

Article

Evaluation of Market Access of Pembrolizumab: A Comparative Study Between Portugal, Spain and the United Kingdom

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Abstract

Equity plays a key role in public administration, with social equity important for achieving equitable outcomes. In oncology, the sustainability of the system is a major concern, as rising prices of cancer medicines have increased spending on cancer care, posing affordability challenges even in high-income countries with public health systems. Pembrolizumab has changed the course of many oncologic diseases and has a huge impact on hospital budgets. The aim of this study was to evaluate national-level differences in access across Portugal, Spain, and the UK. From the empirical analysis, it is possible to conclude that there is a mean approval delay of more than 350 days, with delays more pronounced in Portugal and the UK, even though this evaluation does not capture uptake at the local and individual levels. It is also a potential measure to improve the national authority's approval. The centralised assessment by the European HTA might reduce inequalities between countries, which is particularly relevant for oncology medicines. The role of patient advocacy groups in market access is yet to be determined. However, a change in the culture of HTA bodies can bring them into every step of the process.

Keywords: Pembrolizumab; market access; European health technology assessment

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1. Introduction

Public value was described in 1995 in response to the “New public management” and defined the role of government as going beyond mere supervision and public service provision, but instead being based on value creation in the public sector [1]. The focus of public value is on public welfare, but also includes the authority of the state to regulate the private sector, either to prevent them from doing harm to public welfare, or to require them to contribute to the overall public good [2]. There has to be a concrete base of social legitimacy, public support, and public financing to produce the desired result, as well as operational capacity to deliver results [2]. Some authors developed guidance based on the four mechanisms that influence societal public value, including intended service usefulness, public leadership, human-centred co-creation practices, and value-in-use perspective [3].

Equity plays a key role in public administration and public policy [4]. There are more recent concepts of social equity, including access, procedural fairness and processes, quality of services, and outcomes of services. Equity in health is an ethical value, inherently normative, grounded in the moral principle of distributive justice, and consonant with human rights principles [5]. The concept of health equity focuses attention on the distribution of resources and other processes [5].

The main drivers for equity have been identified, including representative bureaucracy, administrative burden, horizontal and vertical decentralisation, privatisation, co-production, and performance management [4]. Drivers of equity were identified such as street-level discretion, stable financing systems, information availability and type, and technical managerial capacity [4]. However, public sector fragmentation and service arrangements promote efficiency over equity [4]. In future, for public administration to achieve social equity, it will be important to improve government trust, uphold democratic principles, and achieve equitable outcomes [6].

Other authors emphasise the importance of including the 4 E's in public administration, in addition to traditional values (economy, efficiency, effectiveness, and equity), as well as engagement, empathy, equity, and ethics. This will allow for centring care (empathy), engaging with the people where they are (engagement), promoting fairness for all (equity), and advancing public interest and public benefit (ethics) [7].

A recent study regarding efficiency in Organisation for Economic Cooperation and Development (OECD) health systems found a bidirectional causality between health system efficiency and equity [8]. As efficiency increases in the health system, the socioeconomic inequalities increase, particularly in countries with predominantly private health services [8]. Interestingly, decreases in socioeconomic inequalities promote greater healthcare system efficiency, especially in countries where the health system relies on public services [8]. It is important to consider the 10 types of health systems and their differences regarding regulation, financing, and provision, five of which are in the OECD [9]. All health systems share the same attributes: efficiency, trustworthiness, and affordability [10].

The healthcare systems in Portugal and the United Kingdom are national health systems, regulated and financed by the state, with services provided by the state [9]. Spain differs from Portugal and the United Kingdom, as it is politically organised as a quasi-federal state, in which the 17 Autonomous Communities have full capacity for planning, financing, and providing healthcare, education, and social protection [11].

The sustainability of health systems worldwide is being challenged, and this is expected to worsen as life expectancy increases and healthcare needs rise [12]. The introduction of new medicines, with higher costs and uncertainty regarding effectiveness in the real world, further undermines the feasibility of the healthcare system to provide adequate services [12].

It has been considered a European health technology assessment (HTA) since 2025 to improve access to oncologic treatments across Europe, with a primary role in reimbursement assessment following market authorisation by the European Medicines Agency (EMA) [13]. Its implementation raises many concerns and needs to address the approach: uncertainty in clinical development; comparator choice; consistency in approaching patient-relevant endpoints; and transparent, consistent management of both HTA and regulatory procedures, as well as their interface, including all involved stakeholder groups [14].

In oncology, the sustainability of the system is a major concern, as rising prices of cancer medicines have increased spending on cancer care, posing affordability challenges even in high-income countries with public health systems [15]. The financial impact of new medicines has become a significant factor in public coverage and reimbursement,

with most countries highlighting its importance amid higher drug prices and the growing number of new medicines [15].

Pembrolizumab has changed the course of many oncologic diseases, with a huge impact on patient outcomes and, consequently, treatment costs [16]. In Switzerland, Pembrolizumab contributed to an increase of 75% in the treatment of triple-negative breast cancer, even though it can be compensated through tax revenue [17].

The total cost of the Pembrolizumab regimen in triple-negative breast cancer is estimated at €162,314, yielding 17.75 QALYs (quality-adjusted life-years). The combination was more effective, with 2.62 additional QALYs and 3.37 additional life-years (LYs) gained [18]. The incremental analysis showed an ICER of €20,830 per QALY gained compared with the comparator [18].

The total of Pembrolizumab in first-line advanced non-small cell lung cancer is superior, and it has average costs per patient of €178,600 in long-term survivors vs. €58,800 for chemotherapy, and Pembrolizumab was cost-effective (ICER of €43,100/QALY), with 3.52 QALYs as compared to 0.65 QALYs for patients on chemotherapy [19].

In the case of cervical cancer, the total average cost per patient with Pembrolizumab plus standard of care was estimated at €157,368, compared to €73,360 for standard of care alone. The combination of Pembrolizumab was more effective, providing 6.104 LYs versus 2.991 LY, which translated into 3.412 and 1.799 QALYs, respectively; overall incremental LYs were 3.113 and the incremental QALYs were 1.613. The ICER was estimated at €52,081/QALY [20].

The objective of this paper was to perform an empirical analysis regarding access to Pembrolizumab in the European countries (Portugal, Spain, and the United Kingdom (UK)) and to respond to the following investigation questions:

Question 1: Is the market access of Pembrolizumab similar across Portugal, Spain, and the UK?

Question 2: What are the post-marketing obligations in the three countries after EMA or MHRA regulatory approval?

Question 3: What is the potential impact of the delays in the approvals on triple-negative breast cancer, non-small cell lung carcinoma and cervical cancer?

With this empirical analysis, the authors intend to evaluate equity in the approval of Pembrolizumab, based on regulatory approvals, and quantify the potential impact on disease progression, recurrence, mortality, and QALYs.

2. Methods

For this comparative analysis, three countries (Portugal, Spain, and the UK) are considered in terms of a universal public healthcare system model.

To respond to the investigation questions, a comparative analysis is performed, based on OECD reports, EMA and MHRA (Medicines and Healthcare products Regulatory Agency) in the UK, regarding approval of Pembrolizumab, and individual reports from the regulatory authorities in the specific countries, namely INFARMED (Portuguese National Authority for Medicines and Health Products) and AEMPS (Spanish Agency for Medicines and Health Products). For the analysis, data were collected from the national authorities responsible for approving new medications and for regulatory monitoring. In the UK, the treatment indications for Pembrolizumab are set by NICE (National Institute for Health and Care Excellence). A summary is given of product characteristics (SPC) of Pembrolizumab, as well as the European Public Assessment Report (EPAR) and the Committee for Medicinal Products for Human Use (CHMP) reports.

Information was collected regarding Pembrolizumab, mainly marketing authorisation, and dates of approval for non-small cell lung carcinoma, triple-negative breast cancer

and cervical cancer in the three countries, due to its prevalence and relevance for the hospital budget. The type of economic analysis considered for approval was also accounted for, as well as whether patient advocacy groups participated in the approval process, and post-marketing recommendations.

It was conducted as a descriptive analysis in SPSS® 30, including the delay in approval compared to the EMA for each country, and a boxplot analysis was also conducted.

For the economic analysis, an estimative analysis of the potential impact of the different approvals at the national level was considered, based on data available from the clinical trials. The burden of disease in each country was considered for reference. For the characteristics of specific cancers, OECD reports from 2025 were considered, with reported data referring to 2022, mainly incidence per 100,000 habitants [21]. There was an estimate of triple-negative breast cancer and non-small cell lung cancer, based on their prevalence in the total of breast cancer and lung cancer, respectively. Utility values, efficacy, and safety data were derived from KEYNOTE-189 [19], KEYNOTE-522 [22] and KEYNOTE-A18 [23]. Primary outcomes were QALYs and LY, when available. For the analysis, only the incremental value of Pembrolizumab (difference in survival or disease progression-free survival of Pembrolizumab vs. comparator, and difference in QALY and LY of Pembrolizumab vs. comparator) was considered [20].

3. Results

Regarding the analysis of the three national agencies' documents, it is possible to conclude that, overall, there are data availability and transparency on the agencies' websites, and the information is readily accessible. It is important to note that in UK agencies, the report provides more detailed information about the experts who participated in the analysis.

Table 1 presents the main results on the approval and market access of Pembrolizumab, including the key indications and specific approvals for non-small cell lung cancer, triple-negative breast cancer, and cervical cancer.

Table 1. Market access of Pembrolizumab in Portugal, Spain and the UK.

	EMA	Portugal	Spain	United Kingdom
Market authorisation issued	17 July 2015	16 October 2017	23 September 2016	12 July 2017
	10 October 2018	Approved indication for melanoma and non-small cell lung carcinoma	08 November 2021	18 July 2018
	Extension of indication for 1st-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with chemotherapy	24 January 2021	Extension of indication for 1st-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with chemotherapy	Extension of indication for 1st-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC)
	12 April 2019	Extension of indication for 1st-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with chemotherapy	24 October 2022	19 October 2022
	Extension of indication for first-line treatment of metastatic squamous NSCLC in adults	18 July 2023	Extension of indication for triple-negative breast cancer at high risk of recurrence	Extension of indication for renal cell carcinoma
	25 April 2022	Extension of indication for triple-negative breast cancer	4 March 2024	29 June 2022
				Extension of indication for triple-negative breast cancer

	Extension of indication for the treatment of cervical cancer	cancer at high risk of recurrence, and cervical cancer	Extension of information on non-small cell lung carcinoma	03 May 2023 Extension of indication for cervical cancer
	19 May 2022 Extension of indication for triple-negative breast cancer at high risk of recurrence	11 October 2024 Extension of the indication for locally advanced unresectable or metastatic biliary tract carcinoma	22 October 2024 Extension of indication for cervical cancer	5 February 2025 Extension of indication for resected non-small-cell lung cancer
	12 October 2023 Extension of indication for non-small cell lung carcinoma			
	25 March 2024 Extension of indication for non-small cell lung carcinoma			
Efficacy studies	Randomised clinical trial—keynote studies	Randomised clinical trial—keynote studies	Randomised clinical trial—keynote studies	Randomised clinical trial—keynote studies
Economic analysis	Cost-effectiveness	Cost-effectiveness, cost-utility	Not mentioned	Cost-effectiveness Cost-utility Equality impact assessment
Participation of patient advocacy groups	Not mentioned	Not mentioned	Not mentioned	Yes
Weight-adjusted doses	Recommended standard dosage	Pharmacy and Therapeutics Committee (January 2026): based on real-world evidence available, therapeutic equivalency is expected	Not applicable Real-world evidence available	Not applicable
Other conditions or restrictions to the safe and effective use of the medical product	Risk management plan Additional risk minimization measures: educational programme Obligation to conduct post-authorization efficacy studies	Risk management plan Additional risk minimization measures: educational programme Obligation to conduct post-authorization efficacy studies	Not mentioned	Risk management plan

Considering the main indications and differences relative to the main approvals, Figure 1 shows aggregated data from the three countries. The mean difference from EMA approval was 660 days for market authorisation (std. deviation 202), with a maximum of 822 days in Portugal; for non-small cell lung cancer, it was 626 days (std. deviation 524), with a maximum 1012 days in the UK; for triple-negative breast cancer, it was 208 days (std. deviation of 197), with a maximum of 425 days for Portugal; for cervical cancer, it was 595 days (std. deviation of 283), with a maximum of 913 days in Spain.

Due to the high cost of Pembrolizumab, some countries have begun adopting weight-based prescribing. In Portugal, the national Pharmacy and Therapeutics Committee has recommended its off-label use since 2026; in other countries, there are no formal indications, but in Spain, there is real-world evidence.

Regarding the post-authorisation indications, it is considered in the Portuguese national agency, and partially in the UK's national document, but not mentioned in the Spanish approval documents.

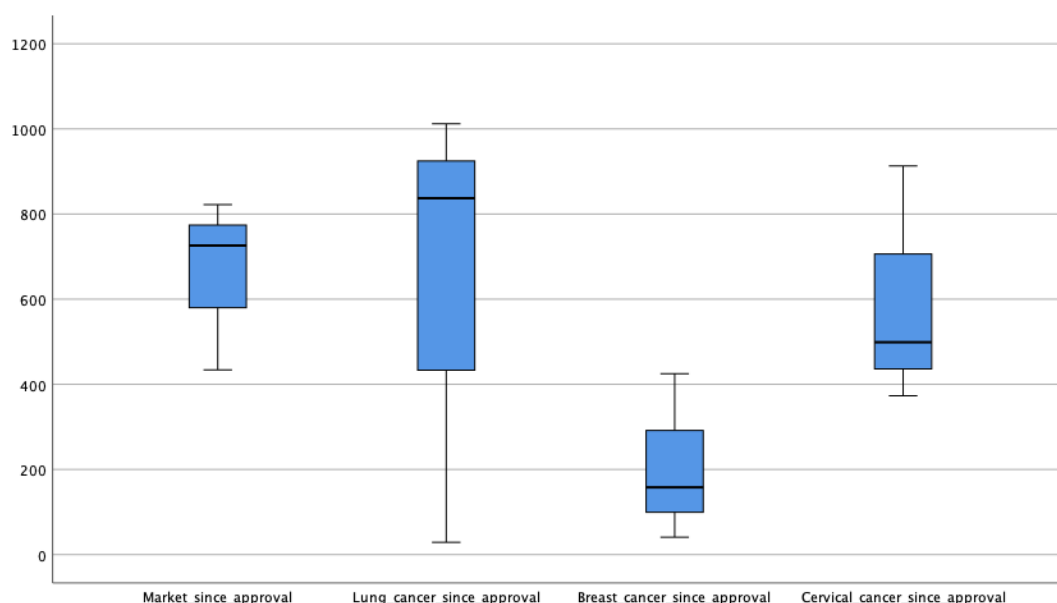


Figure 1. Boxplot—differences regarding market access of Pembrolizumab for non-small cell lung cancer, breast cancer and cervical cancer in Portugal, Spain, and the UK.

Considering the outcomes from the randomised clinical trial and the cost-effectiveness analysis, the potential impact of the delay in approval on outcomes (disease progression, recurrence of disease) and on QALYs and LYs is described in Table 2 for triple-negative breast cancer, Table 3 for NSCLC, and Table 4 for cervical cancer.

Table 2. Estimated impact of the delays on outcomes and costs considering the delays of approvals—breast cancer.

Early Triple-Negative Breast Cancer	Portugal	Spain	United Kingdom
Incidence of breast cancer	143	131	170
Incidence of triple-negative breast cancer (estimated 15% total) per 100,000 habitants	21.5 (2022)	19.65 (2022)	25.5 (2021)
Approval delay	425 days (14 months)	158 days (5.3 months)	41 days (1.4 months)
Pembrolizumab: 4.4% increase with disease progression, recurrence or death—15.5 months	Estimate: −4% increase	Estimate: −1.5% increase	Estimate: −0.4% increase
Pembrolizumab: incremental 2.62 QALYs	−3.1 QALYs	−1.2 QALYs	−0.3 QALYs
Incremental 3.3 LYs	−3.85 LYs	−1.2 LYs	−0.4 LYs

Table 3. Estimated impact of the delays on outcomes and costs considering the delays of approvals—lung cancer.

Advanced Non-Small Cell Lung Cancer	Portugal	Spain	United Kingdom
Incidence of lung cancer	107	127	148.2
Incidence of non-small cell lung cancer (estimated 85% total) per 100,000 habitants	91 (2022)	108 (2022)	125.97 (2021)
Approval delay	837 days (28 months)	29 days (1 month)	1012 days (34 months)

Pembrolizumab survival for 12 months: 19.8% increase	Estimate: -46% survival	Estimate: -1.65% survival	Estimate: -56% survival
Pembrolizumab: incremental 2.87 QALYs	-6.70 QALYs	-0.24 QALYs	-8.13 QALYs

Table 4. Estimated impact of the delays on outcomes and costs considering the delays of approvals—cervical cancer.

Advanced Cervical Cancer	Portugal	Spain	United Kingdom
Incidence of cervical cancer (per 100,000 habitants)	21 (2022)	25 (2022)	9.8 (2021)
Approval delay	499 days (17 months)	913 days (30 month)	373 days (12 months)
Pembrolizumab survival for 24 months: 11% increase	Estimate: -8% survival	Estimate: -14% survival	Estimate: -6% survival
Pembrolizumab: incremental 1.40 QALYs	-1.9 QALYs	-3.5 QALYs	-1.4 QALYs

Based on the impact analysis, the most relevant finding was for non-small cell lung cancer, as it has a major impact on survival and QALY in the UK. Regarding triple-negative breast cancer, the greatest impact was observed in Portugal, as it has a considerable delay in approval.

It is also relevant to take into consideration the burden of disease of each cancer per country, as translated by the incidence per 100,000 habitants, with greater impact for lung cancer. For each cancer, considering the country with the longest approval delay, it is possible to notice that this was the case for the disease with the highest incidence or burden.

4. Discussion

Considering the approvals of Pembrolizumab, there is a mean delay of more than 1 year for subsequent approvals in each country, with the delay being more pronounced in Portugal and the UK. However, considering the approvals for newer indications, the delay has been reduced over the last few years. Other authors have identified Portugal as one of the countries with the longest time until patient access [13].

For the analysis, approvals at individual hospitals or regions were not considered, because this information is not readily available. Given national market authorisation, local access is delayed, so the estimated results do not reflect the effective access to a new medication or indication in each country or region. It is also important to note that, in addition to the approvals throughout the year, the hospital budget is set annually and may not allow for the inclusion of additional medications, which can increase costs and contribute to further delays in approvals and effective treatment. At the individual level, other socioeconomic determinants can impact access to new medications and should be addressed in future investigations [7].

The bureaucracy of the assessment process might contribute to delays in approvals, with revisions of the literature by local experts, until the final report and national approval. Other authors identified distinct value drivers across Europe, mainly differing evidence requirements and methodological standards for individual processes, treatment algorithms, and national recommendations, which might contribute to delays in different countries [14].

In one example from Canada, in response to delays in treatment approvals, the authors propose international collaborations, information sharing, and national standards for timelines in oncology drug access. These measures could reduce approval time [24].

The centralised assessment for reimbursements, European HTA, could bring advantages and save time between different authorities. However, both agencies would be

more aligned, mainly in the subdomains with the greatest differences: acceptance of the limitations of the target population and their extrapolation to the population; progression-free survival and other surrogate endpoints as outcomes; crossover designs; short trial duration; and the clinical relevance of the effect size [13]. Other authors have studied the potential impact of real-world evidence as an external control in comparative studies, but due to methodological biases, it contributes to discrepancies in acceptance between the EMA and European HTA [25]. Regarding the countries evidenced in this study, the alignment between INFARMED and EMA was 33%, as opposed to the UK, which had a higher percentage of alignment of 53% [13]. As discussed by other authors, it will be necessary to have joint early dialogues, joint relative effectiveness assessments, and the use of managed entry agreements, which can bring flexibility in accepting some uncertainty and could therefore reduce evidence gaps [13]. It is also crucial for European HTA bodies and EMA to develop synergetic standards for the use of RWE to ensure equitable and timely access to medicines [25].

Other authors consider the changes in processes across jurisdictions, and the consistency in European HTA practices suggests that there is no uniformly best practice [26]. Different countries have different values, which can result in different preferences for reimbursement (e.g., automatic reimbursement at regulatory approval or a more closed system) [26].

In further studies, it will be important to compare with the UK, given the UK's departure from most EU institutions in 2020, which has led to changes in regulatory approaches and the adoption of new health technologies [27]. Given the small size of its market relative to the purchasing power of the EU, the UK maintained access to new medicines and technologies by creating an agile and flexible regulatory environment [27].

Only in the UK are patient advocacy group members reported to be included in the approval process. Some authors claim that partnerships and co-creation between HTA professionals, researchers, and patient advocates can strengthen the HTA process and better align it with service delivery, making it person-centred and involving shared decision-making [28]. Patient preference studies can be used to balance benefits with potential harms, and patient-reported outcomes can measure what matters to patients over time [28].

The economic evaluation has a great impact on the decision of approval by national agencies; as for reimbursement purposes, however, the requirements in the different national agencies will need to be clarified.

The potential impact of patient advocacy groups is on training and capacity building, and on related funding for patient representatives; the establishment of a patient involvement committee to define rules, procedures, templates, and methodology for patient input; and the establishment of a dedicated "patient unit" at the European Commission secretariat level [29]. However, challenges identified for patients to fulfil this role include the lack of resources/unreadiness, funding, management of conflicts of interest, educational needs, and inconsistent recognition of the value of patient input [29].

To address the increasing impact of Pembrolizumab on hospital budgets, weight-dose-adjusted Pembrolizumab, even though not formally approved, can be considered in some patients and may affect the treatment of oncology patients; this should be addressed in future investigations.

There is a research gap regarding equitable access to medications, particularly relevant in oncology. It might be relevant to understand local constraints on its availability, including the reimbursement negotiation process and uptake at regional and local levels, as these were not addressed in this paper.

5. Conclusions

In conclusion, there are significant differences in market access of Pembrolizumab between Portugal, Spain, and the UK, with the differences being more pronounced in Portugal and the UK and having a major impact on NSCLC and triple-negative breast cancer. The requirements, including the post-marketing recommendations of Pembrolizumab, are the same between the national agencies.

The role of common European policies, in the case of medicine assessment, is yet to be determined. The centralised assessment process for European HTA might help reduce inequities across countries, particularly for oncology medicines; however, there must be alignment with national agencies, and reimbursement negotiation processes must be individualised by country.

The role of patient advocacy groups in market access is yet to be determined. However, a change in the culture of HTA bodies can bring them into every step of the process.

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