QUALYS: Quality-Adjusted Life Years; REA: Relative Effectiveness Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-021-06784-8.

Additional file 1.

Acknowledgements

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by David Elvira and Mercè Obach. The first draft of the manuscript was written by David Elvira and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received for the conduct of the study.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files (supplementary file.xls).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

David Elvira is a full-time employee of Sanofi. Caridad Pontes and Mercè Obach are public employees with no other conflicts of interest.

Received: 11 February 2021 Accepted: 12 July 2021
Published online: 14 August 2021

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Publisher's Note

Annex 3: Article submitted on reimbursement price decisions for onco-hematology drugs in Spain.

frontiers

Reporting reimbursement price decisions for onco-hematology drugs in Spain.

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Submitted to Journal:
Frontiers in Public Health

Specialty Section:
Health Economics

Article type:
Original Research Article

Manuscript ID:
1265323

Received on:
22 Jul 2023

Revised on:
05 Sep 2023

Journal website link:
www.frontiersin.org

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

CRediT Author Statement

Caridad Pontes: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Mercè Obach:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing - review & editing. **David Elvira Martínez:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Daniel Gay:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing - review & editing. **Daniel Varon:** Conceptualization, Data curation, Investigation, Methodology, Writing - review & editing. **Ferran Torres:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing - review & editing. **Gemma Puig:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing - review & editing. **Josep Tabernero:** Conceptualization, Supervision, Validation, Writing - review & editing. **Roser Vives:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing - review & editing. **Thaïs de Pando:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing - review & editing.

Keywords

Health Technology Assessment, Multicriteria Assessment Methods, Price and Reimbursement Systems, Onco-Hematologic Prices, Value assessment

Abstract

Word count: 116

The study suggests that indicators related to the type of standard of care, references to long-lasting responders, the convenience in the use of the drug and the impact of treatment on patient's autonomy as well as contextual indicators such as the existence of previous clinical consensus are drivers to set oncology drug prices in Spain. The implementation of MCDA-EVIDEM methodologies may be useful to capture the influence on pricing decisions of additional factors not included in legislation or consolidated assessment frameworks such as European Network for Health Technology Assessment (EunetHTA) core model. It may be opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and pricing and reimbursement procedures.

Contribution to the field

The article is particularly appropriate for the journal's scope focused on empirical articles about how to improve the quality and reliability of healthcare services including discussions and reporting on price and reimbursement processes. The research provides evidence on the relationship between oncology and hematology drug prices and structured value parameters (using a multi criteria assessment - EVIDEM - framework) at the time of reimbursement decision in Spain, to identify potential price determinants beyond those reported. Our findings suggest that indicators related to the type of standard of care, references to long-lasting responders, the convenience in the use of the drug and the impact of treatment on patient's autonomy as well as contextual indicators such as the existence of previous clinical consensus are drivers to set oncology drug prices in Spain. The implementation of MCDA-EVIDEM methodologies may be useful to capture the influence on pricing decisions of additional factors not included in legislation or consolidated assessment frameworks such as European Network for Health Technology Assessment (EunetHTA) core model. It may be opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and pricing and reimbursement procedures.. We trust that your readers will find our conclusions of interest to guide the evolution of price and reimbursement processes using value based multicriteria frameworks.

Funding statement

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Ethics statements

Studies involving animal subjects
Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects
Generated Statement: No human studies are presented in the manuscript.

Inclusion of identifiable human data
Generated Statement: No potentially identifiable images or data are presented in this study.

Data availability statement

Generated Statement: The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

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2 Abstract

Introduction

Even using well-stablished technology assessment processes, the basis of the decisions on drug price and reimbursement are sometimes perceived as poorly informed, and sometimes may be seen as disconnected to value. The literature remains inconclusive about how Health Technology Assessment Bodies (HTAb) should report the determinants of their decisions. This study evaluates the relationship between oncology and hematology drug list prices and structured value parameters at the time of reimbursement decision in Spain.

Methods

The study included all new onco-hematological products (22) with a first indication authorized between January 2017 and December 2019 in Spain, and pricing decisions published until October 2022. For each product 56 contextual and non-contextual indicators reflecting the structured multiple criteria decision analysis (MCDA) - Evidence based Decision-Making (EVIDEM) framework were measured. The relationship between prices and the MCDA-EVIDEM framework was explored using univariate statistical analyses.

Results

Higher prices were observed when the standard of care included combinations, if there were references to long-lasting responses, for fixed duration of treatment as compared to treatment until progression and for lower frequencies of administration; lower prices for oral route as compared to other routes of administration. Statistically significant associations were observed between prices and the median duration of treatment, the impact on patient's autonomy, the easiness to use the drug, as well as the recommendation of experts.

Discussion

The study suggests that indicators related to the type of standard of care, references to long-lasting responders, the convenience in the use of the drug and the impact of treatment on patient's autonomy as well as contextual indicators such as the existence of previous clinical consensus are drivers to set oncology drug prices in Spain. The implementation of MCDA-EVIDEM methodologies may be useful to capture the influence on pricing decisions of additional factors not included in legislation or consolidated assessment frameworks such as European Network for Health Technology Assessment (EunetHTA) core model. It may be opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and pricing and reimbursement procedures.

Keywords

Health Technology Assessment, Multicriteria Assessment Methods, Price and Reimbursement Systems, Onco-Hematologic Prices, Value Assessment.

3 Introduction

Concerns about the increasing cost for oncological and hematologic innovation in Europe are growing as prices of cancer drugs are high but not always related to a proportional improvement on patients' health status [1]. In Europe, the increase rate of health spending on cancer has been faster than the increase in cancer incidence during the last 20 years. Similarly, the loss of productivity related to premature cancer mortality has decreased, while productivity loss related to morbidity is still uncertain [2].

Progressively flexible regulatory criteria for authorization in the setting of precision medicine points the focus of market access decision to the pricing and reimbursement process. Studies of authorization decisions in Europe estimated that after monitoring post authorization real world evidence for 3,3 years, benefits on survival of those authorized drugs were only observed in 7% of the cases, and improvement on reported quality of life was achieved in only 11% of them [3]. A recent study [4] confirms that this trend is consolidated, and regulatory practice is biased towards earlier access at the expense of production of post-authorization robust evidence, especially when the drug covers clinical unmet needs in diseases with poor prognosis [5]. Pricing and reimbursement decisions are tough when evidence is scarce and lacking comparative data, risking opportunity costs [6]. In order to minimize those, new access management models have been implemented across Europe during the last decades [7] although in a limited amount and with a lack of methodological harmonization [8]. The increase of prices of oncologic products has generated additional international concerns [9] about the disconnection between price and value.

There is still an open debate in Europe about which are the adequate methods to assess the value of drugs [10]. Methods to set "fair prices" are generally focused on clinical benefits or expanded to the so-called value-based pricing which is usually focused on cost-effectiveness analysis [11-12-13]. Cancer drugs are normally classified as innovation based on implicit clinical value through Quality-Adjusted Life-Years - QALYS (e.g., UK, Australia, Sweden) or using innovation scales (e.g., Canada, Japan, France, Germany, Austria, Italy) [14]. However, healthcare authorities do not normally unveil the details of the methodology applied to assess value, while new cancer drugs are increasingly reimbursed at a higher price than the available alternatives [15].

Recent studies [16] show that even in countries with well-stablished technology assessment processes (such as UK, Germany, France, and Switzerland), prices may still be considered as disconnected to value. In fact, in countries such as France, Australia, or UK, prices are only weakly associated with drug clinical benefits [17–19].

Besides lack of elements to check consistency between price and value, the literature remains inconclusive about the factors that Health Technology Assessment Bodies (HTAb) are using to make their decisions on value and how the payers are deciding and reporting price decisions, especially when applying managed entry agreements [20]. Recent studies [21] show that EVIDEM's framework provides a complete and suitable value assessment framework, including contextual dimensions, and it has been progressively adopted by some HTAb in Europe. Additionally, differences may exist in the concept of value between payers and patients: while payers are generally focused on objective clinical outcomes to determine reimbursement conditions, the importance of patient's preferences is not clear [22–23].

In Spain, the pricing and decision process starts after the European marketing authorization is formally adopted by the Spanish Agency of Medicines and Medical Devices (AEMPS) [24]. Subsequently, a Therapeutic Positioning Report (TPR) is issued by REvalMed network [25] to inform about the added therapeutic value of the drug as compared to current therapeutic alternatives. The TPR includes a therapeutic evaluation from the AEMPS; an economic assessment from the General Directorate for Common Portfolio of the NHS and Pharmacy Services (DGCCSF); and a final technical revision by external experts and scientific societies appointed by the REvalMed network. The TPR, together with the application dossier filed by the marketing authorization holder and DGCCSF own reports, are supposed to be the main driver for reimbursement decisions. The Inter-ministerial Committee on Pricing of Medicines and Healthcare Products (CIPM) is the body responsible for the final resolution of price and reimbursement conditions [26]. The CIPM decision is published as a listed price (not net price) and motivation in general terms, which are based on the criteria listed in the RDL 1/2015, but the information provided by the Ministry of Health (MoH) is not detailed enough to know how the value of the drug has been stablished. It has been questioned whether the Spanish pricing model is based only in budgetary impact and lower European nominal price, without accounting contextual criteria and societal needs.

In fact, detailed information on how Spanish healthcare authorities define price and reimbursement conditions of new drugs is not available, and lack of predictability, potentially driving to inconsistency between value and price has been alleged [27–28]. The Royal Legislative Decree 1/2015 (RDL 1/2015) of the Law on Guarantees and Rational

Use of Medicines and Health Products [29] lists only a restricted set of criteria to be used by the Spanish National Health System to stablish prices of public funded medicines.

Based on recent data released by MoH [30], 90% of assessed oncologic medicines in Spain are publicly funded with a listed price 15 times higher than the average price of new non-cancer related drugs. By 2021, cancer drug costs represented 16,9% of the global pharmaceutical Spanish public budget, and the cost of cancer drugs at hospital level grew by 105,9% since 2016. The main objective of this study was to externally evaluate whether there is a relationship between the prices of oncology and hematology drugs and the evidentiary and contextual information available at the time of reimbursement decision in Spain, by applying a structured assessment of parameters measuring drug value, and to identify the most relevant criteria related to price decisions made by health authorities.

4 Materials and Methods

All new chemical entities with a first EMA authorization for a single onco-hematologic indication between January 2017 and December 2019 were identified, and price and reimbursement decisions of the Spanish MoH, including the notified price and public funding authorization, were tracked based on the publicly available database Bifimed [31] and the resolutions published by the MoH until end of October 2022 (Appendix).

For standardization and comparison purposes, a daily treatment cost based on notified prices was assigned following the Summary of Product Characteristics recommended posology for the studied indication. When the treatment duration was fixed, cost was annualized. Products with a negative decision were assigned a prize of zero; no other data imputation was applied.

For each product, a set of indicators from the MCDA-EVIDEM framework was used. A literature review was carried out to identify the indicators [32,33,34,35,36] for each MCDA-EVIDEM dimension (Table 2). The inclusion criteria for the review were articles published from January 2017 to December 2021 that included MCDA-EVIDEM related indicators to assess onco-hematologic drugs as well as country legislation and HTAb official documents available in English or Spanish. The review did not include outdated documents. The indicators for each product were extracted from available European Public Assessment Report (EPAR), TPR [37], European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) evaluations [38], National Institute for Health and

137 Care Excellence (NICE) economic assessments [39] and freely available information from national and regional
138 healthcare authorities [40]. The indicators were informed by a stepwise approach including two independent
139 reviewers for each product and discrepancies were resolved through discussion. Public notified reimbursed prices
140 per product (expressed as annual cost per treatment) were also included.

141 Continuous variables for each MCDA-EVIDEM dimensions' indicators were expressed as mean ± standard
142 deviation, and categorical variables were expressed as percentage.

143 To evaluate the relation between oncology and hematology treatment prices and MCDA-EVIDEM indicators at the
144 time of reimbursement decision, univariate analyses were performed. For correlation analyses, categories were
145 normalized, and summaries calculated by dimension; prices were categorized by terciles where required. To
146 compare variables, the non-parametric Mann-Whitney test was used for continuous variables and the Fisher exact
147 test for categorical variables. Spearman's coefficients and 95% confidence intervals were calculated to assess
148 correlations. The statistical significance was set at 5% two-tailed. The analysis was deemed exploratory, and thus no
149 measures to account for multiplicity were applied.

150

151 **5 Results**

152

153 From January 2017 to December 2019, 24 oncological new chemical entities were granted a first indication
154 marketing authorization in Europe. One product was excluded due to conflict of interest of the team, and an adjuvant
155 product for photodynamic therapy was deemed as not suitable for the exercise [41] (Figure1). Eventually, 22
156 products were analyzed, aimed to treat 11 different tumors. By October 2022, pricing and reimbursement had been
157 granted for 18 products and denied to 4 products (Table 1). Most frequent indications were breast and lung cancer
158 and 9 drugs had orphan designation (Table 1). Only 2 products had no therapeutic alternatives (in lung and agnostic
159 indications) and roughly half of the products had targeted therapies as alternative options. Likewise, half of the
160 treatments had impact on patients' autonomy (long intravenous administration, daycare admission), mostly in acute
161 leukemia, lymphomas, melanoma, and neuroblastoma. Products for the treatment of melanoma, breast,
162 neuroblastoma, and agnostic indications showed longer Progression Free Survival - PFS (observed and compared to

control) over the median (14 months) and better Overall Survival (OS) versus control was seen for products to treat leukemia and neuroblastoma. Most of the products were aimed to non-curative settings (19/22), with a moderate MCBS score (13/22 products under the score of 4) and low quality of evidence (17/22 products under a JADAD score of 3). Most did not require new healthcare service delivery routes (14/22) and were administered orally (15/22). Many had an Incremental Cost-Effectiveness Ratio (ICER) over the NICE threshold and were included in the NICE Cancer Drugs Fund (16/22), and most were related to cancers included in a National or Regional Health Plans (18/22). More than half of the products (12/22) were explicitly recommended by experts' consensus or included in clinical practice guidelines while 4/22 products were explicitly not recommended (Table 2).

The univariate analysis (Table 3 and Table 4) showed significantly higher listed prices when the standard of care was combined treatments, if long-lasting responders were reported, and for several characteristics of the treatment: higher prices for fixed duration as compared to treatment until progression and lower frequencies of administration, and lower prices for oral route as compared to other routes of administration. There were significant correlations between price and the easiness of use of the drug, the impact of treatment on patient's autonomy, and the existence of recommendations by experts. Regarding summaries by dimensions, the only association to price values was observed for the "expert consensus/clinical practice guidelines recommendations" dimension, that contained a single item.

6 Discussion

Our findings suggest that the initial price of oncology and hematology products tends to be influenced (higher prices) only by few variables: the type of standard of care, the reporting of long-lasting responders, the convenience of use of drugs, the impact on patient's autonomy, a limited duration of the treatment, as well as contextual indicators such as the existence of previous clinical consensus. None of the individual items for comparative efficacy, safety or quality of life reached significance for price correlation. Attempts to summarize values by dimensions, as compared to description of individual items, did not improve explanation of price differences. However, the lack of standardized metrics and harmonized interpretation of contextual indicators limits the interpretation of the results.

The limitations to move forward with more transparent and standardized drug pricing processes is mainly the lack of shared convention about the definition of "price" as an expression of "value" [42]. For example, concepts such as quality-adjusted life-years (to standardize health gains) are not capturing the social perception of health benefit when life expectancy of diseases differ [43]. Additionally, price setting processes are conditioned by available and previous therapeutic alternatives, influencing prices of pharmaceutical innovation based on historical inertias and baseline costs of the disease for the system [44]. Additionally, dose, posology, or treatment duration, add complexity to direct comparison of value-based prices of new drugs.

There is a diversity of standardized clinical outcomes (overall survival, progression free survival, quality of life, and safety) that medical societies and European healthcare authorities [38] are using to guide or define reimbursement conditions of oncology drugs [45]. Other reports [18,19,20,21,22,46] suggest that perceived additional therapeutic benefits based on weak variables (such as response rates) or perception of severity (when this is measured) may be driving oncology drug prices. In our data, these clinical variables as well as "hard" variables such as overall survival were not good pricing predictors. However, we observed higher prices for products reporting references to long-lasting responders. Furthermore, our research also shows that other intermediate indicators such PFS, generally accepted as indicators of the capacity of a drug to cure or alter the natural history of the disease [47], were not strong predictors of prices either. The lack of consistent evidence based on long-term efficacy data, or on relative efficacy data of new drugs versus frequently used drugs at the time of price negotiations, does not seem to penalty the price and reimbursement decisions in Spain. The study also suggests the influence of contextual indicators, such as the existence of expert consensus and the impact of the route of administration to patients, in setting prices.

Several limitations of the study should be considered. Firstly, only few new oncology drugs authorized for a first indication were analyzed. The influence that multiple indications may have in price negotiations requires further analysis. Secondly, the value assessment was made by evaluators working in a context of payers of healthcare services, so that may not fully reflect the perspectives of pricing and reimbursement decision making. Third, we did not calculate summary indicators or overall scores for MCDA-EVIDEM, as suggested by others[44], since the exercise was aimed to check whether a more transparent reporting of the criteria used for decisions may help all stakeholders to predict the key determinants of value, to support both the expectations of manufacturers, the

information to lay public and the consistency in decision making by authorities. Finally, we did not do a systematic search of the literature using diversity of databases to identify all potential studies analyzing the relationship between prices and the MCDA-EVIDEM framework, and there is scarcity of references available on methods and definitions for data extraction and analysis; we cannot exclude that our work may be influenced by publication biases.

Our work may provide a basis for some proposals in the context of upcoming regulations and changes in the setting of Health Technology Assessments. The new European regulation [49] states that inclusive joint clinical assessments able to respond to all Member States' requirements must be produced at the EU level, ideally through consensus, and become part of multi-step national procedures. This new regulation enhances in this way the relevance of multiple domains (clinical, social or economic) of assessment in the process of decision making by national price and reimbursement organisms, being EVIDEM a solid starting point. In this view, further research is needed to standardize measures and determine the socially acceptable weights among EVIDEM dimensions, as well as a set of financial factors by dimension. So far, only very limited experiences [49] have been tested with this broader approach aimed to more transparent and fair pricing, but still lacking solutions to tackle additional limitations such as a potential disincentive effect on R&D efficiency discouraging future disruptive innovation.

7 Conclusions

Our exercise shows that, regardless the paucity of explicative criteria on the decisions, the use of an standardized multidimensional framework allowed to identify that the listed prices of new cancer products with a single first reimbursed indication in Spain are related to the type of standard of care, references to long-lasting responses, the convenience of use of the drug and its impact on patient's autonomy, as well as contextual indicators such as the existence of previous clinical consensus. While individual items are quite explanatory, grouping by the synthetic MCDA-EVIDEM dimensions does not improve explicative value or information.

Based on our results and the lack of detailed information on how Spanish healthcare authorities define price and reimbursement conditions of new onco-hematologic drugs, we propose that the implementation of MCDA-EVIDEM

247 methodologies may help to capture and report additional factors generally not included in consolidated assessment
248 frameworks, such as European Network for Health Technology Assessment (EunetHTA) core model. It may be
249 opportune to consider this in the upcoming revision of the Spanish regulation for health technology assessments and
250 pricing and reimbursement procedures [50].
251

252 ## 8 List of abbreviations

253 AEMPS: Spanish Agency of Medicines and Medical Devices
254 CIPM: Inter-ministerial Committee on Pricing of Medicines and Healthcare Products
255 DGCCSF: General Directorate for Common Portfolio of the NHS and Pharmacy Services
256 EPAR: European Public Assessment Report
257 ESMO-MCBS: European Society of Medical Oncology-Magnitude of Clinical Benefit Scale
258 EUnetHTA: European Network for Health Technology Assessment
259 EVIDEM: Evidence and Value Impact on Decision Making
260 HTAb: Health Technology Assessment Bodies
261 ICER: Incremental Cost-Effectiveness Ratio
262 MCDA: Multi-Criteria Decision Analysis
263 MoH: Ministry of Health
264 NHS: National Health Service
265 NICE: National Institute for Health and Care Excellence
266 OS: Overall Survival
267 PFS: Progression Free Survival
268 QALYS: Quality-Adjusted Life-Years
269 TPR: Therapeutic Positioning Report
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271 ## 9 Declarations

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273 **Funding**: No funding was received for this research.

Conflicts of interest/Competing interests: David Elvira and Mercè Obach are full-time employees of Sanofi. Caridad Pontes, Ferran Torres, Roser Vives, Gemma Puig, Daniel Gay, Thais de Pando, Daniel Varon, Josep Tabernero are public employees with no other conflicts of interest. Josep Tabernero reports personal financial interest in form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, Inspirna Inc, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, Tessa Therapeutics, TheraMyc and Tolremo Therapeutics. Stocks: Oniria Therapeutics and also educational collaboration with Imedex/HMP, Medscape Education, MJH Life Sciences, PeerView Institute for Medical Education and Physicians Education Resource (PER).

Availability of data and material: not applicable

Code availability: Not applicable

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by David Elvira and Caridad Pontes, Ferran Torres, Roser Vives, Gemma Puig, Daniel Gay, Thais de Pando, Daniel Varón. The first draft of the manuscript was written by David Elvira and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

10 Tables and figures

Caption to table 1: Table 1: Price and funding decisions by October 2022 for oncological products with first regulatory authorization from January 2017 to December 2019.

Footnote to table 1: * Cemiplimab was excluded because of conflict of interest; padeliporfin was excluded because the indication was as an adjuvant for photodynamic therapy. ~ Cost calculated according to posology in the product information for the studied indication and annualized where required if fixed maximum length of treatment. Costs of 0.00 € reflect negative price and reimbursement decisions by October 2022.

#Time from the date of European Marketing Authorization until inclusion in the national reimbursement listing; since negative decisions and successive resubmissions may occur until reimbursement is granted, it does not reflect the length of pricing and reimbursement procedure..

Caption to table 2: Table 2: Description of MCDA-EVIDEM dimensions and metrics.

302 ***Footnote to table 2:*** (*) non-curative indications range from 1 (lowest) to 5 (highest) benefit. Curative indications
303 range from A to C. A equalized to 5 and C to 1; (**) JADAD scores range from 0 (lowest) to 5 (highest) quality of
304 trials.
305 ***Caption to table 3:*** Table 3: Description of the mean (SD) listed yearly prices of oncology drugs according to the
306 values of MCDA categorical items.
307 ***Footnote to table 3***: SD: standard deviation; 95% CI: 95% Confidence interval; AEs: Adverse events; ESMO-
308 MCBS: European Society of Medical Oncology – Magnitude of Clinical Benefit Score; ICER: Incremental Cost-
309 effectiveness ratio; NICE: National Institute for Health and Care Excellence
310 ***Caption to table 4:*** Table 4: Univariate analysis of the association between listed prices of oncology drugs and the
311 dimensions of MCDA and subitems within each dimension.
312 ***Footnote to table 4***: Dimension 7 was analyzed separately for preventive and therapeutic benefits since these used
313 different scoring. Dimensions 9 to 12 had a single item each so that the estimate for the dimension is the same than
314 that of the item. Due to lack of data the dimensions number 9 "comparative cost consequences – other Medical
315 costs" and the corresponding item " Cost treatment (procedures and tests-physician visits-hospitalizations) / Year"
316 and number 10 "comparative cost consequences –non-medical costs" and the corresponding item "Cost/ Year" were
317 not analysed for correlation.
318 ***Caption to Figure 1***: Figure 1: Product selection.
319

320

321 *Table 1:* Price and funding decisions by October 2022 for oncological products with first regulatory authorization*

322 from January 2017 to December 2019.

Active principle	Indication	Date authorization	Date final P&R decision	Public funding	Time# to final P&R decision (days)	Yearly treatment cost~ (public listing price)
Inotuzumab ozogamicin	Acute lymphoblastic leukemia	21/07/2017	1/7/2019	yes	710	189,431.35 €
Dinutuximab beta	Neuroblastoma	06/09/2018	1/6/2022	yes	1,364	171,998.95 €
Mogamulizumab	Squamous cell carcinoma	05/06/2019	1/7/2021	yes	757	160,158.35 €
Polatuzumab vedotin	Acute myeloid leukemia	18/02/2020	1/9/2021	yes	561	139,200.05 €
Brigatinib	Lung cancer	28/11/2019	1/5/2021	yes	520	109,781.05 €
Durvalumab	Lung cancer	31/10/2018	1/1/2020	yes	427	98,550.00 €
Rucaparib	Breast cancer	10/05/2019	1/1/2020	yes	236	91,129.55 €
Midostaurin	Chronic myelogenous leukemia	30/10/2017	1/4/2019	yes	518	86,997.75 €
Encorafenib	Melanoma	04/10/2018	1/9/2019	yes	332	86,844.45 €
Binimetinib	Melanoma	19/10/2018	1/9/2019	yes	317	86,844.45 €
Niraparib	Ovarian cancer	08/03/2018	1/8/2019	yes	511	64,918.90 €
Lorlatinib	Lung cancer	20/06/2019	1/2/2021	yes	592	63,630.45 €
Neratinib	Breast cancer	07/01/2020	1/7/2022	no	906	61,320.00 €
Ribociclib	Breast cancer	04/09/2017	1/11/2017	yes	58	57,936.45 €
Tivozanib	Renal cancer	09/04/2018	1/3/2019	yes	326	47,650.75 €
Abemaciclib	Breast cancer	26/10/2018	1/5/2019	yes	187	46,668.90 €

Citarabine/ daunorubicin	Acute myeloid leukemia	19/12/2018	1/3/2022	yes	1.168	42,639.30 €
Gemtuzumab ozogamicin	Acute myeloid leukemia	25/05/2018	1/7/2019	yes	402	35,999.95 €
Dacomitinib	Lung cancer	23/05/2019	1/8/2020	yes	436	32,850.00 €
Talazoparib	Breast cancer	24/07/2019	1/8/2021	no	739	0.00 €
Gilteritinib	Acute myeloid leukemia	05/12/2019	1/6/2021	no	544	0.00 €
Larotrectinib	Agnostic indication	21/11/2019	1/4/2022	no	862	0.00 €

** Cemiplimab was excluded because of conflict of interest; padeliporfin was excluded because the indication was as an adjuvant for photodynamic therapy. ~ Cost calculated according to posology in the product information for the studied indication and annualized where required if fixed maximum length of treatment. Costs of 0.00 € reflect negative price and reimbursement decisions by October 2022.*

#Time from the date of European Marketing Authorization until inclusion in the national reimbursement listing; since negative decisions and successive resubmissions may occur until reimbursement is granted, it does not reflect the length of pricing and reimbursement procedure.

332 *Table 2:* Description of MCDA-EVIDEM dimensions and metrics.

Dimensions and indicators	Metrics	Mean (SD) or %	(N)
Non contextual			
Disease severity			
Speed tumor growth	*Time of duplication (months)*	*13.64 (19.61)*	*20*
% Metastasized	*Percentage of patients with metastasis at diagnosis*	*50% (40%)*	*22*
Expected survival 5-years	*Percentage of patients with expected survival ≥ 5 years*	*29% (25%)*	*22*
Physical function and general health	*Normalized Score of SF36 - EQ5D – EORTC QLC or C30*	*62.41 (21.72)*	*12*
Size of affected population			
Prevalence	*Cases per 10.000 inhabitants*	*23.83 (219.32)*	*22*
Incidence	*New cases per 10.000 inhabitants and year*	*27.06 (29.57)*	*22*
Unmet needs			
Treatment options	*Percentage with/without alternative treatment options*	*With: 90%* *Without: 9%*	*22*
Type of standard of care	*Percentage of chemotherapy / immunotherapy / directed agents /surgery / radio/ combined /others / none*	*Chemotherapy:21%* *Directed agents: 47%* *Combined:17%* *Others: 4%* *None: 9%*	*22*
Comparative effectiveness			
Progression free survival	*Months (median) during which patients have not experienced disease progression*	*13.69 (7.83)*	*22*

Progression free survival vs control	*Difference in months (median) during which patients have not experienced disease progression vs control*	*6.73 (4.59)*	*22*
Objective response rate (RECIST/MRD)	*Percentage of patients that experience complete response and partial response*	*0.55 (0.17)*	*19*
Objective response rate (RECIST/MRD) vs Control	*Difference in percentage of patients that experience complete response and partial response vs control*	*20% (14%)*	*14*
Complete response (RECIST/MRD)	*Percentage of patients that experience complete response*	*23% (27%)*	*20*
Complete response (RECIST/MRD) vs control	*Difference in percentage of patients that experience complete response vs control*	*9% (13%)*	*15*
Partial response (RECIST /MRD)	*Percentage of patients that experience partial response*	*33% (18%)*	*18*
Partial response (RECIST /MRD) vs control	*Difference in percentage of patients that experience partial response vs control*	*10% (7%)*	*13*
Long responders	*Percentage of patients mentioned as long responders*	*Yes: 9%* *No: 91%*	*22*
Overall survival	*Months (median) of treatment randomized to death*	*25.61 (16.43)*	*15*
Overall survival vs control	*Difference in months (median) of treatment randomized to death vs control*	*9.23 (13.25)*	*12*
Comparative safety and tolerability			
Any adverse event	*Percentage of patients experiencing an adverse event*	*97% (6%)*	*22*
Any adverse event vs control	*difference in percentage of patients experiencing an adverse event vs control*	*5% (10%)*	*16*

Non-fatal serious adverse events (>3)	*Percentage of patients experiencing an adverse event of grade 3 to 5*	*57% (26%)*	*16*
Non-fatal serious adverse events (>3) vs control	*Difference in percentage of patients experiencing an adverse event of grade 3 to 5 vs control*	*15% (19%)*	*16*
Fatal adverse events (Grade 5)	*Percentage of patients experiencing an adverse event of grade 5*	*7% (7%)*	*21*
Fatal adverse events (Grade 5)	*Difference in percentage of patients experiencing an adverse event of grade 5 vs control*	*1% (5%)*	*16*
Dosage adjustment due to adverse events	*Mention (yes/no) of dosage adjustment due to adverse effects*	*Yes: 73%* *No: 14%* *Not relevant: 13%*	*22*
Treatment discontinuation due to adverse events	*Percentage of patients discontinuing treatment due to adverse events*	*14% (10%)*	*22*
Treatment discontinuation due to adverse events vs control	*Difference in percentage of patients discontinuing treatment due to adverse events vs control*	*8% (7%)*	*22*
Median duration of treatment	*Months (median) of duration of treatment*	*21.27 (24.54)*	*17*
Other Indications (patients exposed)	*Number of potential patients for all indications (exposed population as reported in EPAR)*	*920.95 (665.65)*	*22*
Comparative patient-perceived health and patient-reported outcomes			
Quality of Life	*Normalized score of quality-of-life scale*	*0.06 (0.22)*	*14*
Impact on autonomy	*Mentioned (yes/no) disruption of daily activities due to delivering of treatment*	*Yes: 41%* *No: 59%*	*22*

Frequency of treatment (administration)	*Dose administration by unit of time*	*Once month: 4%* *Twice month: 4%* *Once week: 4%* *Twice week: 0%* *>Twice week: 9%* *Once day: 48%* *Twice day: 17%*	*22*
Variable treatment guideline	*Mentioned (yes/no) treatment guideline's changes*	*Yes: 13%* *No: 68%*	*22*
Time of treatment	*Mentioned (fixed/up to progression/variable) time of treatment*	*Fixed: 17%* *Up to progress: 50%* *Other: 36.4%*	*22*
Easy to use, mode and set of administration	*Mentioned (oral/injection/intrathecal) way of administration*	*Oral: 68%* *Injection: 27%* *Intrathecal: 4%*	*22*
Combined chemotherapy	*Mentioned (with/without) combination with chemotherapy*	*With: 18%* *Without: 81%*	*22*
Magnitude of therapeutic benefit (*)			
Magnitude of clinical benefits MCBS	*Scale of MCBS*	*3.14 (0.77)*	*22*
Type of benefit			
Curative/Non-Curative	*Mentioned (curative/non curative) clinical benefit*	*Curative:18.2%* *Non-Curative:81.8%*	*22*
Comparative cost consequences – cost of intervention			
NICE ICER > threshold	*Mentioned (yes/no) NICE ICER > threshold before any patient access scheme in place.*	*NA:4.5%* *Yes: 72.7%* *No: 22.7%*	*21*

NICE cancer fund	*Mentioned (yes/no) inclusion as a NICE Cancer Fund's Drug*	*Yes: 36.4%* *No: 63.6.7%*	*22*
ICER (NICE value)	*Δ monthly target therapy cost / Δ time to disease progression as per NICE information*	*52,363.9 (28,859.4)*	*18*
Comparative cost consequences – other medical costs			
Cost treatment (procedures and tests-physician visits-hospitalizations…)	*Yearly direct medical costs (€) excluding purchasing costs of the technology (i) concomitant medications, ii) outpatient visits, diagnostic/laboratory tests, hospitalizations, and other monitoring costs (including management AEs), and iii) terminal care.*	*NA: 50%* *0: 45.5%* *>0: 4.5%*	*11*
Comparative cost consequences – non-medical costs			
Cost treatment	*Yearly cost of (€) treatment (based on notified prices)*	*NA: 100%*	*0*
Quality of evidence (**)			
JADAD scale	*JADAD scale*	*2.50 (1.40)*	*22*
Expert consensus and clinical practice guidelines			
Recommendation by experts	*Mentioned (yes/no) recommendation included in consensus available at the time of pricing*	*Recommended: 24.0%* *Not recommended: 76.4%*	*17*
Contextual			
Mandate and scope of the healthcare system			
Included in National/Sub-National Health Plan	*Type of cancer mentioned (yes/no) in healthcare plans*	*Included:81.8%* *Not included: 18.2%*	*22*

Population priorities and access			
Preferences of the population as a need	*Type of cancer mentioned (yes/no) in official positions or documents from NGO's and Patient Advocacy Groups*	*Identified: 18.2%* *Not identified: 81,8%*	*22*
Common goal and specific interests			
Stakeholders' expression of interest and alignment	*Type of cancer mentioned (yes/no) in societal sources (mass or digital media)*	*Identified: 22.7%* *Not identified: 77.3%*	*22*
Environmental impact			
Impact of the intervention on environment - packaging, production	*Relevant environmental impact mentioned (yes/no) in EPAR*	*Yes:21.1%* *No: 78.9%*	*19*
System capacity and appropriate use of intervention			
Healthcare services delivery change	*Mentioned (yes/no) change in healthcare service delivery or inversion (e.g., new biomarkers) to deliver care*	*Yes: 36.4%* *No: 63.6%*	*22*
Political, historical, or cultural context			
Societal acceptability of the decisions	*Type of cancer mentioned (yes/no) at legal level or included in political statements*	*Identified:9.1%* *Not identified: 90.9%*	*22*

333 *(*) Non-curative indications range from 1 (lowest) to 5 (highest) benefit. Curative indications range from A to C [A*

334 *equalized to 5 and C to 1].*

335 *(**) JADAD scores range from 0 (lowest) to 5 (highest) quality of trials.*

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337 *Table 3:* Description of the mean (SD) listed yearly prices of oncology drugs according to the values of MCDA

338 categorical items.

Variables and values	Mean	SD	Lower limit 95% CI	Upper limit 95% CI
Alternative treatment options				
with	78,800.06 €	52,983.23 €	55,308.61 €	131,783.30 €
without	49,275.00 €	69,685.37 €	18,378.24 €	80,171.76 €
Type of standard of care				
Chemotherapy	68,353.67 €	66,410.51 €	38,908.90 €	97,798.44 €
Combined	143,946.84 €	43,194.75 €	124,795.36 €	163,098.32 €
Directed agents	59,858.69 €	29,376.64 €	46,833.81 €	72,883.56 €
None	49,275.00 €	69,685.37 €	18,378.24 €	80,171.76 €
Long responders				
Not mentioned	60,764.84 €	29,538.65 €	47,668.13 €	73,861.54 €
Yes	98,389.07 €	16,110.32 €	91,246.16 €	105,531.99 €
NA	89,928.88 €	75,408.73 €	56,494.52 €	123,363.23 €
Dosage adjustment due to AEs active				
No	86,236.67 €	80,786.88 €	50,417.77 €	122,055.56 €
Not Relevant	83,546.67 €	76,674.75 €	49,550.99 €	117,542.34 €
Yes	72,825.08 €	47,833.71 €	51,616.80 €	94,033.36 €
Impact of treatment on Autonomy				
No	50,990.95 €	35,392.51 €	35,298.79 €	86,289.74 €
Yes	112,407.66 €	55,550.03 €	87,778.15 €	137,037.16 €
Interval of treatment administration				
Daily	55,771.42 €	35,111.77 €	40,203.73 €	71,339.10 €
Weekly or less frequent	104,747.50 €	71,259.64 €	73,152.75 €	136,342.25 €
Variable treatment guideline				

No	76,789.96 €	54,409.58 €	52,666.11 €	100,913.81 €
Yes	74,671.70 €	55,243.71 €	50,178.01 €	99,165.38 €
Duration of treatment				
Fixed schedule	110,623.33 €	56,319.09 €	85,652.85 €	135,593.82 €
Other	89,918.15 €	66,683.08 €	60,352.53 €	119,483.78 €
Up to progression	56,666.91 €	36,126.07 €	40,649.51 €	72,684.32 €
Easy to Use / Mode & Set of Administration				
Injection	108,091.67 €	58.881.72 €	81.984.97 €	134.198.36 €
Intrathecal	189,430.00 €	- €	- €	- €
Oral	55,771.42 €	35,111.77 €	40,203.73 €	71,339.10 €
Combined chemotherapy				
With	108,549.34 €	59,703.00 €	82,078.51 €	135,020.17 €
Without	68,908.55 €	50,841.26 €	46,366.80 €	91,450.30 €
ESMO -MCBS setting Curative/Non-Curative				
Curative	89,079.34 €	59,071.05 €	62,888.70 €	115,269.98 €
Non-Curative	73,235.22 €	53,406.60 €	49,556.06 €	96,914.38 €
ICER (> NICE threshold)				
No	71,603.22 €	14,199.42 €	64,542.02 €	78,664.43 €
yes	82,283.45 €	59,142.59 €	52,872.53 €	111,694.36 €
ICER (NICE cancer fund)				
no	81,547.28 €	62,812.10 €	53,697.95 €	109,396.60 €
yes	66,611.17 €	32,409.99 €	52,241.39 €	80,980.96 €
Recommendation by experts				
NA	63,000.00 €	69,753.90 €	28,821.22 €	97,178.78 €
Not Recommended	35,209.46 €	26,193.69 €	22,374.79 €	48,044.14 €
Recommended	88,901.03 €	49,442.76 €	64,674.53 €	113,127.54 €
Included in National/Sub-National Health Plan				
Included	73,752.18 €	49,723.26 €	51,706.12 €	95,798.24 €

Not Included	86,753.01 €	75,706.10 €	53,186.81 €	120,319.22 €
Preferences of the population as a need?				
Identified	110,990.61 €	45,170.96 €	90,962.93 €	201,953.55 €
Not identified	68,366.05 €	52,976.65 €	44,877.51 €	91,854.58 €
Stakeholders' expression of interest & alignment				
Identified	98,322.90 €	48,297.69 €	76,908.91 €	119,736.90 €
Not identified	69,584.52 €	54,346.47 €	45,488.64 €	93,680.39 €
Impact of the intervention on environment - packaging, production				
NA	108,149.44 €	57,269.58 €	80,546.39 €	135,752.50 €
No	77,689.18 €	54,898.41 €	51,228.99 €	104,149.37 €
Yes	46,191.30 €	37,980.02 €	27,885.52 €	64,497.09 €
Healthcare services delivery change				
No	69,930.29 €	48,388.88 €	48,475.86 €	91,384.71 €
Yes	86,940.90 €	63,093.87 €	58,966.65 €	114,915.16 €
Societal acceptability of the decisions				
Identified	102,425.00 €	98,393.91 €	58,799.58 €	146,050.42 €
Not identified	73,485.06 €	50,562.17 €	51,067.05 €	95,903.07 €
All products				
Yearly price	76,115.97 €	53,353.38 €	52,460.40 €	99,771.53 €

SD: standard deviation; 95% CI: 95% Confidence interval; AEs: Adverse events; ESMO-MCBS: European Society of Medical Oncology – Magnitude of Clinical Benefit Score; ICER: Incremental Cost- effectiveness ratio; NICE: National Institute for Health and Care Excellence

344 MCDA and subitems within each dimension.

Dimensions and individual items	N	Correlation Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	p Value for H0: Rho=0
1. Disease severity	**22**	**-0,29**	**-0,63**	**0,15**	**0,18**
Speed tumor growth	20	-0.26	-0.61	0.18	0.23
% Metastasized	22	-0.23	-0.60	0.21	0.29
Expected survival 5-years	22	-0.37	-0.68	0.06	0.08
Overall Survival	20	0.09	-0.34	0.49	0.68
Physical function and general health (SF36 - EQ5D - EORTC QLQ-C30)	12	-0.11	-0.50	0.33	0.63
2. Size of affected population	**22**	**0,17**	**-0,27**	**0,55**	**0,44**
Prevalence	22	0.23	-0.21	0.59	0.30
Incidence	22	0.16	-0.28	0.54	0.47
3. Unmet needs	**22**	**0,05**	**-0,38**	**0,46**	**0,81**
Treatment options	22	-0.07	-0.48	0.36	0.74
Type of standard of care	22	0.05	-0.38	0.46	0.81
4. Comparative effectiveness	**22**	**0,15**	**-0,29**	**0,54**	**0,50**
Progression Free Survival observed observed	22	-0.14	-0.53	0.30	0.53
Progression Free Survival difference to control	18	0.14	-0.30	0.53	0.52
Objective Response Rate (RECIST/MRD) observed	19	-0.35	-0.67	0.09	0.10

Objective Response Rate (RECIST/MRD) difference to control	14	0.20	-0.24	0.57	0.37
Complete response (RECIST/MRD) observed	20	-0.01	-0.43	0.41	0.96
Complete response (RECIST/MRD) difference to control	15	0.38	-0.04	0.69	0.07
Partial response (RECIST /MRD) observed	18	-0.15	-0.54	0.29	0.49
Partial response (RECIST /MRD) difference to control	13	0.27	-0.17	0.62	0.22
Long responders (Yes/no)	11	0.17	-0.27	0.55	0.44
Overall Survival observed	15	0.21	-0.23	0.58	0.33
Overall Survival difference to control	12	0.29	-0.15	0.63	0.18
5. Comparative safety/tolerability	**22**	**-0,13**	**-0,53**	**0,30**	**0,55**
Any Adverse Events observed	22	-0.18	-0.56	0.26	0.42
Any Adverse Events difference to control	16	0.04	-0.39	0.45	0.87
Non-Fatal Serious Adverse Events (>3) observed	22	0.15	-0.29	0.54	0.50
Non-Fatal Serious Adverse Events (>3) difference to control	16	-0.02	-0.44	0.40	0.91
Fatal Adverse Events (Grade 5 AEs) observed	21	-0.06	-0.47	0.37	0.78
Fatal Adverse Events (Grade 5 AEs) difference to control	16	0.08	-0.35	0.48	0.72
Dosage adjustment due to adverse effects	22	0.06	-0.37	0.47	0.78
Treatment discontinuation (due to AEs) active	22	-0.25	-0.61	0.19	0.25

Treatment discontinuation (due to AEs) difference to control	17	-0.07	-0.48	0.35	0.74
Median duration of treatment	22	-0.49	-0.75	-0.09	*0.01*
Extent of exposure: Other indications, number of indications	22	-0.22	-0.58	0.22	0.31
6. Comparative patient-perceived health / PRO	**22**	**-0,14**	**-0,53**	**0,30**	**0,54**
HRQoL	14	0.37	-0.06	0.68	0.08
Impact on Autonomy	22	-0.45	-0.73	-0.04	*0.03*
Frequency of treatment (how often is administered)	22	0.40	-0.03	0.70	0.06
Variable treatment schedule	22	0.02	-0.40	0.44	0.92
Time of treatment	22	0.41	-0.01	0.71	0.05
Easy to Use / Mode & Set of Administration	22	-0.48	-0.75	-0.08	*0.02*
Combined chemotherapy	22	-0.27	-0.62	0.17	0.21
7.a. Magnitude of preventive benefit	**18**	**0.16**	**-0.28**	**0.55**	**0.47**
Magnitude of preventive benefit	18	0.16	-0.28	0.55	0.47
7.b. Magnitude of therapeutic benefit	**22**	**0.13**	**-0.31**	**0.52**	**0.57**
Magnitude of therapeutic benefit	22	0.13	-0.31	0.52	0.57
8. Comparative cost consequences – cost of intervention	**22**	**-0,03**	**-0,45**	**0,39**	**0,87**
Incremental Cost-effectiveness ratio (ICER) over NICE threshold (yes/no)	21	-0.09	-0.49	0.34	0.69
ICER: NICE assigns cancer fund (Yes / no)	22	-0.01	-0.43	0.41	0.95
ICER: NICE value (€ or pounds – with 95% CI)	18	-0.08	-0.49	0.35	0.70

11. Quality of evidence:	**22**	**-0,02**	**-0,44**	**0,40**	**0,91**
JADAD/ESMO assessment of quality (from 1 to 5 where 5 maximum)	22	-0.02	-0.44	0.40	0.91
12. Expert consensus/clinical practice guidelines	**17**	**0,56**	**0,17**	**0,79**	**0,00**
Availability of guidance for use and recommendation in guidance/by experts	17	0.56	0.17	0.79	*0.00*
13. Contextual criteria	**22**	**0,03**	**-0,40**	**0,44**	**0,90**
Mandate and scope of the healthcare system	22	-0.05	-0.46	0.38	0.81
Population priorities and access	22	0.35	-0.09	0.67	0.11
Common goal and specific interests	22	0.26	-0.18	0.61	0.24
Environmental impact	19	0.01	-0.41	0.43	0.97
System capacity and appropriate use of intervention	22	-0.17	-0.55	0.26	0.43
Political/historical/cultural context	22	0.05	-0.38	0.46	0.83

Dimension 7 was analyzed separately for preventive and therapeutic benefits since these used different scoring. Dimensions 9 to 12 had a single item each so that the estimate for the dimension is the same than that of the item. Due to lack of data the dimensions number 9" comparative cost consequences – other medical costs" and the corresponding item "Cost treatment (procedures and tests-physician visits-hospitalizations) / Year" and number 10 "comparative cost consequences –non-medical costs" and the corresponding item "Cost/ Year" were not analyzed for correlation.

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360 *Figure 1. Product selection*

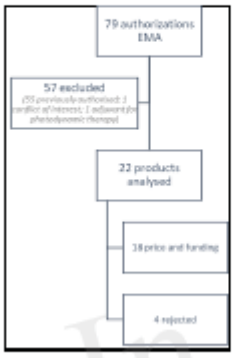

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Figure 1.JPEG