Monoclonal Antibody Drugs for Cancer Treatment: a Brazilian Perspective

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Fármacos Anticorpos Monoclonais para o Tratamento do Câncer: uma Perspectiva Brasileira
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Júlia Teixeira de Menezes; Maria Carolina Theisen; Vanessa da Costa Flores; Fernando Fumagalli

**ABSTRACT**

Monoclonal antibodies (mAb) are an important therapeutic alternative in cancer treatment. However, access to this therapy is unequal in countries with heterogeneous incomes. **Objective:** Compare the mAb approved for cancer in the USA with those already approved in Brazil, as well as to discuss, through the mechanism of action, the available therapeutic alternatives. **Method:** The list of mAb approved by the US FDA were collected from previous publications and the agency’s site. Mechanism of action, date of approval and clinical indications were obtained from the drug labels on the FDA website and the date of Anvisa approval was obtained from this agency’s website. The drugs were organized according to their structural characteristics (murine, chimeric, humanized and human) and separated into four major groups, according to their mechanism of action. **Results:** Until 2022, 48 mAb have been approved for cancer by the FDA. Of these, 37 have already been approved by Anvisa for use in Brazil, with an average time between approval abroad and in Brazil close to two years. The majority of these mAb are human or humanized (77%) and vary greatly in terms of their mechanism of action, with the B lymphocyte antigen CD20 and the immune checkpoint PD-1/PD-L1 as the main targets of the mAb evaluated. **Conclusion:** Although some drugs approved abroad are not yet approved in Brazil, the delay in the registration does not seem to be related to Anvisa. Furthermore, for most of the cases of drugs not yet approved in Brazil, therapeutic alternatives are available.

**Key words:** Brazilian Health Surveillance Agency; Drug Approval; Antineoplastic/standards; Antibodies, Monoclonal.
INTRODUCTION

Twenty-five years after the Brazilian Health Surveillance Agency (Anvisa) approved the first monoclonal antibodies (mAb) drug for treating cancer (rituximab), the use of these biological drugs is a reality in the therapeutic schemes for treating the disease.

Structurally, mAb can be classified in 4 types: murine, chimeric, humanized and human (Figure 1a)⁴,⁵, the last three resulting from some development alterations with the purpose of increasing mAb likeness to human antibodies, thus reducing the occurrence of adverse events commonly caused by totally murine mAb. Moreover, some mAb are conjugated to drugs (ADC – Antibodies Conjugated to Drugs) or radiolabeled, playing an important role in diagnosis and therapy, in addition to helping drive cytotoxic drugs to the tumoral cells.

As to the action of these drugs on the body, their antitumoral effects may be mediated by the immune response or direct mAb action (Figures 1b and 1c)⁶. The mAb may lead to cytotoxicity in cancer cells by activating the complement cascade that triggers cytolysis or by the action of immune system effector cells, such as natural killer cells, provoking lysis on the mAb-labeled cell. Another strategy is to label the tumoral cell so that it suffers opsonization by phagocytic cells. They can also affect cancer cells directly, blocking the binding of their survival mediators or inhibiting a receptor’s dimerization, therefore, blocking an activation sign or even inducing an apoptotic signal through the receptor binding.

Surely, the efficiency of this therapy has brought great advances in the treatment of cancer, but the availability of these medications in different parts of the world, as well as a country and their population’s purchasing power, prevent lower income groups of accessing these treatments. To discover how Brazil stands in this scenario, this study presents an updated landscape about the availability of this therapy in Brazil in comparison to a developed country. It also discusses the mechanisms of action of the target disease to verify if the Brazilian population has mAb-based therapeutic alternatives to the drugs of this class that have not yet been registered or approved in Brazil.

METHOD

Retrospective study that lists all the new approved mAb drugs for cancer treatment in the United States (USA) since 1997 based on data from a literature review article⁵ and the Food and Drug Administration (FDA)
Antigens. In Brazil, 37 (77%) of the 48 FDA-approved mAbs with new conjugated drugs were considered, excluding those with mAb associations already commercialized.

For mAbs approved by the FDA up to 2022, variables such as approval date by the FDA (first drug record in the agency), commercial name, monoclonal antibody type, mechanism of action and clinical indications were integrally extracted from the drugs’ package insert verified on the FDA website, last visited on June 2023. The search was performed by typing the drug name on the search bar “Product Names”. The date of approval by Anvisa was obtained from searching the drug name on their query website, last visited on June 2023. Drugs that returned no search results were considered “not approved by Anvisa” in contrast to those that returned results and were therefore considered “approved by Anvisa”, with the first record date being the date of approval by Anvisa.

The drugs were arranged on a table, organized, and quantified as to their structural characteristics, as well as separated in four big groups according to their mechanism of action to facilitate discussion. The time range between approval by Anvisa and by the FDA for each drug defined a delay time for the Brazilian record. The term “therapeutic alternative” was used to refer to mAbs available in Brazil that are not biosimilar but have the same mechanism of action or target cancer of mAbs that were only approved by the FDA. All drugs that had an expired Anvisa record or had not been registered in Brazil and were public announced as discontinued by their manufacturers were considered discontinued.

Following Resolution number 510/2016 of the National Health Council (NHC), studies that use deidentified data and public database are exempt from ethical analysis.

RESULTS

Data collection allowed to identify that 48 mAbs were approved for cancer treatment by the FDA up to 2022 (Charts 1 to 3). Between 1997 and 2013, no more than two antineoplastic mAbs were approved each year, with no mAb being approved in five of the years within that period. This changed in 2014, when, on average, three mAbs were approved yearly for cancer treatment, with at least two antitumoral mAbs being approved each year.

Among the 48 mAbs, 8% are murine, 15% chimeric, 33% human and 44% humanized. A considerable portion of these drugs (13 mAbs, 27%) have some other antineoplastic agent conjugated to the antibody with four of them (8%) are bispecific, binding to two different antigens. In Brazil, 37 (77%) of the 48 FDA-approved mAbs were approved and approved by Anvisa. The average time range between approvals by the American agency and Anvisa was approximately two years. In the last five years, this average time range has not exceeded a year and a half.

Among the 48 mAbs analyzed, the most common clinical indication was non-small cell lung carcinoma (NSCLC) with 11 mAbs (23%) and hepatocellular carcinoma (HCC) with six mAbs (12.5%). However, multiple myeloma (MM) had more drugs (five mAbs, 10%) approved exclusively for this tumor. The drugs with the most clinical indications were nivolumab and pembrolizumab (Charts 2 and 3, respectively). Considering the mechanism of action of the 48 drugs, 10 mAbs (20.8%) act on immunological/immune response modulation checkpoints, 16 mAbs (33.4%) act on B-cells, 10 mAbs (20.8%) label or bind to membrane antigens, and 12 mAbs (25%) act in receptor tyrosine kinase (Figure 2).

DISCUSSION

Due to their highly specific and less prone to side effects nature, mAbs therapies have revolutionized the treatments of diseases such as cancer. However, access to this medication class in Brazil is quite limited to patients due to their high cost.

Over the last ten years, there has been a significant increase in the approval of new mAb-based cancer therapies in Brazil as well as in the USA. Specifically, over 70% (35 out of 48 by the FDA and 29 out of 35 by Anvisa) of antineoplastic mAbs were approved for human use in the last decade. However, some of these drugs (5 out of 48, 10%) are no longer commercialized for cancer treatment. Manufacturers usually claim commercial reasons to justify withdrawing their drugs from the market, as was the case with tositumomab, necetumumab, alemtuzumab and ofatumumab. Regarding these last two drugs, their manufacturers have invested in FDA and Anvisa approval for another disease, multiple sclerosis. In addition to commercial reasons, the olaratumab drug was also discontinued due to lack of therapeutic efficacy. Regarding the gentuzumab drug, it had been approved, then pulled from the market for commercial reasons, and finally resubmitted for approval for the same treatment years later.

When analyzing the FDA-approved drugs that were not yet approved by Anvisa (11 out of 48, 23%), it was verified that only three had been on the market for over five years (with two of them having already been discontinued), while the other eight had only recently been approved by the FDA (less than three years ago). Thus, though it takes on average two years for mAbs approved abroad to be approved in Brazil, this is not

website. Only drugs that contained new mAb or mAb with new conjugated drugs were considered, excluding those with mAb associations already commercialized.

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apparently due to a lack of interest on the Brazilian market’s part.

Considering the yet-to-be-approved mAb in Brazil, mirvetuximab has no approved equivalent in terms of mechanism of action. It is indicated for treating ovarian, fallopian tube and peritoneal cancer, with a mechanism of action (Figure 2c) that involves binding to the folate receptor (Frα) and cytotoxic activity of conjugated agent ravtansine (DM4). As an alternative for treating ovarian cancer, dostarlimab (Figure 2a) and pembrolizumab (Figure 2a) can be used, as long as in association with other antineoplastic agents, since their mechanism of action in the immunological checkpoint PD-1/PD-L1 ends up having a modest monotherapy response for this type of cancer. Though it is not expressed in the medication’s package insert, bevacizumab angiogenesis inhibitor (that binds to the vascular endothelial growth factor – VEGFA, Figure 2d) may also be used in drug combinations for ovarian cancer treatment.

Still regarding cancer types that occur in women, margetuximab, used in breast cancer, has not yet been registered in Brazil (Figure 2d). However, other drugs containing pertuzumab and trastuzumab (Figure 2d), that have the same mechanism of action, are available in the Brazilian market. These three mAb bind to the human epidermal growth factor receptor 2 (HER2) and can also trigger antibody-dependent cellular cytotoxicity (ADCC). For the treatment of triple-negative breast cancer only sacituzumab is available (Figure 2c), which is a mAb coupled to topoisomerase I inhibitor (SN-38, active metabolite of irinotecan) that binds to the trophoblast cell-surface antigen 2 (Trop-2), expressed in the majority of breast cancers.

Regarding mAb-based treatments for non-Hodgkin lymphoma, the ibritumomab drug has not yet been registered in Brazil, however, rituximab, which binds to the same target (CD-20) (Figure 2b), is available in the country. Other two mAb drugs that bind to the same target but are indicated to treat follicular lymphoma, obinutuzumab and mosunetuzumab, are globally available (Figure 2b). The latter, however, has not yet been registered by Anvisa.

Another cancer type that targets B-cells is diffuse large B-cell lymphoma (DLBCL). Recently, three mAb (Figure 2b) have been included as therapeutic assets for this disease, however, only polatuzumab has been approved in Brazil so far, conjugated with an antimitotic agent (monomethyl auristatin E – MMAE). The tafasitamab and loncastuximab drugs target CD-19, which is commonly super-expressed in tumoral B-cells,
Chart 2. Human monoclonal antibody-type antineoplastic drugs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Commercial Name</th>
<th>FDA Approval</th>
<th>Anvisa Approval</th>
<th>Clinical Indication</th>
</tr>
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<tbody>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
<td>2006</td>
<td>2010</td>
<td>mCRC</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Arzerra</td>
<td>2009</td>
<td>2015</td>
<td>CLL</td>
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<td>2012</td>
<td>RCC, mCRC, HCC, NSCLC, mMEL, MPM</td>
</tr>
<tr>
<td>Ramucirumab</td>
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<td>2014</td>
<td>2016</td>
<td>mGC, NSCLC, mCRC, HCC</td>
</tr>
<tr>
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<td>Opdivo</td>
<td>2014</td>
<td>2016</td>
<td>MEL, NSCLC, MPM, RCC, CRC, HCC</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Darzalex/</td>
<td>2015</td>
<td>2017</td>
<td>MM</td>
</tr>
<tr>
<td>Dalinvi*</td>
<td></td>
<td>2015</td>
<td>2017</td>
<td>MM</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>Portrazza</td>
<td>2015</td>
<td>-</td>
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<tr>
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<td>Lartruvo</td>
<td>2016</td>
<td>2017</td>
<td>STS</td>
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<td>Bavencio</td>
<td>2017</td>
<td>2018</td>
<td>MCC, UC, RCC</td>
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<td>2017</td>
<td>NSCLC, BTC, SCLC</td>
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<td>Libtayo</td>
<td>2018</td>
<td>2019</td>
<td>cSCC, BCC, e NSCLC</td>
</tr>
<tr>
<td>Enfortumab vedotin</td>
<td>Padcev</td>
<td>2019</td>
<td>2022</td>
<td>mUC</td>
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<tr>
<td>Amivantamab</td>
<td>Rybrevant</td>
<td>2021</td>
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<td>2021</td>
<td>-</td>
<td>CVC</td>
</tr>
<tr>
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<td>Opdualag</td>
<td>2022</td>
<td>-</td>
<td>mMEL</td>
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<tr>
<td>Tremelimumab</td>
<td>Imjudo</td>
<td>2022</td>
<td>2023</td>
<td>HCC, NSCLC</td>
</tr>
</tbody>
</table>

Captions: CLL = chronic lymphocytic leukemia; mCRC = metastatic colorectal cancer; mMEL = metastatic melanoma; mGC = metastatic gastric cancer; CRC = colorectal carcinoma; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung carcinoma; SCLC = small cell lung carcinoma; MEL = melanoma; UC = uterine cervical carcinoma; mUC = metastatic urothelial carcinoma; mMEL = malignant melanoma; MPM = malignant pleural mesothelioma; ESCLC = esophageal squamous cell carcinoma.;

*In Brazil, the daratumumab drug is sold as Dalinvi*.

the first activating ADCC and the second releasing their DNA intercalating agent (tesirine, SG3199) for inducing tumoral cell death.

As to patients with MM, there are mAb available for treating this disease since 2015. Among the five mAb-based drugs already approved by the FDA for MM treatment, elotuzumab (Figure 2c) acts in the activation of natural killer cell as well as by labeling tumoral plasmatic cells through SLAMF7 protein binding. As to isatuximab and daratumumab (Figure 2c), they bind to the Cluster of Differentiation 38 (CD38) and trigger ADCC. In addition to these two targets, MM mAb-based treatment can occur through B-cell maturation antigen (BCMA) bind. In that case, two drugs have been recently approved by the FDA, teclistamab and belantamab (Figure 2b), with the latter not yet approved by Anvisa. Belantamab is a mAb conjugated to MMAE antimitotic agent, while teclistamab is bispecific, binding to CD3 of T-cells, then directing these cells to trigger lysis of BCMA-expressing tumoral cells.

Another drug not registered by Anvisa is tisotumab (Figure 2c). This mAb is conjugated to MMAE antimitotic agent and binds to the tumoral cell tissue factor. This membrane glycoprotein is super-expressed in cervical cancer cells and is associated with a negative disease prognosis. Though tisotumab is a first-line therapy, other mAb drugs can be used, such as pembrolizumab.

One last mAb not approved in Brazil is relatlimab, capable of blocking LAG-3, a protein that negatively regulates T-cells (Figure 2a). This mAb is sold in association with nivolumab (anti-PD1) for treating metastatic melanoma (mMEL), synergistically acting to maintain T-cell activity against the tumoral cell. This is not the only mAb-based therapeutic alternative to treating mMEL though. Pembrolizumab and ipilimumab have been previously approved for treating this type of cancer.

Among the mAb drugs approved for cancer treatment available in the market, their main clinical indication is
for NSCLC\(^4\). Seven of them act by supporting T-cell antitumoral action process, in which pembrolizumab, nivolumab, cemiplimab, atezolizumab, and durvalumab (Figure 2a) bind to the PD-1/PD-L1 system and ipilimumab and tremelimumab bind to CTLA-4 (Figure 2a)\(^3\). Ramucirumab and bevacizumab are angiogenesis inhibitors (Figure 2c)\(^4\). There is also bispecific antibody amivantamab (Figure 2c), which blocks cellular division signaling\(^5\).

Other drugs not yet discussed in this study are indicated to different types of cancer. For instance, dinutuximab and naxitamab (Figure 2c) bind to membrane glycosphingolipid GD2 in neuroblastoma.
tumor cells, triggering CCDA\textsuperscript{44}. In addition to those, gemtuzumab (Figure 2c) is a mAb conjugated to the DNA-binding cytotoxic agent calicheamicin that binds to CD33 present on leukemic myeloblasts in patients with acute myeloid leukemia\textsuperscript{45}.

There are still other mAb related to B-cells (Figure 2b). Inotuzumab and blinatumomab (Figure 2b) are indicated to treat acute lymphoblastic leukemia. The former is a mAb conjugated to antitumoral agent calicheamicin that binds to CD22, while the latter is a bispecific antigen that binds to both CD19 and CD3, driving effector T-cells action against the tumor\textsuperscript{46}. For hairy cell leukemia treatment, there is moxetumomab, which is also a conjugated antibody (pseudomonas exotoxin A, PE38) that binds to CD22\textsuperscript{47}. In addition to those, there is brentuximab (Figure 2b), which is also conjugated to MMAE that binds to CD30 protein, being indicated for treating Hodgkin lymphoma and systemic anaplastic large cell lymphoma (ALCL)\textsuperscript{48}.

For cancers that target the genitourinary system, enfortumab (Figure 2c) and avelumab (initially approved for Merkel carcinoma\textsuperscript{49}, Figure 2a) can be used for urothelial carcinoma, as well as sacituzumab, previously mentioned for breast cancer treatment. Enfortumab is a mAb conjugated to MMAE that binds to the nectin-4 cell surface receptor\textsuperscript{50}, while avelumab acts on the PF-1/ PD-L1 immunological checkpoint\textsuperscript{51}.

Finally, there are two drugs that bind to human epidermal growth factor receptor HER1, panitumumab and cetuximab. In addition to binding to the same receptor, these two mAb are also indicated for treating the same disease, colorectal cancer\textsuperscript{52}.

**CONCLUSION**

The availability of mAb drugs for cancer treatment in Brazil has been growing over the past decade in line with the USA. The great majority of drugs that have not yet been registered in Brazil have just recently been approved by the FDA. In view of this, the non-availability of these drugs in the Brazilian market does not seem to be related to a registration delay on the part of Anvisa, whose registration analysis time has decreased over the last couple of years. Moreover, in most cases, there are mAb-based therapeutic alternatives to the drugs not yet available in Brazil.

\textbf{Figure 2.} Representation of the mechanisms of action of mAb drugs used in cancer treatment

\textbf{Captions:} mAb = monoclonal antibodies.

*Drugs withdrawn from the market.
CONTRIBUTIONS

Júlia Teixeira de Menezes and Fernando Fumagalli have substantially contributed to the study design, acquisition, analysis and interpretation of the data, wording, and critical review. Vanessa da Costa Flores and Maria Carolina Theisen have contributed to the study design, wording, and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

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REFERENCES

8. FDA: Food and Drug Administration [Internet]. Maryland: Departamento de Saúde e Serviços Humanos dos Estados Unidos; c1906-2023. New Drugs at FDA: CDER’s new molecular entities and new therapeutic biological products. [acesso 2023 nov 9]. https://www.fda.gov/drugs/development-approval-process-drugs/
17. FDA: Food and Drug Administration [Internet]. Maryland: Departamento de Saúde e Serviços Humanos dos Estados Unidos; c1906-2023. Novartis Withdraws Chronic leukemia drug arzerra from non-U.S. markets. [acesso 2023 nov 9]. Disponível em: https://www.fdanews.com/articles/185419-novartis-
withdraws-chronic-leukemia-drug-arzerra-from-non-us-markets


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