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Special article

[Translated article] The relevance of therapeutic positioning in the post-approval evaluation of new drugs

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ABSTRACT

The objective of regulatory authorities is to ensure a favourable risk–benefit balance for medicines in their licenced indication, without seeking to establish their place in the therapeutic armamentarium beyond that. The licenced indication covers heterogeneous subpopulations and often does not sufficiently specify the characteristics of the patients who may benefit. The regulatory information does not always show the benefit over the standard treatment(s); moreover, it only reacts to the conditions specified in the developer's application, and lacks an assessment of the clinical relevance of the benefit and its uncertainties.

Many cases highlight the need to establish a more specific therapeutic benefit scenario than the licenced indication. For example, abemaciclib was approved in the adjuvant setting for high-risk patients with early breast cancer, but the appropriate level of risk and how to assess it needs to be specified. Also, pembrolizumab is approved for neoadjuvant plus adjuvant treatment in lung cancer; but it remains to be analysed whether it is superior to nivolumab in neoadjuvant treatment alone, which involves less treatment and economic burden.

As therapeutic positioning is always a necessary decision, whether made at a national, regional, local, or individual level, it must be made in the most appropriate way. The absence of a multidisciplinary discussion and consensus, relying only on individual decisions to determine positioning from the outset, underestimates information gaps, inter-individual variability, and the influence of drug promotion. It can be harmful and costly.

To properly manage the introduction of new medicines, it is essential to establish their benefit scenario in a multidisciplinary way. This, together with consideration of the clinical benefit provided versus the appropriate alternatives and the uncertainties of the benefit, constitutes the objective of the clinical assessment and the basis for designing a well-focused economic analysis. This allows policy-makers to make the most appropriate decisions on pricing and funding new treatments. In an ideal situation, the benefit scenario considered for the new medicine would coincide with the one established for funding, but costs that are difficult to bear may lead to restrictions and affect the final positioning after the economic and budgetary impact assessment.

La importancia del posicionamiento terapéutico en la evaluación post-autorización de nuevos medicamentos

Palabras clave:
Evaluación de medicamentos
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RESUMEN

El objetivo de las agencias reguladoras es asegurar un balance beneficio/riesgo favorable para los medicamentos en su indicación autorizada, sin entrar a establecer su lugar en terapéutica más allá de eso. La indicación autorizada abarca subgrupos heterogéneos y a menudo no especifica lo suficiente las características de los pacientes que se pueden beneficiar. La información regulatoria no muestra siempre el beneficio frente al

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tratamiento o tratamientos estándar; además, se limita a responder exclusivamente a las condiciones especificadas en la solicitud del promotor y carece de valoración de la relevancia clínica del beneficio y sus incertidumbres.

Numerosos casos revelan la necesidad de establecer un escenario de utilidad terapéutica más específico que la indicación autorizada. Así, por ejemplo, abemaciclib se autorizó en adyuvancia para pacientes de alto riesgo con cáncer de mama precoz, pero es preciso especificar el nivel de riesgo adecuado y la forma de valorarlo. Igualmente, pembrolizumab está autorizado en neoadyuvancia más adyuvancia en cáncer de pulmón, pero falta analizar si es superior a nivolumab en neoadyuvancia solamente, que supone menor carga de tratamiento y económica.

Puesto que el posicionamiento terapéutico es una decisión siempre necesaria, ya se tome a nivel estatal, regional, local o individual, es preciso realizarlo de la forma más adecuada posible. Prescindir de una discusión y consenso multidisciplinares, pretendiendo que sean exclusivamente las decisiones individuales las que vayan estableciendo el posicionamiento desde el principio, implica subestimar las carencias de información, la variabilidad interindividual y la influencia de la promoción. En consecuencia, puede resultar perjudicial y oneroso.

Para gestionar de forma adecuada la introducción de nuevos medicamentos, resulta imprescindible establecer su escenario de utilidad de forma multidisciplinar. Esto, unido a considerar el beneficio clínico aportado frente a las alternativas adecuadas, así como las incertidumbres del mismo, constituye el objetivo de la evaluación clínica y la base para diseñar un análisis económico bien enfocado. Así, las autoridades pueden tomar las decisiones más adecuadas sobre el precio y financiación de los nuevos tratamientos. En una situación ideal, el escenario de utilidad considerado para el nuevo medicamento coincidiría con lo establecido para la financiación, pero costes difícilmente asumibles pueden conllevar restricciones y afectar al posicionamiento final, tras la evaluación económica y de impacto presupuestario.

Introduction

The assessment of new drugs by regulatory agencies (such as the EMA and the FDA) is limited to the objective of ensuring that their risk/benefit ratio is positive at the population level, allowing them to be marketed and prescribed based on their potential utility for individual patients.[1] This potential utility is specified in the product information (label), which includes the authorised indication. However, the label does not address all questions regarding the specific place of a drug in actual therapeutic practice compared to other treatment options. The gaps in public regulatory information in guiding the introduction of a new treatment into therapeutic practice—apart from the significant economic considerations—can be summarised in 5 key aspects (Table 1).

The regulatory assessment culminates in a marketing authorisation granted by the European Commission (EC). This is followed by an application for pricing and funding/reimbursement by the companies in each country, which may experience delays. After negotiation with the public funder, a decision on price and funding is issued. If the decision is unfavourable, the companies can either market the drug for limited private use at a price of its choosing or it can refrain from marketing it at all.

For the development of this negotiation and decision-making process, it is essential to specify the position of the drug in therapeutic practice and to assess the economic aspects. Regulatory information and the decision on the authorised indication provide essential data; however, additional comparative assessment and decision-making are needed to efficiently optimise patient benefits.

Managing the reasonable introduction of new drugs into therapeutic practice

Any new therapy introduced into clinical practice will occupy a niche or place in therapeutics. Unless it addresses a previously untreated condition or fills a *therapeutic gap*, it will eventually displace other treatments, either because it offers better health outcomes, improves patient comfort or ease of use, or competes on cost as a similar alternative. This positioning phase is crucial for optimising the benefits of new drugs while minimising risk and cost.

One option, sometimes implicitly or explicitly proposed or valued, is to fund all treatments at the lowest possible price with no conditions of use. In this scenario, the individual decisions of the prescribers ultimately determine the positioning of the new products in therapeutic practice, relying on the rules of a clearly imperfect market. This is the case in healthcare systems that, either by choice or due to poor management, lack effective post-regulatory positioning, whether at the national, regional, or local level (such as through pharmacy commissions). Apart from the shortcomings of regulatory information that we have already identified in guiding the introduction of new drugs into therapeutic practice, the most pressing issue with this naïve model is that it transfers variability in such decisions to individuals, leaving the field wide open to the influence of commercial interests. Therapeutic positioning is something that always has to be conducted, whether at the state, regional, local, or individual level. The problems of variability that often arise when decisions are made at the local or regional level[8] will not be reduced by eliminating multidisciplinary decision-making bodies and leaving the positioning of new drugs to individual discretion. Moreover, the variability of therapeutic decisions in scenarios of high uncertainty, which are relatively common with new treatments, could increase if all decisions are left to individual prescribers. Of course, centralised positioning must also allow the prescriber to make therapeutic adaptations at the level of the individual patient.

In addition, positioning and niche market are parallel concepts in pharmaceutical marketing. As is well known, and has been the case for a long time,[9] training and refresher courses for health professionals are largely funded[10] and, consequently, mediated by the pharmaceutical industry (in terms of programme selection, speakers, and the introduction of biased ideas). Apart from direct promotion, the industry also pays for congresses, training sessions, courses, and conferences. In fact, 75% of the training developed by the scientific societies themselves is funded in this way.[11] It also pays for information with promotional overtones that can be difficult to identify in healthcare and general media.[12] Most authors of clinical practice guidelines have economic conflicts of interest with the pharmaceutical industry whose drugs they recommend.[13] They also provide funding to patient associations[14] and health centres for equipment, research, training, and more. The amount companies invest in promotion far exceeds their investment

Table 1
Gaps in public regulatory information in guiding the introduction of a new treatment into clinical practice.

Drawbacks in the summary of product characteristics		Specific examples
Specification	The authorised indication is a brief description that often fails to clearly specify the type of patients in whom the drug has been studied or those to whom its clinical benefit can be reasonably extrapolated.	Abemaciclib, as an adjuvant therapy for breast cancer, has an authorised indication in patients who are *node-positive with a high risk of recurrence.*[2] But what does *high* risk mean? The answer to this question will strongly influence the size of the target population.
Disaggregation	The authorised indication often includes a heterogeneous patient population, and the results of pivotal trials may not be equally beneficial for all patients.	Mepolizumab is an eosinophil antibody inhibitor, authorised for patients with *severe refractory eosinophilic asthma.*[3] This indication includes patients with very different levels of eosinophils. The benefit of mepolizumab depends to a large extent on these levels, as consistently observed in subgroup analyses of various studies.[4]
Comparison	Clinical benefit must be established against the standard therapy or therapies that may be in use for the indication. Often, they have not even been compared in clinical trials and have to rely on adjusted indirect comparisons.[5]	Many biologic therapies for autoimmune diseases, such as psoriasis, rheumatoid arthritis, and ulcerative colitis, share the authorised indication, but have not been compared with most previously available treatments. When introducing a new treatment, it is essential to determine whether its risk/benefit ratio is superior to that of existing treatments.
Perspective	Regulatory assessment is limited to assessing the indications for a drug requested by the company. The focus of this request, driven by commercial interests, may omit aspects that could lead to it being modified due to interests on the part of the healthcare system.	Tafamidis has been authorised for the cardiac condition of a rare disease at a dose 4 times higher than that previously authorised for another indication. The high dose has shown no superiority in efficacy over the low dose and has been associated with increased toxicity.[6] The EC has restricted its authorisation to the only dose requested by the companies for this new indication, which is the high dose.
Assessment	The relevance of clinical benefit and its uncertainties is not assessed to determine whether the new treatment would displace current standards, compete as a similar alternative, or be reserved for certain conditions.	The ESMO-MCBS assesses the relevance of clinical benefit, providing a score ranging from 1 to 5 for advanced cancer, where scores of 4 and 5 indicate substantial clinical benefit. According to this scale, olaparib combined with abiraterone in prostate cancer does not receive a substantial rating, whereas trastuzumab–deruxtecan in second-line breast cancer does.[7]

ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit Scale; EC, European Commission.

in R&D,[15] and is also reflected in the price. Spain is not exactly at the bottom of pharmaceutical investment in promotion: promotional investment in Spain exceeds that of the UK.[16] Additionally, industry payments to doctors in Spain (€181 million) surpass the combined total of those in the UK (€58 million) and Germany (€109 million).[17] Obviously, such an enormous outlay would be absurd if it did not influence prescribing practices and, consequently, the niche that the drug ultimately occupies in therapeutic practice. For example, it has been shown that conflicts of interest in recommendation documents—from clinical practice guidelines to expert consensus—are associated with positions in favour of the funder's therapy.[18]

In this situation, which has received criticism from civil society,[19] trusting that this imperfect market will self-regulate without well-informed management of healthcare systems could prove to be a costly illusion. This could severely harm the sustainability of the public healthcare system itself and potentially endanger certain patients by using new products that have not demonstrated real health benefits compared to standard treatments, while exposing them to toxicity. To effectively manage the appropriate introduction of new therapeutic products into the market, it is essential to consider their therapeutic positioning. This positioning necessarily relies on complementary post-regulatory assessment but goes beyond it. It is not sufficient to simply gather, provide, and analyse additional results and comparisons; these findings must be prudently applied to current clinical practice. Moreover, an ideal therapeutic positioning for the new drug must be specified to achieve the best health outcomes for patients.

Establishing the utility scenario

Before considering economic criteria, the public health system needs to specifically assess, within the framework of the approved indication, which specific patients would benefit from the drug, in which situations it would be used, and with which alternatives it would compete, either as a preferred option or as a similar treatment. Therefore, it can be said that this is a *pre-positioning* prior to and independent of the economic assessment, as the final positioning must be conducted after the economic assessment and pricing. Some examples are given below to help better understand the issue of the utility scenario/pre-positioning and its significant real-world scope.

The position of a new treatment in therapeutic practice, assigned relative to the standard of care, hinges on whether it provides a relevant additional clinical benefit.[20] Several countries and organisations around the world utilise clinical benefit classifications for post-regulatory therapeutic comparative assessment (Table 2).

Table 2
Clinical benefit classifications for comparative post-regulatory therapeutic evaluation in relevant countries and organisations in our environment.

Stakeholder	Classification
AIFA, Italy[21]	Added therapeutic value: 1. Maximum 2. Important 3. Moderate 4. Scarce 5. None
IQWIG, Germany[22]	Magnitude of additional benefit: 1. Major (large and sustained improvement) 2. Considerable (marked improvement) 3. Minor (moderate but not marginal improvement) [1–3 imply clinically relevant additional benefit] 4. Unquantifiable 5. Unproven additional benefit 6. Inferior benefit (less than comparator)
HAS (France)[23,24]	Improvement of the provided medical service (ASMR; French acronym): I. Major II. Important III. Moderate IV. Minor V. Nonexistent; meaning *no therapeutic progress*
ESMO-MCBS (oncology)[25]	Magnitude of clinical benefit: Curative scenarios: A–B–C Noncurative scenarios: 1–2–3–4–5 A, B, and 4, 5, are considered substantial benefit

AIFA, Agenzia Italiana del Farmaco; IQWIG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; HAS, Haute Autorité de Santé; ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit Scale.

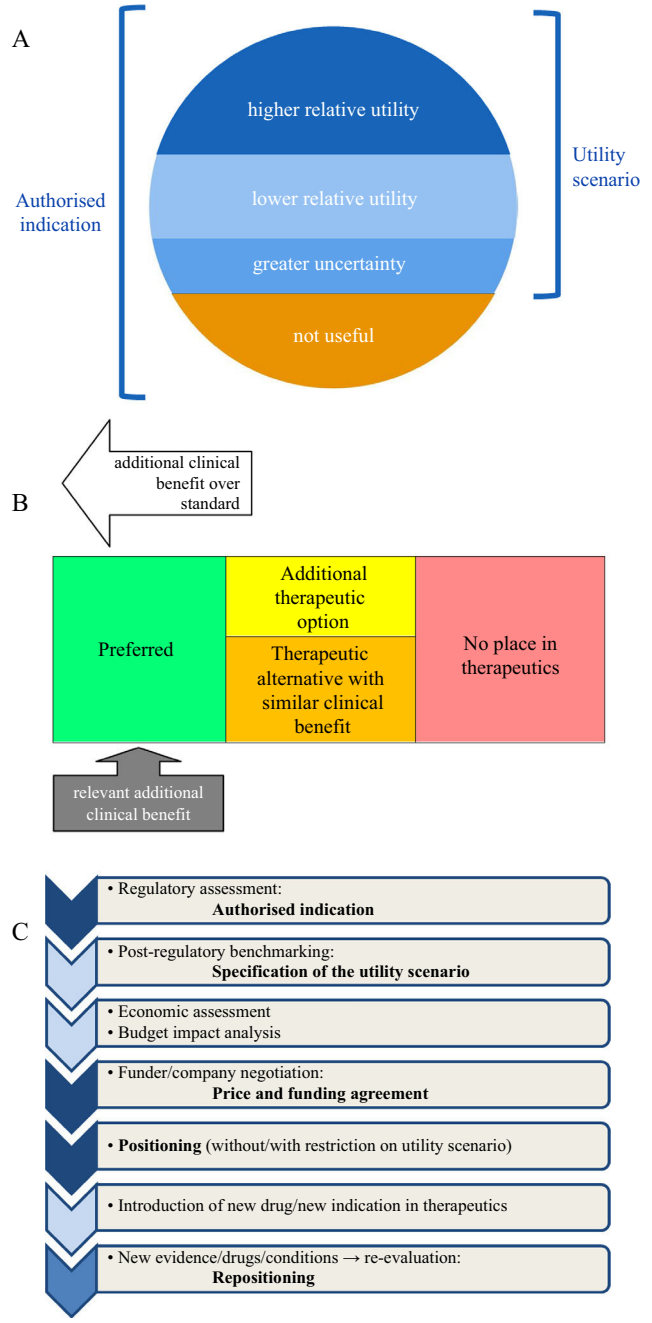

Fig. 1. Pre-positioning prior to economic evaluation and budget impact analysis as a result of applying post-regulatory benchmarking. A) Utility scenario. B) Classification options versus other available options. C) Sequence of procedures for the assessment and positioning of new drugs/indications.

Fig. 1A outlines the proposed assessment and positioning model. This model began to be implemented in Spain with the creation of REvalMed network in 2021,[26] although the network has since been dissolved. The utility scenario is established by utilising the information on the comparative risk/benefit information versus the standard. Fig. 1B illustrates the outcome of applying this post-regulatory therapeutic assessment to a new treatment. Within the authorised indication, situations or subpopulations may experience greater, lesser, or no clinical benefit compared to existing therapeutic alternatives, as well as scenarios where uncertainty remains. Compared to alternatives, which may be multiple and vary across different subpopulations, the new therapy may or may not provide a relevant additional clinical benefit and may or may not be considered preferable to them. If no relevant differences in benefit are identified, the treatments under consideration may be regarded as alternatives with similar clinical benefits, allowing for a choice between them. Alternatively, they may simply be viewed as therapeutic options when important differences hinder a clear selection, requiring a more individualised choice based on factors such as safety profiles, form of administration, convenience, and so on (Fig. 1C).

This situation is complicated and involves significant additional uncertainty because, in 34% of cases, the new drug has not been directly compared to the current standard,[27] necessitating adjusted indirect comparisons. It is also possible that the magnitude of benefit may vary among subpopulations or subgroups.[28]

The fourth guarantee (therapeutic positioning and efficiency)

Any authorised drug must have successfully overcome what were known from a marketing perspective as the *three hurdles*: proven quality, safety, and efficacy.[29] From a health perspective—specifically, that of the patient for whom they are intended—they should more accurately be referred to as *guarantees*. The most advanced health systems with public coverage have introduced a *fourth guarantee*,[30,31] aimed at ensuring that drugs are also cost-effective.[29] This initiative aligns with the WHO's definition of the rational use of drugs, which includes the issue of cost,[32] which is essential for patient access to treatment.[33] Although the fourth guarantee is not included in the regulatory environment, it should also be addressed as a mandatory requirement within the decision-making process regarding drug funding (Spanish Law on Guarantees).[34]

A proper economic and budgetary impact assessment cannot be conducted simplistically by relying solely on the comparisons provided by the pivotal trial within the authorised indication. As noted above, other comparators may exist, direct comparisons with the standard are often lacking, and the authorised indication is often not specific enough to clearly define the target population.

All of this requires making decisions about the utility scenario and accurately assessing the inputs to effectively design the economic evaluation. The complexity of these decisions necessitates the evaluation of evidence, accurate clinical interpretation, and a reasonable and consensual implementation of the resulting insights that aligns with the realities of current therapeutic practice in the healthcare system. While this can be addressed by the authors themselves in the early stages of economic studies, an economic evaluation intended to support public funding in a country should involve a multidisciplinary consensus of experts (including evaluators and clinicians)[35] to define the utility scenario, reflecting the specific expectations of the healthcare system regarding the intended use of the new therapy. This is all the more critical as the commission to conduct the economic evaluation may be awarded to the company itself, which has its own interests in the therapeutic niche occupied by its drug.[20] Therefore, the economic analysis for the public health system—whether conducted by independent evaluators or by the pharma companies and subsequently reviewed by independent evaluators—must be based on a consensus on the utility scenario and the alternatives or comparators.

Finally, the funding body will need to consider both the ideal therapeutic position and its uncertainties, as well as economic aspects, in order to negotiate the price and determine whether it can (and should) be funded. If so, consideration should also be given to whether this should apply to the entire pre-specified utility scenario (Fig. 1A) or whether it should be restricted due to issues related to efficiency or budgetary impact (Fig. 2). A pricing agreement covering the entire utility scenario is potentially the most favourable outcome for both the funder and the company, as it ensures that a reasonable price is accessible to all patients who could obtain clinical benefit. In contrast, if the utility scenario is funded with restrictions, the drug's full therapeutic potential remains unrealised, and the funder loses out as patients who could benefit are left untreated. Moreover, the companies probably do not obtain all of their potential profits either. Thus, although the companies also lose

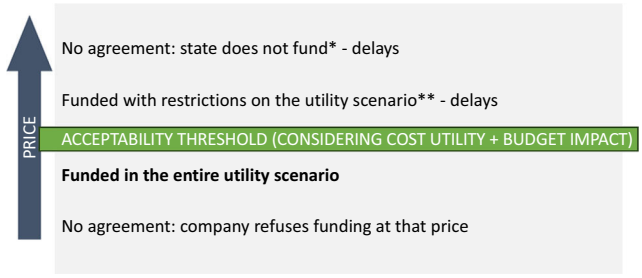

Fig. 2. Selective funding model based on price and budget impact for new drugs/indications with additional clinical benefit. *Challenges for healthcare systems when new drugs have relevant additional clinical benefit. **In the NICE (National Institute for Health and Care Excellence; England and Wales) environment, a cost-utility that does not exceed the threshold indicates funding; exceeding the threshold leads to price renegotiation and additional restrictions according to the Patient Access Scheme (conditions of access for patients).

out, this situation sometimes arises from a lack of negotiating flexibility, stemming from the rigidity of the company's core positions, which pivot around the higher prices achieved in other countries. In public healthcare systems with extensive funding and universal coverage—where pharma companies have difficulty adapting prices—it is important that funding be at least delimited by the utility scenario.

To illustrate the above points, 2 current examples of drugs with a significant health and economic impact are presented below. These examples demonstrate that establishing the utility scenario in a post-regulatory assessment is essential for ensuring the appropriate use of drugs, maximising clinical benefit for patients, and avoiding unnecessary and wasteful expenditure.

Abemaciclib in adjuvant therapy

Abemaciclib in adjuvant therapy is a recent, paradigmatic case with significant clinical and budgetary impact, making it an ideal example to evaluate the perspective of post-regulatory assessment systems. This drug was authorised by the EC in 2022 for the adjuvant therapy of hormone-sensitive breast cancer alongside standard hormone therapy. The pivotal trial commenced by recruiting high-risk patients identified through clinical disease assessment (cohort 1; 90% of patients). After the protocol was modified, the remaining 10% of patients with a high Ki-67 risk index value of ≥20% were included (cohort 2). The EMA Committee for Medicinal Products for Human Use (CHMP) considered that benefit was only demonstrated in cohort 1, as reported in the European Public Assessment Report[36] (i.e., in patients with 4 or more involved nodes, or 1–3 and at least 1 of the following criteria: tumour ≥5 cm or histological grade 3).

However, the indication authorised by the EC in the label only refers to patients with *positive nodes with a high risk of recurrence*, indicating that the criteria for considering 'high risk' would remain open to interpretation in clinical practice.

Therefore, patient selection is poorly defined in the authorised indication. Nothing in the label suggests that this lack of definition arose from an intentional extrapolation to other patient groups. On the contrary, when the efficacy results were presented, only those from cohort 1 were indicated, although the reason for this is not explicitly stated. Simply put, the indication that appears in the label is the one requested by the company, as the risk/benefit ratio for that indication is considered positive.[36] This illustrates the limited perspective and mission of the regulatory agency, which has not considered modifying the requested indication to facilitate the identification of patients for whom clinical benefit has been established.

However, in clinical practice, it is essential to identify the patients who will benefit from this drug. Treating patients who do not benefit implies exposing them to unnecessary adverse reactions and the premature depletion of the supply of abemaciclib. Abemaciclib and another drug with the same mechanism of action are the preferred treatment that can improve survival in patients who experience later relapses.[37]

In terms of economic evaluation, the estimated cost-utility in cohort 1 would not be fully extrapolable to the undefined population of high-risk patients referenced in the indication. On the other hand, the budget impact analysis would be underestimated if it were calculated using the specified criteria of cohort 1 and then applied broadly to any *high-risk patient* as expressed in the indication without further clarification. Table 3 shows the recommendations of the various agencies involved.

Consequently, a post-regulatory assessment that specifies the true utility scenario of abemaciclib in adjuvant therapy is crucial for guiding its inclusion in therapeutic practice, and for defining the scenario and inputs for the economic evaluation and budget impact analysis. In this situation, the healthcare and economic impact of decisions is significant: breast cancer has one of the highest annual incidences (the highest among women), the hormonal subtype is the most prevalent, early-stage cases outnumber those in advanced stages, and the cost of treatment with abemaciclib exceeds €1500 per month.

Pembrolizumab in the adjuvant therapy of lung cancer

A recent comparative clinical trial was conducted to evaluate pembrolizumab as an immunotherapy treatment for lung cancer in a neoadjuvant plus adjuvant setting. The results show a clear benefit over

Table 3
Conditions for the adjuvant use of abemaciclib as recommended by various agencies in the indication of hormone receptor-positive/HER2-positive breast cancer patients.

	Condition for candidate patients	Reference population in relation to the pivotal trial (MONARCH-E)
Original (EMA) label[36]	Nodal involvement with high risk of recurrence	Pivotal trial cohorts 1 + 2 (+ other undefined *high-risk*)
TPR-(REvalMed[a]) (Spain)[38]	≥4 involved nodes or 1–3 and at least 1 of the following criteria: tumour ≥5 cm or histological grade 3	Cohort 1 of the pivotal trial
HAS (France)[39]	≥4 involved nodes or 1–3 and at least 1 of the following criteria: tumour ≥5 cm or histological grade 3	Cohort 1 of the pivotal trial
NICE (England and Wales)[40]	≥4 involved nodes or 1–3 and at least 1 of the following criteria: tumour ≥5 cm or histological grade 3	Cohort 1 of the pivotal trial[b,44]
SMC (Scotland)[41]	Patient Access Scheme (restriction on the SPI, non-public)	Non-public
IQWiG (Germany)[42] - Joint Federal Committee[43]	Nodal involvement with high risk of recurrence, benefit demonstrated only in pre- or perimenopausal women	Part of cohorts 1 + 2 of pivotal trial (+ other undefined *high-risk*: restricted to pre- or perimenopausal women

EMA, European Drugs Agency; TPR, therapeutic positioning reports; HAS, Haute Autorité de Santé; NICE, National Institute for Health and Care Excellence; SMC, Scottish Drugs Consortium; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen.

[a] Evaluation and positioning procedure incorporating multidisciplinary nodes, in force in Spain from 2021 to July 2023.

[b] The economic model submitted by the companies to NICE included cohorts 1 and 2; however, after review, it had to be restricted to cohort 1, as this was considered more representative of what would be expected in the UK.[44]

chemotherapy alone, as there was a reduction in the percentage of patients who relapsed or progressed after surgery. This approach has been authorised by the FDA and the EC.

However, months earlier, nivolumab was authorised in Europe for neoadjuvant use, having been compared in a trial against chemotherapy alone. Pembrolizumab and nivolumab have not been compared; however, the results suggest that pembrolizumab would not be superior to nivolumab, which is effective only in PD-L1-positive patients (≥1%).[45] A post-regulatory evaluation of pembrolizumab would divide this indication into 2 parts: in PD-L1-negative patients (<1%), it would be compared to chemotherapy, where it would emerge as the preferred option based on the pivotal trial; in patients with PD-L1 ≥ 1%, the efficacy would be similar to nivolumab in neoadjuvant therapy; however, since nivolumab does not need to be administered for as long as pembrolizumab, it would be safer and less likely to compromise the possibility of the tumour remaining sensitive to immunotherapy in the event of relapse. It might therefore be preferable in terms of the risk/benefit ratio. There is uncertainty regarding the benefit of adjuvant therapy following prior neoadjuvant therapy, particularly in patients with a complete pathological response.[46]

The consequences of this pre-positioning for patients, pending a confirmatory adjusted indirect comparison, could include increased safety, and it is reasonable to expect greater treatment efficacy in patients who relapse, as immunotherapy can be reinitiated with higher expectations. For the economic analysis, this pre-positioning would establish 2 scenarios based on PD-L1 status. The budgetary impact of pembrolizumab in patients with PD-L1 < 1%, when used for an extended period (neoadjuvant plus adjuvant), could reach €120 million, while the impact of nivolumab could amount to €23 million.[45]

The cases of abemaciclib and pembrolizumab, along with the examples presented in Table 1, are just a few of the many cases where a more specific utility scenario is needed beyond what is stated in the text of the indication. For example, the case of ataluren in Duchenne muscular dystrophy is well known: although its trial showed no benefit and the CHMP did not recommend its authorisation, the EC granted approval contingent upon a second trial in a subgroup of patients. This second trial was conducted but once again failed to show benefit. The Therapeutic Positioning Report (TPR) clearly highlighted these failures to demonstrate utility,[47] which was likely a decisive factor in the decision not to fund it in Spain, given the cost of more than €150 000 per year. It was withdrawn in Europe 8 years later,[48] yet the company's global sales of this drug in 2022 reached $288.6 million.[49]

Tremelimumab and durvalumab have been shown to be more effective than sorafenib in treating hepatocarcinoma, a treatment that is now considered obsolete, despite being the comparison presented in the SPC. An adjusted indirect comparison suggested that it would be no better than atezolizumab + bevacizumab, which is the current standard.[50] This decision is complicated by the positive CHMP opinion for durvalumab as monotherapy for this indication,[51] which is based on a third arm of the same pivotal trial.

In heart failure, sacubitril/valsartan[52] and dapagliflozin[53] have key details in their TPRs that facilitate their appropriate off-label use in patients who need them because of treatment failure with other drugs.

For endometrial cancer in patients with biomarkers indicating microsatellite instability or DNA repair deficiencies, the authorised indication in Europe allows for the use of pembrolizumab either as monotherapy or in combination with lenvatinib. However, there is a lack of comparative data between the 2 options.[54] If no efficacy advantage is demonstrated by adding lenvatinib, using pembrolizumab as monotherapy would result in less toxicity for patients and lower costs for the healthcare system.

Conclusion

The way in which new drugs are introduced into therapeutic practice is a key factor in the sustainability of European public health systems. This process involves assessing them to determine their position (i.e., to establish their place in therapeutic practice in relation to other options).

Appropriate positioning involves 2 phases. In the first phase, independent of cost, a pre-positioning is determined based on the drug's utility scenario. In addition, it is important to consider whether the drug would become the preferred option, act as a therapeutic alternative with similar clinical benefits, or serve as an additional option in specific situations.

The second phase begins with an economic evaluation, based on the clinical utility scenario. The economic evaluation—which includes the closest possible approximation of the drug's manufacturing and development costs as well as a budget impact analysis—is used to negotiate the price and funding, leading to the final positioning of the drug.

Ideally, the final positioning, after price negotiation, would be identical to the utility scenario considered in the clinical evaluation phase. However, very high prices may result in a denial of funding or restricted coverage solely for patients who would derive the most significant benefit or for whom there is greater certainty regarding such benefit.

Therefore, post-regulatory therapeutic evaluation, which establishes the therapeutic utility scenario of a new drug, identifies its uncertainties, and provides a comparative pre-positioning, is crucial both for both designing the subsequent economic evaluation and guiding the introduction of the new drug into therapeutic practice. The evaluation process comprises 2 main aspects for drug positioning: it involves not only demonstrating the evidence of benefit compared to the standard treatment and addressing its uncertainties—as outlined in the centralised European evaluation—but also assessing and applying this evidence using the best clinical and evaluative criteria. This process involves making decisions that best position the new treatments within current clinical practice. After the unfortunate dissolution of the REvalMed network, it is essential for Spanish pharmaceutical policy to reinstate this dimension, referred to as *the fourth guarantee*, if the introduction of new therapies in public health is to be managed in a reasonable and efficient way, guided by the clinical benefits for patients.

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Authorship

Emilio Alegre conceived the work and drafted a preliminary text (pre-draft), which was circulated in September 2023 to Silvia Fénix, Dolores Fraga, Francesc Puigventós, and Eduardo López Briz, all of whom recognised the timeliness and interest of the work. In December 2023 and January 2024, the first draft was sent to all of them and Manuel Cárdenas and Carmen María Domínguez were added to the group. They all reviewed the draft and provided relevant comments and contributions, including modifications, deletions, and additions to the text, tables, figures, and the references. All authors reviewed and approved the final version.

CRediT authorship contribution statement

Emilio Jesús Alegre-del Rey: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Silvia Fénix-Caballero:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. **María Dolores Fraga Fuentes:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis. **Manuel Jesús Cárdenas Aranzana:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Eduardo Lopez-Briz:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Francesc Puigventós Latorre:** Writing – review & editing, Visualization, Validation,

Supervision, Formal analysis, Conceptualization. **Carmen María Domínguez-Santana:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis.

Declaration of competing interest

Manuel Jesús Cárdenas Aranzana has served on advisory boards for Merck Serono and Incyte.

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