Immune checkpoint inhibitors in Brazil: regulatory approval and public procurement within the Unified Health System

Debora Cristina Viana Pereira, Louise Sousa de Souza, Andrei Stéfano Queiroz Gonçalves, Ingryd Nayara de Farias Ramos, André Salim Khayat, Maria Izabel Florindo Guedes, Paulo Pimentel de Assumpção, Lívia Érika Carlos Marques

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Debora Cristina Viana Pereira[1]
https://orcid.org/0009-0009-5845-3284

Louise Sousa de Souza[1]
https://orcid.org/0009-0004-7200-2889

Andrei Stéfano Queiroz Gonçalves[1]
https://orcid.org/0009-0003-6620-740X

Ingryd Nayara de Farias Ramos[1]
https://orcid.org/0000-0001-5574-163X

André Salim Khayat[1]
https://orcid.org/0000-0002-3451-6369

Maria Izabel Florindo Guedes[2]
https://orcid.org/0000-0002-4569-8663

Paulo Pimentel de Assumpção[1]
https://orcid.org/0000-0003-3846-8445

Livia Érika Carlos Marques[1,+]
https://orcid.org/0000-0002-0320-7934

[1]Universidade Federal do Pará, Núcleo de Pesquisas em Oncologia, Belém, PA, Brasil
[2]Universidade Estadual do Ceará, Laboratório de Biotecnologia e Biologia Molecular, Fortaleza, CE, Brasil

+ Corresponding author: liviamarques@ufpa.br

Abstract

Immune checkpoint inhibitors (ICIs) represent a major advance in cancer immunotherapy, providing durable clinical responses in several malignancies. Despite their growing clinical relevance, information on regulatory approval and public procurement of ICIs in middle-income countries remains limited. In this context, the upcoming expiration of patents for several ICIs, expected from 2026 onward, may substantially impact access and pricing. This study describes the regulatory landscape and federal acquisition of ICIs in Brazil between 2014 and 2023. A retrospective descriptive analysis was conducted using publicly available databases from the Brazilian Health Regulatory Agency (ANVISA) and the Federal

Government procurement system. All ICIs approved during the study period were evaluated according to molecular target (PD-1, PD-L1, CTLA-4), antibody type, expression system, approved clinical indications, number of units acquired, and acquisition costs. Nine ICIs had active marketing authorization in Brazil, eight of which were procured by the Federal Government. Nivolumab and pembrolizumab accounted for the highest number of units acquired and the largest share of total expenditure. Overall federal spending on ICIs exceeded BRL 861 million during the study period, with PD-1 inhibitors representing approximately 78% of total costs. Most units (66%) were allocated to centralized logistics centers of the Brazilian Unified Health System (SUS), while regional distribution data revealed a concentration of acquisitions in the South and Southeast regions. No ICI biosimilars were approved during the study period, despite the anticipated patent expiration of key molecules beginning in 2026. Although federal investment in ICIs has increased, access within the Brazilian public health system remains uneven, limited by high costs, centralized distribution, and the current absence of biosimilars. The forthcoming patent expirations may represent a strategic opportunity to expand access through biosimilar incorporation and local production. Strengthening regulatory strategies, improving transparency in distribution, and fostering innovation are essential to promote equitable access to cancer immunotherapy in Brazil.

Keywords

SUS, Cancer Immunotherapy, Monoclonal Antibodies, Health Policy

1. Introduction

Cancer is a general term used to describe a group of over 100 diseases characterized by uncontrolled cell proliferation [(1)]. It represents a major global public health issue, with approximately 20 million new cases and 9.7 million deaths recorded in 2022. Projections from the International Agency for Research on Cancer (IARC) indicate that the global cancer burden may exceed 35 million cases by 2050, representing a 77% increase compared to 2022 [(2)].

In Brazil, a similar upward trend has been observed. According to the National Cancer Institute (INCA), the estimated number of new cancer cases increased from 625,000 in 2020 to nearly 700,000 in 2023 [(3)]. Moreover, cancer is expected to become the leading cause of death in the country by 2030 [(4)]. In this context, expanding access to effective and innovative therapeutic strategies is essential to improve survival outcomes, particularly within public health systems.

Among emerging therapeutic approaches, immunotherapy has gained prominence as a major advance in cancer treatment. Immunotherapy comprises strategies designed to restore or enhance the immune system's ability to recognize and eliminate malignant cells [(5)].

Although early observations linking immune activation to tumor regression date back to the late 19th century, advances in immunology over recent decades have enabled the development of targeted and clinically effective immunotherapeutic modalities, particularly immune checkpoint inhibitors (ICIs) [6].

Immune checkpoints are regulatory molecules that modulate T-cell activation and function, playing a critical role in maintaining peripheral immune tolerance and preventing autoimmunity [7]. Tumor cells exploit this mechanism by overexpressing checkpoint ligands, thereby suppressing T-cell activation and evading immune detection [7]. This immune evasion mechanism provided the biological rationale for the development of ICIs, which aim to block inhibitory signaling pathways and restore antitumor immunity.

Currently, the clinically approved ICIs target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand PD-L1. CTLA-4 is expressed on T cells and primarily regulates the early stages of T-cell activation, with its blockade promoting effector T-cell expansion and reducing regulatory T-cell-mediated suppression [8,9]. In contrast, PD-1 is expressed on multiple immune cell populations within the tumor microenvironment, including T cells, B cells, natural killer cells, monocytes, and dendritic cells, and functions mainly during later stages of the immune response in peripheral tissues [8,9]. PD-L1 is widely expressed by tumor and immune cells and has been associated with immune evasion, tumor progression, and clinical response to anti-PD-1/PD-L1 therapies [9,10].

The ICIs monoclonal antibodies (mAbs) in the market are dominated by fully human molecules classified as humanized, or fully human molecules. Fully human antibodies are composed exclusively of human immunoglobulin sequences and are commonly generated using phage display techniques or transgenic animal platforms [11]. Most ICs belong to the IgG class, particularly IgG and IgG4 subclasses, with IgG1 favored for its extended half-life, potent effector function, and structural stability [12,13]. Regulatory information shows that mammalian expression systems dominate ICIs mAb production.

The clinical relevance of ICIs was established following the approval of the first immune checkpoint inhibitor, ipilimumab, by the U.S. Food and Drug Administration (FDA) in 2011 for the treatment of advanced melanoma [14]. This milestone was followed by the approval of PD-1 inhibitors pembrolizumab and nivolumab in 2014, and the first PD-L1 inhibitor, atezolizumab, in 2016 [15]. Since then, ICIs have been approved for the treatment of multiple malignancies and have become an integral component of contemporary oncologic care.

Despite their proven clinical benefits,, the incorporation of ICIs into public healthcare systems poses substantial regulatory, economic, and logistical challenges, particularly in middle-income countries such as Brazil. Issues related to regulatory approval timelines, public procurement, pricing, and equitable access remain insufficiently characterized in the national context. A comprehensive understanding of how these therapies are approved and acquired is essential to inform health policy decisions and optimize resource allocation.

Therefore, the present study aimed to map the use of immune checkpoint inhibitors in the cancer immunotherapy in Brazil, based on regulatory approvals granted by the Brazilian Health Regulatory Agency (ANVISA) and federal government procurement records, providing an overview of their incorporation into the Brazilian public health system.

2 Materials and Methods

2.1 Study design and data sources

This is a retrospective descriptive study that analyzed immune checkpoint inhibitors (ICIs) approved by the Brazilian Health Regulatory Agency (ANVISA) between 2014 and 2023. The data collection involved a systematic search of official public databases maintained by the Brazilian Federal Government.

Initially, a comprehensive list of ICIs was compiled using two main datasets: the Catálogo de Materiais (CATMAT) spreadsheet, obtained from the Integrated System for Administration and General Services (SIASG), available at: https://www.gov.br/compras/pt-br/acesso-a-informacao/consulta-detalhada/planilha-catmat-catser/catmat.xlsx. This catalog contains a list of materials eligible for procurement by the Federal Public Administration and the Câmara de Regulação do Mercado de Medicamentos (CMED) database, available through ANVISA. This database provides pricing information for both regulated drugs, in accordance with CMED Resolution No. 2 of March 5, 2004, and liberated drugs, in accordance with CMED Resolution No. 2 of March 20, 2019.

To identify monoclonal antibodies, a keyword search was performed using the suffixes *"mab"* or *"mabe"*. From the resulting list, only the ICIs were selected for inclusion in the study.

The registration status of each selected antibody was then verified in the ANVISA drug registration system to confirm approval for oncological indications. Additionally, cross-referencing was conducted using the Antibody Therapeutics Product Data spreadsheet, available on the website of The Antibody Society (https://www.antibodysociety.org).

Public procurement data for each identified ICI were collected from the Government Procurement Portal (ComprasNet), based on bidding and acquisition records (http://comprasnet.gov.br/acesso.asp?url=/Livre/Ata/ConsultaAta00.asp). The variables collected included: the ICI name, quantity of items purchased, purchase value, contract signing date, and the awarded companies in each bidding session.

2.2 Data analysis and ethical considerations

All collected data were consolidated into a single spreadsheet and analyzed descriptively using Microsoft Excel Professional Plus 2021. Results were evaluated according to temporal trends, therapeutic target (PD-1, PD-L1, or CTLA-4), antibody type (fully human, or humanized) and structure of mAbs, procurement profile and regional distribution.

As this study was based exclusively on publicly available secondary data and did not involve individual patient information, approval by a Research Ethics Committee and informed consent were not required.

3. Results

3.1 Regulatory approvals of immune checkpoint inhibitors in Brazil

Between 2014 and 2023, nine immune checkpoint inhibitors (ICIs) were identified with active marketing authorization in Brazil (approved by ANVISA). The average approval time in Brazil was up to one year after approval by international regulatory agencies, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

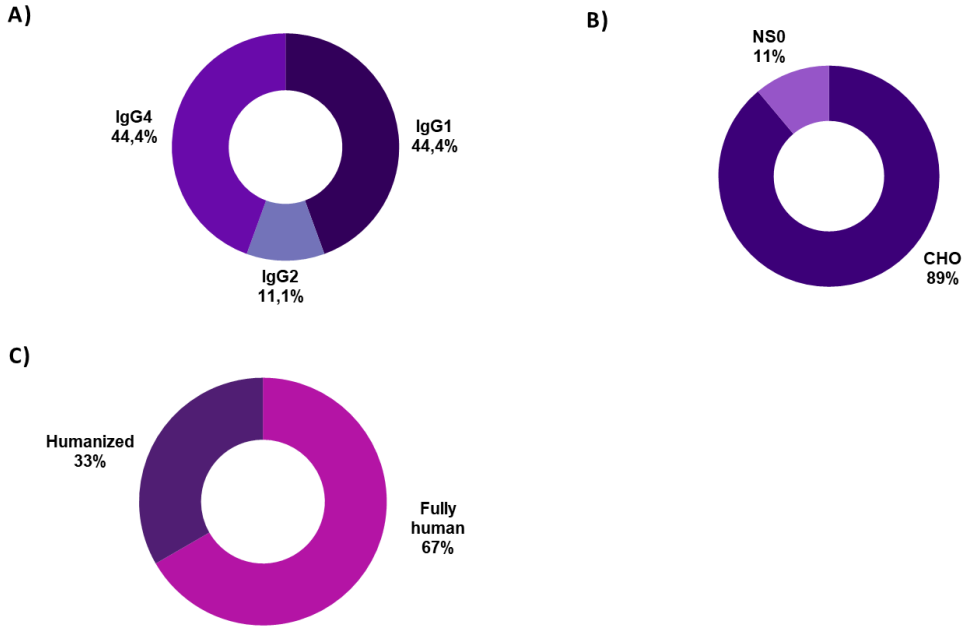
Among the approved ICIs, eight presented records of public procurement during the analyzed period. Five were fully human monoclonal antibodies (mAbs)—avelumab, durvalumab, cemiplimab, nivolumab, and ipilimumab—and three are humanized mAbs—atezolizumab, dostarlimab, and pembrolizumab (Figure 1).

Inspection of the molecular structure of the monoclonal antibodies and their expression systems revealed the human nature of mAbs, which are mostly engineered on the IgG1 or IgG4 subclasses, and are exclusively produced in mammalian cell lines (Figure 1). The expression systems used employed tremelimumab as the only antibody produced in a

specific system that utilizes non-secreting murine myeloma cells (NS0). All the other mAbs were made from Chinese hamster ovary (CHO) cells (Figure 1).

Regarding therapeutic targets, CTLA-4 is targeted by two fully human antibodies, ipilimumab and tremelimumab. PD-1 is targeted by four antibodies: two fully human (cemiplimab and nivolumab) and two humanized (pembrolizumab and dostarlimab). PD-L1 is targeted by three antibodies, which include two fully human (durvalumab and avelumab) and one humanized (atezolizumab).

Figure 1. Molecular and production characteristics of immune checkpoint inhibitors with active marketing authorization by ANVISA between 2014 and 2023. (A) Monoclonal antibody structure. (B) Expression system used for antibody production. (C) Antibody type (fully human or humanized).



The main clinical indications for ICIs approved by international regulatory agencies include metastatic melanoma, hepatocellular carcinoma, cutaneous squamous cell carcinoma, endometrial cancer, non-small cell lung cancer, bladder cancer, and Merkel cell carcinoma. Table 1 shows that ANVISA has approved additional clinical indications for various cancer types over time, and three ICIs have been incorporated into SUS to treat specific cancer types until date.

Table 1. First clinical indications approved by international regulatory agencies and corresponding indications approved by ANVISA for immune checkpoint inhibitors.

Target	Name	First indication	Indications approved by ANVISA	Indications incorporated by SUS (until Jun/2025)
CTLA-4	Ipilimumab	Metastatic melanoma	Metastatic melanoma, renal cell carcinoma, hepatocellular carcinoma, malignant pleural mesothelioma, metastatic non-small cell lung cancer, esophageal squamous cell carcinoma	Not incorporated
CTLA-4	Tremelimumab	Liver cancer	Advanced or unresectable hepatocellular carcinoma (HCC)	Not incorporated
PD-1	Pembrolizumab	Melanoma	Melanoma, Urothelial carcinoma, Non-small cell lung cancer, Gastric cancer, Classical Hodgkin's lymphoma, Primary Mediastinal large B-cell lymphoma, Renal cell carcinoma, Head and neck cancer, Esophageal cancer, Cancer with high microsatellite instability, Colorectal cancer, Non-colorectal cancer, Endometrial cancer, Triple-negative breast cancer, Cervical cancer, Cutaneous squamous cell carcinoma, Cancer with high tumor mutational load	First-line treatment of advanced non-surgical and metastatic melanoma, according to the cancer care model
PD-1	Cemiplimab	Cutaneous squamous cell carcinoma	Cutaneous squamous cell carcinoma (SCC), Basal cell carcinoma (BCC), Non-small cell lung cancer (NSCLC), Cervical cancer	Not incorporated
PD-1	Dostarlima	Endometrial	Endometrial cancer	Not incorporated

	b	cancer		
PD-1	Nivolumab	Melanoma, non-small cell lung cancer	Advanced melanoma (unresectable or metastatic), adjuvant melanoma, Non-Small Cell Lung Cancer (NSCLC), Advanced Renal Cell Carcinoma (RCC), Urothelial Carcinoma, Squamous Cell Carcinoma of the Esophagus, Adjuvant treatment of Esophageal Cancer or Gastroesophageal Junction Cancer, completely resected, Hepatocellular Carcinoma, Malignant Pleural Mesothelioma, Gastric Cancer, Gastroesophageal Junction Cancer and Esophageal Adenocarcinoma.	First-line treatment of advanced non-surgical and metastatic melanoma, according to the cancer care model
PD-L1	Durvalumab	Bladder cancer	Urothelial Carcinoma, Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC), Biliary Tract Cancer (BTC), Hepatocellular Cancer (HCC)	Unresectable stage III non-small cell lung cancer, whose disease has not progressed after platinum-based chemoradiation therapy, according to the Clinical Protocol of the Ministry of Health
PD-L1	Atezolizumab	Bladder cancer	Urothelial carcinoma, Non-small cell lung cancer (initial and metastatic), Small cell lung cancer, Hepatocellular cancer, Triple-negative breast cancer	Not incorporated
PD-L1	Avelumab	Merkel cell carcinoma	Metastatic Merkel cell carcinoma (MCC),	Not incorporated

		locally advanced or metastatic urothelial carcinoma (UC), advanced renal cell carcinoma (RCC)

3.2 Public procurement trends of ICIs

Between 2014 and 2023, approximately 104,840 units were purchased. Nivolumab accounted for the highest number of units acquired during the period, followed by pembrolizumab, as shown in Figure 2. In contrast, tremelimumab showed no procurement records during the study period.

A significant increase in financial investment directed toward the acquisition of ICIs reaching over BRL 386 million in 2023 alone (Figure 3). Figure 4 illustrates that this upward trend is reflected in the increasing number of antibody units purchased over the years, culminating in 61,960 units acquired in 2023.

Figure 2. Total number of immune checkpoint inhibitor monoclonal antibody units acquired in Brazil between 2014 and 2023, according to the Federal Government procurement records.

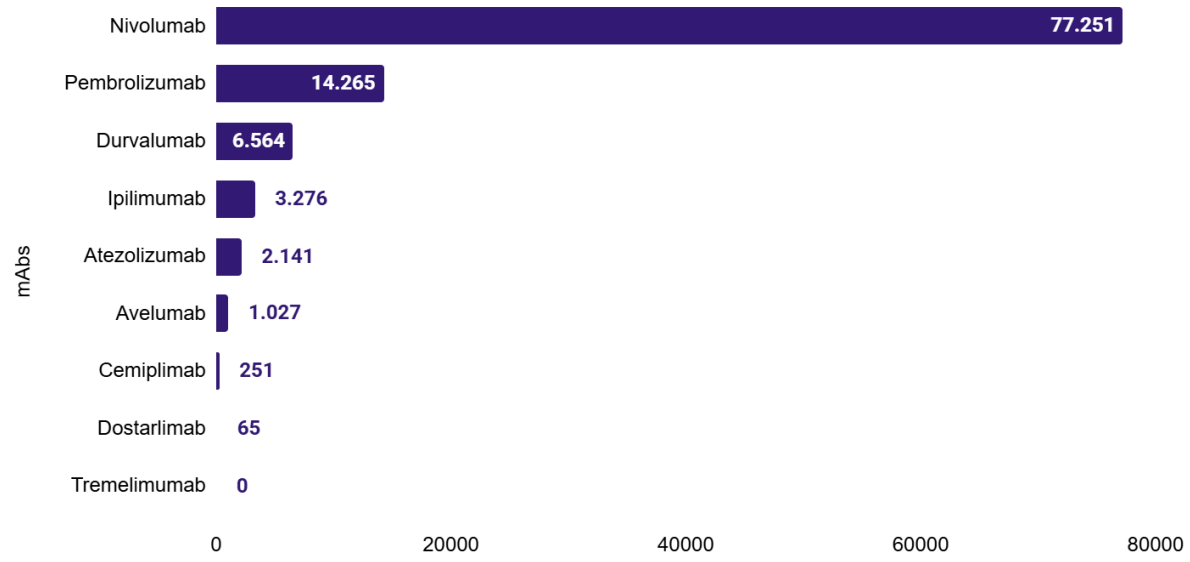


Figure 3. Annual acquisition costs of immune checkpoint inhibitor monoclonal antibodies in Brazil from 2014 to 2023.

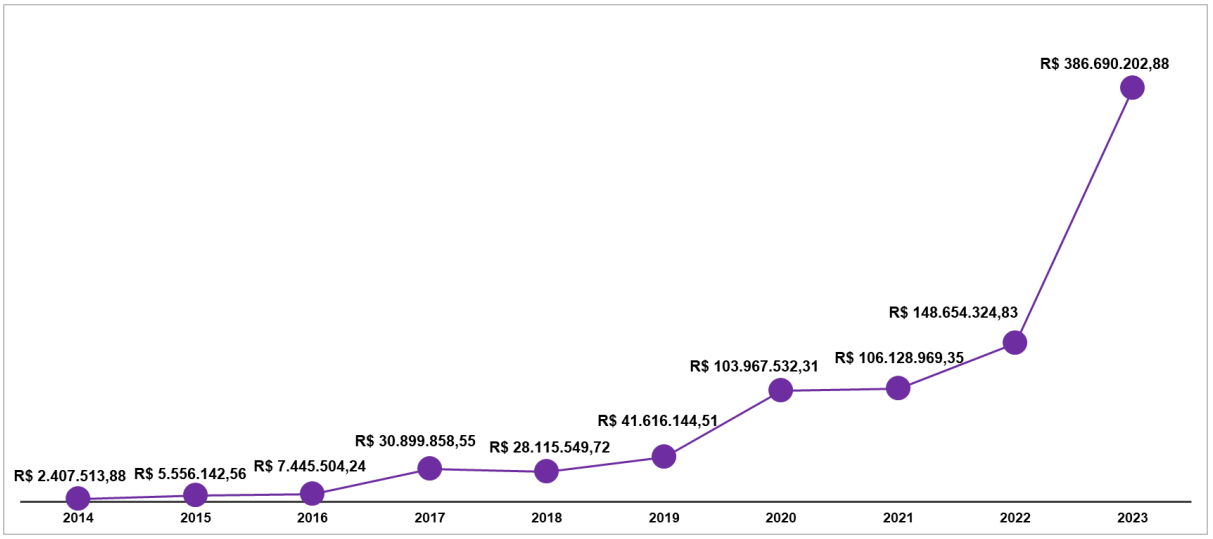
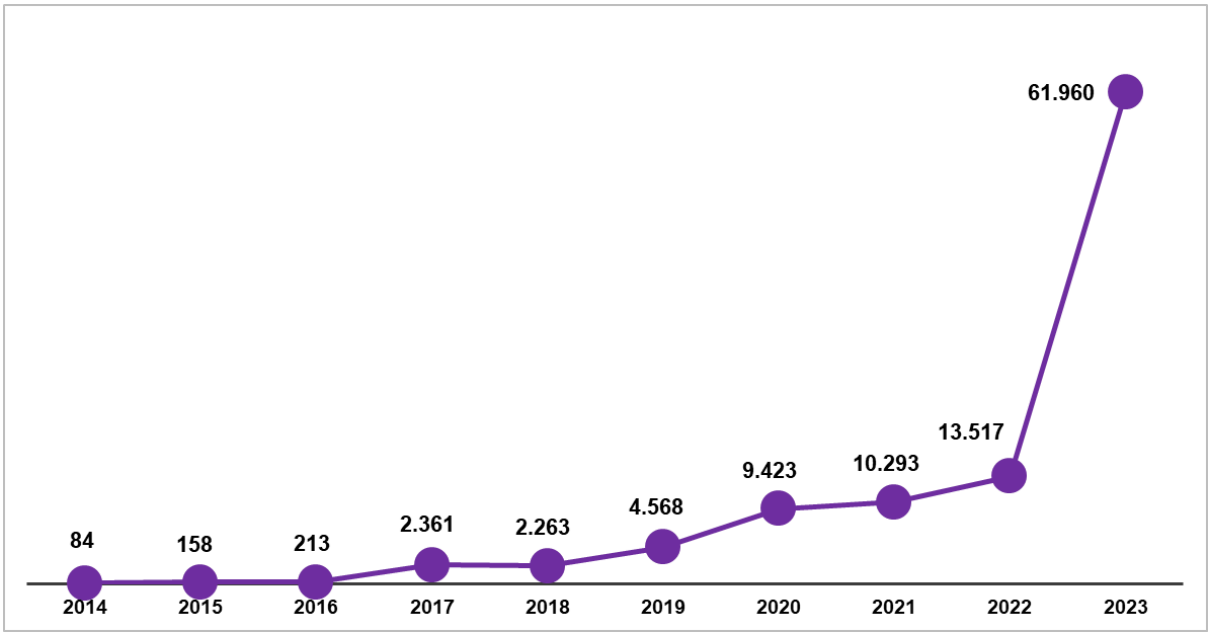


Figure 4. Annual number of immune checkpoint inhibitor units purchased in Brazil between 2014 and 2023.



3.3 Costs related to immune checkpoint inhibitors procurement

The total estimated expenditure on immune checkpoint inhibitors in Brazil between 2014 and 2023 amounted to BRL 861,481,742.83. Nivolumab represented the highest cumulative acquisition cost among all ICIs, as detailed in Table 2. When stratified by

therapeutic target, PD-1 inhibitors represented the largest share of total expenditure, with an estimated cumulative cost of BRL 671,385,013.04 (Table 3).

Table 2. Acquisition costs of immune checkpoint inhibitor mABs in Brazil between 2014 and 2023.

mAb	Costs (R$) 2014-2023
Nivolumab	R$ 463.622.310,25
Pembrolizumab	R$ 195.831.840,71
Ipilimumab	R$ 80.812.360,65
Atezolizumab	R$ 52.627.595,82
Durvalumab	R$ 50.430.685,78
Cemiplimab	R$ 9.918.284,18
Avelumab	R$ 6.226.087,54
Dostarlimab	R$ 2.012.577,90
Tremelimumab	R$ 0,00
Total	**R$ 861.481.742,83**

Table 3. Acquisition costs of immune checkpoint inhibitors in Brazil according to therapeutic target between 2014 and 2023

mAb	Costs (R$) 2014-2023
PD-1	R$ 671.385.013,04
PD-L1	R$ 109.284.369,14
CTLA-4	R$ 80.812.360,65
Total	**R$ 861.481.742,83**

3.4 Marketing holders of approved ICIs

Since 2014 ICIs have been approved and introduced in the global market, based on public information provided by the FDA, EMA and ANVISA (Table 4). The market for Brazilian-approved immune checkpoint inhibitors (ICIs) is held by six companies.. These include Bristol-Myers Squibb (ipilimumab and nivolumab), Merck Sharp & Dohme (pembrolizumab), Sanofi Medley (cemiplimab), GlaxoSmithKline (dostarlimab), AstraZeneca (durvalumab), Roche (atezolizumab), and Merck (avelumab), as detailed in Table 4.

Table 4. Comparison between international regulatory approvals and ANVISA marketing authorizations for immune checkpoint inhibitors during the study period.

Target	International non-proprietary names	brand name	Company	International approval	ANVISA approval
PD-1	Dostarlimab	JEMPERLI®	GLAXOSMITHKLINE	EMA, 2021/ FDA, 2023	2022
CTLA-4	Ipilimumab	YERVOY®	BRISTOL-MYERS SQUIBB	FDA, 2011	2012
PD-1	Nivolumab	OPDIVO®	BRISTOL-MYERS SQUIBB	FDA, 2014	2016
PD-1	Pembrolizumab	KEYTRUDA	MERCK SHARP & DOHME.	FDA, 2014	2016
PD-L1	Atezolizumab	TECENTRIQ®	ROCHE	FDA, 2016	2017
PD-L1	Avelumab	BAVENCIO®	MERCK	FDA, 2017	2018
PD-L1	Durvalumab	IMFINZI ®	ASTRAZENECA	FDA, 2017	2017
PD-1	Cemiplimab	LIBTAYO®	SANOFI MEDLEY.	FDA, 2018	2019
CTLA-4	Tremelimumab	IMJUDO®	ASTRAZENECA	FDA, 2022	2023

3.5 Regional distribution of ICIs from 2020 to 2023

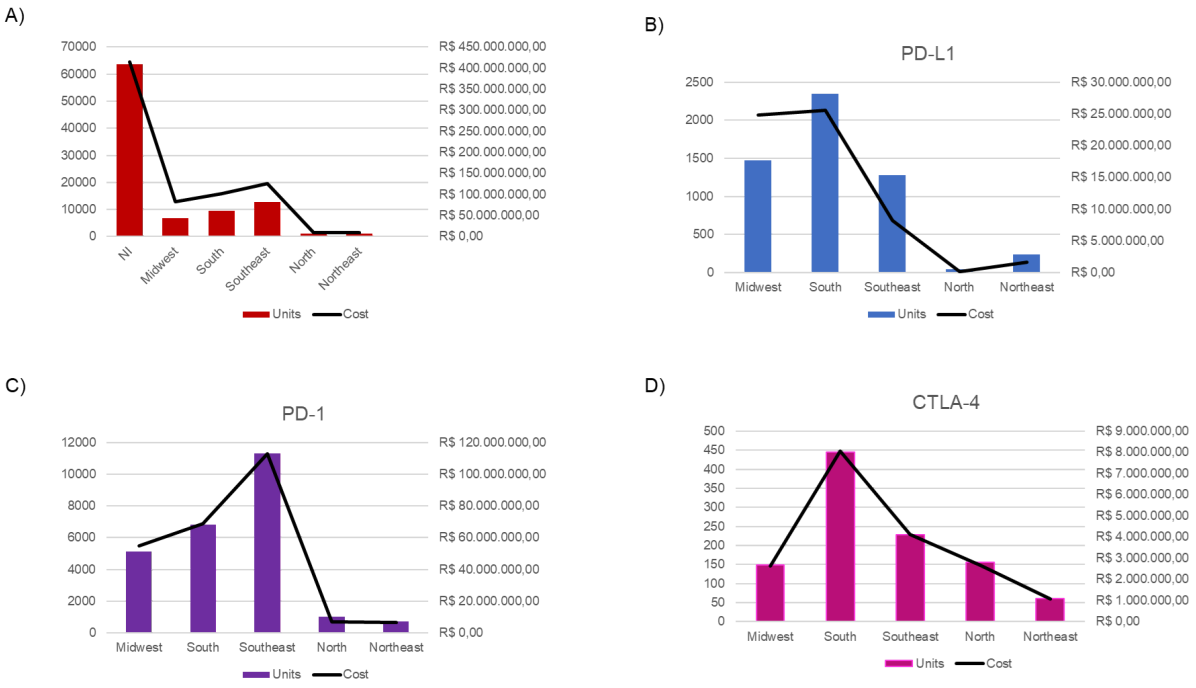
Although immune checkpoint inhibitor monoclonal antibodies have been incorporated to the Brazilian Unified Health System (SUS) for the specific cancer types treatment, their distribution across Brazilian regions demonstrates significant disparities (Figure 5). Between 2020 and 2023, a total of 95,023 units were procured nationwide. Of these, approximately 67%, (around 63,000 units) were allocated to SUS Drug Procurement and Distribution Centers, without detailed information regarding their final regional destinations.

Among acquisitions with identifiable regional allocation, approximately 23% of the total volume (more than 22.000 units) was concentrated in the South and Southeast regions of the country (Figure 5A). In contrast, the North and Northeast regions accounted for the substantially lower procurement volumes, with only hundreds of units acquired during the same period.

In addition to regional disparities in volume, differences were observed between the number of units acquired and the corresponding financial investment. As shown in figure 5 (D) shows a discrepancy between the quantity acquired and the financial value, particularly in the case of CTLA-4, which has a smaller number of units associated with high cost. Conversely, PD-1 inhibitors accounted for the largest number of units procured and, consequently, the greatest budgetary impact during the analyzed period.

Overall, these findings show an uneven regional distribution of immunotherapies in the country, with most of them being acquired in the more economically developed regions and centralized SUS logistics centers.

Figure 5. Regional distribution of immune checkpoint inhibitors in Brazil between 2020 and 2023, showing (A) total units acquired by region, (B–D) distribution by therapeutic target, and relationship between number of units acquired and total procurement cost.



4. Discussion

Immunotherapy has transformed cancer treatment, with immune checkpoint inhibitors (ICIs) emerging as one of the most effective therapeutic strategies in modern oncology. By targeting immune checkpoints exploited by cancer cells to evade immune surveillance, ICIs restore antitumor immune responses and have demonstrated significant clinical benefits across multiple cancer types, either as monotherapy or in combination regimens [1,2]. Advances in monoclonal antibody engineering have also contributed to improved safety profiles and reduced immunogenicity, enhancing treatment tolerability [3].

In this context, the present study provides a comprehensive and individualized analysis of immune checkpoint inhibitor procurement in Brazil, addressing a gap in the literature, as previous investigations evaluated monoclonal antibodies in a broader context or focused on oncology drugs without stratification by immune checkpoint class. By integrating regulatory approval data and federal procurement records, this work offers a novel perspective on the availability and incorporation of ICIs within the Brazilian public health system.

Furthermore, our study stands out by presenting real-world data on the acquisition of ICIs by the Federal Government, offering an unprecedented overview of the availability of these drugs in Brazil. The analysis of these purchases allows us to infer the expansion of access to immunotherapy in the country and to evaluate the prioritization of these treatments

within the public healthcare system, contributing to future discussions on policies for the incorporation and availability of ICIs in the Brazilian Unified Health System (SUS).

The analysis of federal acquisitions allows indirect assessment of access expansion and institutional prioritization of immunotherapy in Brazil. Compared with earlier studies, a marked regulatory expansion is evident. Carvalho (2013) [16] identified only ipilimumab as an approved ICI in Brazil, while Vidal et al. (2018) [17] reported the addition of nivolumab. In contrast, our findings demonstrate the approval of nine ICIs by ANVISA, including antibodies targeting PD-1, PD-L1, and CTLA-4. This increase reflects global advances in immune checkpoint blockade therapies and highlights Brazil's progressive regulatory alignment with international standards.

Another relevant finding is that the monoclonal antibodies (mAbs) acquired by the Brazilian Federal Government reflect an effort to incorporate newer technologies and align with international market trends. The predominance of fully human and humanized antibodies aligns with global market data, in which fully human antibodies account for approximately 54% of approved therapeutic mAbs, followed by humanized (32%) and chimeric antibodies (14%) [18]. Similarly, production platforms observed in this study are consistent with international manufacturing practices: eight of the nine approved ICIs are produced in Chinese hamster ovary (CHO) cells, while only one uses murine myeloma NS0 cells. This distribution parallels previous reports indicating that approximately 60% of therapeutic monoclonal antibodies are produced in CHO cells due to their stability, scalability, high protein yield, and extensive regulatory characterization [12, 18].

Regarding antibody subclasses, most ICIs belong to the IgG1 or IgG4 subclasses, a pattern also observed in monoclonal antibodies used across diverse clinical indications. The predominance of IgG1 antibodies is largely attributed to their long half-life, strong effector functions, and well-established manufacturing and characterization processes [12].

Procurement data indicate that nivolumab and pembrolizumab were the most frequently acquired ICIs in Brazil during the study period. Nivolumab has maintained active registration since 2016. Pembrolizumab, was approved by the FDA in 2017 for the treatment of solid tumors with high microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR). This approval marked a significant advancement, as it established Pembrolizumab as a tumor-agnostic therapy, targeting shared biomarkers across multiple cancer types regardless of tissue origin — an attribute that likely contributed to its substantial acquisition volume [19].

A critical factor underlying the increased procurement of these agents, particularly after 2020, is their incorporation into the SUS following National Commission for the Incorporation of Technologies in the SUS (CONITEC) recommendations. Nivolumab and pembrolizumab were incorporated for first-line treatment of unresectable or metastatic melanoma under Ordinance SCTIE/MS No. 23 (August 4, 2020), while durvalumab was incorporated in 2024 for unresectable stage III non-small cell lung cancer after platinum-based chemoradiotherapy (Ordinance SECTICS/MS No. 21, April 18, 2024). The restricted scope of these incorporations suggests that acquisitions of other ICIs likely occurred predominantly through judicialization mechanisms.

According to the CONITEC recommendation report [20], the decision to incorporate these medications was based on both clinical efficacy and cost–benefit considerations for the public healthcare system. Both nivolumab and pembrolizumab demonstrated statistically significant improvements in progression-free survival (PFS) and overall survival (OS) compared with dacarbazine, with reductions in mortality risk of up to 54% [21]. In addition, immunotherapy with these agents was associated with a lower incidence of severe adverse events compared to conventional chemotherapy [22, 23]. From an economic perspective, the CONITEC report highlights that significant price reductions were negotiated for these medications. It favors the sustainability of treatment, with proposals aligned with cost-effectiveness thresholds based on reference values such as three times the gross domestic product (GDP) per capita, which were decisive for their incorporation [20].

Durvalumab also demonstrated significant clinical benefit, based on data from the PACIFIC trial [24], with substantial gains in both median overall survival (from 29.1 to 47.5 months) and median progression-free survival (from 5.6 to 16.9 months) compared with placebo. Although associated with slightly higher rates of serious adverse events (30.5% versus 26.1%). After price negotiations, the incremental cost-effectiveness ratio remained close to the thresholds considered acceptable in Brazil. The projected budget impact for the SUS in the next five years will be between BRL 82 million and BRL 150 million, depending on the incorporation rate, cost variations, and the amount of the eligible population [25].

In 2018, there was an attempt to incorporate ipilimumab into the Brazilian Unified Health System (SUS) for the treatment of patients with metastatic melanoma who had undergone disease progression after chemotherapy. However, due to its high cost and the availability of alternative immunotherapies with more favorable benefit–risk profiles at the time, the CONITEC decided not to include ipilimumab in the SUS formulary [26]. This

decision illustrates the increasingly selective and evidence-based nature of immunotherapy incorporation in Brazil.

Despite therapeutic advances, immune checkpoint inhibitors (ICIs) remain associated with immune-related adverse events (irAEs), including cutaneous manifestations (rash and pruritus), gastrointestinal disorders, and endocrine dysfunctions [26]. However, advancements in molecular engineering have progressively enhanced the safety profile and tolerability of these therapeutic antibodies.

Advancements have taken place since studies by Carvalho (2013) [16] and Vidal (2018) [17], when Bristol-Myers Squibb was the only producer of ICIs. Currently, seven companies hold approvals. Nevertheless, the number of ICIs available for immunotherapy remains limited, with production concentrated among few pharmaceutical firms, contributing to the high cost of these biologic drugs.

It is noteworthy that, to date, only one biosimilar immune checkpoint inhibitor (ICI) has been approved for clinical use [27]. However, this landscape is expected to change substantially with the anticipated expiration of key ICI patents beginning in 2026, including those for nivolumab and pembrolizumab [28]. Economically, biosimilars are crucial for reducing costs and expanding access to innovative therapies. Currently, the only approved ICI biosimilar is HLX13, targeting CTLA-4, developed by Henlius and authorized exclusively in China. Additional biosimilars are under development, including CMAB819, a nivolumab biosimilar by Mabpharm (China), currently in phase 1, and two pembrolizumab biosimilars in preclinical stages: PSG-024 (PersisGen Par, Iran) and FYB206 (Formycon, Germany) [27].

Patent expiration represents a critical opportunity to stimulate biosimilar development, reduce acquisition costs, and expand access to immunotherapy, particularly in middle-income countries [29]. Encouragingly, national initiatives aimed at technological autonomy are already underway. In 2023, a cooperation agreement between the Federal University of Ceará, Fiocruz/Bio-Manguinhos, and PlantForm Corporation was established to develop pembrolizumab using a plant-based expression platform. Such initiatives may position Brazil to benefit strategically from post-patent biosimilar production, potentially reducing dependence on imported biologics and strengthening national health innovation capacity [30].

Emerging therapeutic strategies, including combination regimens such as nivolumab plus ipilimumab [31, 32], as well as the development of novel immune checkpoint targets,

including lymphocyte activation gene-3 (LAG-3) and V-domain immunoglobulin suppressor of T-cell activation (VISTA), further illustrate the rapidly evolving immunotherapy landscape. In 2022, the FDA approved Relatlimab (BMS-986016), the first monoclonal antibody that targets LAG-3, for treating melanoma and has been proven to be effective in patients who are resistant to anti-PD-1/PD-L1 therapies [33]. In parallel, JNJ-61610588, a monoclonal antibody developed by Johnson & Johnson, is under evaluation in a phase I clinical trial to assess safety and pharmacokinetics in patients with advanced malignancies [34]. Another candidate, CA-170, is an oral inhibitor targeting both PD-L1 and VISTA, with promising results in preclinical studies and phase I trials for advanced solid tumors and lymphomas [34].

Data on the procurement of immune checkpoint inhibitors (ICIs) demonstrate a pronounced concentration in Brazil's South and Southeast regions. This distribution may be attributed to greater technological advances, the presence of high-complexity healthcare facilities, and the availability of trained multidisciplinary teams capable of managing a diverse spectrum of disease cases, whether complex or not [35].

Despite the existence of the Ministry of Health's Clinical Protocol and Therapeutic Guidelines (PCDT) for cancer, there is a lack of standardized clinical protocols and unified national guidelines for oncological treatment. Furthermore, not all hospitals providing cancer care have access to the same resources and therapies available within the Brazilian Unified Health System (SUS). This is compounded by delays in the incorporation of these medications by the National Commission for the Incorporation of Technologies in SUS (CONITEC) and the Brazilian Health Regulatory Agency (ANVISA), contributing to heterogeneity in access and therapeutic management across different regions of the country. Consequently, an unequal provision of oncological treatments is observed, which are often outdated compared to international guidelines regarding applicability [36].

Budgetary constraints within the public health system hinder the maintenance of a stable and adequate model for the continuous provision of advanced therapies. This situation demands more effective coordination among healthcare professionals, public managers, and governmental institutions to ensure equitable access to these treatments [37, 38].

Globally, unequal access to therapies is also linked to factors such as regulatory approval, the time lag between approval and commercialization, cost-sharing models, and the effective incorporation of therapies into health systems [39]. In Brazil, these barriers often force cancer patients to travel between states, usually towards centers with a higher concentration of technological resources and specialized medical professionals [40, 41]. This

regional centralization is also reflected in the acquisition of immune checkpoint inhibitors (ICIs), with a marked concentration of purchases in the South and Southeast regions. According to Fonseca et al. (2022) [41], between 2009–2010 and 2017–2018, patients from the North region traveled distances exceeding 2,000 km, while those from the Midwest region traveled more than 300 km to access radiotherapy services. Such prolonged displacement is associated with reduced treatment adherence, particularly among socioeconomically vulnerable patients who are unable to afford the indirect costs of travel and prolonged stays during therapy. These data reinforce regional inequalities in access to advanced cancer treatments [41].

Additionally, the process of judicialization in Brazil, as the judicialization of medicines has a particularly relevant impact in the case of mAbs, which are among the most frequently demanded health technologies [42]. In general, such lawsuits arise from the non-incorporation or limited availability of these drugs within the SUS, leading the Judiciary to order their provision based on individual medical prescriptions, often outside the regular health technology assessment processes.

Although these judicial decisions may ensure immediate access to innovative therapies, they conflict with the collective rationale of public health policies by disregarding prioritization criteria, cost-effectiveness, and budgetary planning. This dynamic results in the inappropriate reallocation of public resources and undermines the equity and sustainability of the SUS. Thus, while the judicialization of these mAbs may respond to urgent individual needs, it tends to exacerbate health inequalities and highlight the need for stronger coordination between the Judiciary and technical-regulatory bodies [43].

The interpretation of our results has some limitations. The use of publicly available data from online platforms in conducting this study may not fully capture all information related to the acquisition of the analyzed medicines. Also, there is a lack of transparency in the data regarding the regional distribution of these antibodies. This hinders a comprehensive mapping of their distribution across the national territory and limits the identification of potential regional disparities in access.

5. Conclusion

This study provides a comprehensive overview of the regulatory approval and federal procurement of immune checkpoint inhibitors in Brazil between 2014 and 2023, revealing substantial expansion in ICI availability within the SUS. Despite increased federal investment

and regulatory alignment with international standards, access to immunotherapy remains uneven, constrained by high acquisition costs, centralized distribution, regional disparities, and the absence of approved biosimilar ICIs. Addressing regional inequities, reducing reliance on judicialization, and ensuring the sustainable incorporation of immunotherapy into the SUS are critical to advancing equitable cancer care in Brazil. Proactive policy planning in the context of the post-patent era will be essential to ensure that the clinical benefits of immune checkpoint inhibition are translated into population-level gains in cancer outcomes. Strengthening data integration, decentralizing distribution, and supporting national innovation initiatives will be essential to ensure that advances translate into improved outcomes for patients throughout the country.

Conflict of interests
The authors declare no conflicts of interest.

Authors' contributions
DCVP organized and drafted the manuscript and performed data retrieval and interpretation. LSS contributed to data interpretation and manuscript writing. ASQG and INFR were responsible for data retrieval and interpretation. ASK, MIFG, and PPA contributed to critical revision of the manuscript and provided scientific guidance. LECM conceived and supervised the study, wrote sections of the manuscript, and performed the final revision.

Data availability statement
The concepts and ideas developed and/or analyzed in the present study are available from the corresponding author on reasonable request.

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