Monoclonal Antibody Drugs for Cancer Treatment: a Brazilian Perspective

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Fármacos Anticorpos Monoclonais para o Tratamento do Câncer: uma Perspectiva Brasileira

Fármacos Anticuerpos Monoclonales para el Tratamiento del Cáncer: una Perspectiva Brasileña

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ABSTRACT

Introduction: 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.

RESUMO

Introdução: Os anticorpos monoclonais (mAb) são alternativa terapêutica importante no tratamento do câncer. Porém, o acesso a essa terapia é desigual entre países com diferentes rendas. **Objetivo:** Comparar os fármacos mAb aprovados para uso contra câncer nos EUA com os aprovados no Brasil e discutir, por meio do mecanismo de ação, alternativas terapêuticas disponíveis. **Método:** A lista de fármacos mAb aprovados pelo FDA foi coletada de publicação prévia e complementada com dados presentes no *site* dessa agência, assim como mecanismo de ação, data de aprovação e indicações clínicas foram obtidos das bulas dos medicamentos nesse mesmo *site.* Da mesma forma, os dados de data de aprovação pela Anvisa foram obtidos em consultas ao *site* dessa agência. Os fármacos foram tabelados e organizados conforme características estruturais e separados em quatro grandes grupos, conforme seu mecanismo de ação. **Resultados:** Até 2022, 48 mAb foram aprovados para uso contra o câncer pelo FDA. Destes, 37 foram aprovados pela Anvisa para uso no Brasil, com tempo médio entre aprovação no exterior e no Brasil próximo a dois anos. A maioria dos mAb são humanos ou humanizados (77%) e variam bastante com relação ao mecanismo de ação, sendo o antígeno de linfócitos B CD20 e o *checkpoint* imunológico PD-1/PD-L1 os principais alvos dos mAb avaliados. **Conclusão:** Apesar de alguns fármacos aprovados no exterior ainda não estarem aprovados no Brasil, o atraso para registro não parece estar relacionado à demora da Anvisa. Além disso, para a maioria dos casos de fármacos ainda não aprovados no Brasil, existem alternativas terapêuticas disponíveis.

Palavras-chave: Agência Nacional de Vigilância Sanitária; Aprovação de Drogas; Antineoplásicos/normas; Anticorpos Monoclonais.

RESUMEN

Introducción: Los anticuerpos monoclonales (mAb) son una importante alternativa terapéutica en el tratamiento del cáncer. Sin embargo, el acceso a esta terapia es desigual en países con diferentes ingresos. **Objetivo:** Este trabajo buscó comparar los mAb aprobados para su uso contra el cáncer en los EUA con los ya aprobados en Brasil, así como discutir, por el mecanismo de acción, las alternativas terapéuticas disponibles. **Método:** La lista de mAb aprobados por la FDA fue recopilada de publicación anterior y complementada con datos presentes en el sitio web de esta agencia. El mecanismo de acción, la fecha de aprobación y las indicaciones clínicas se obtuvieron de los prospectos del medicamento en el sitio web de la FDA y los datos sobre la fecha de aprobación por parte de la Anvisa se obtuvieron de consultas en el sitio web de esta agencia. Los fármacos fueron tabulados y organizados según sus características estructurales (murinos, quiméricos, humanizados y humanos) y separados en cuatro grandes grupos, según su mecanismo de acción. **Resultados:** Hasta 2022, la FDA ha aprobado 48 mAb para su uso contra el cáncer. De ellos, 37 ya fueron aprobados por Anvisa para su uso en Brasil, con el tiempo promedio entre la aprobación en el extranjero y en Brasil es de alrededor de dos años. La mayoría de estos mAb son humanos o humanizados (77%) y varían mucho en cuanto a su mecanismo de acción, siendo el antígeno de linfocitos B CD20 y el *checkpoint* inmunológico PD-1/PD-L1 las principales dianas farmacológicas de los mAb evaluados. **Conclusión:** Aunque algunos medicamentos aprobados en el exterior aún no están aprobados en Brasil, la tardanza en ese registro no parece estar relacionada con demora por parte de Anvisa. Además, para la mayoría de los casos de estos medicamentos aún no aprobados en Brasil, existen alternativas terapéuticas disponibles.

Palabras clave: Agencia Nacional de Vigilancia Sanitaria; Aprobación de Drogas; antineoplásico/normas; Anticuerpos Monoclonales.

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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[1].

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[2]. 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[3].

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[5].

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 article[5] and the Food and Drug Administration (FDA)

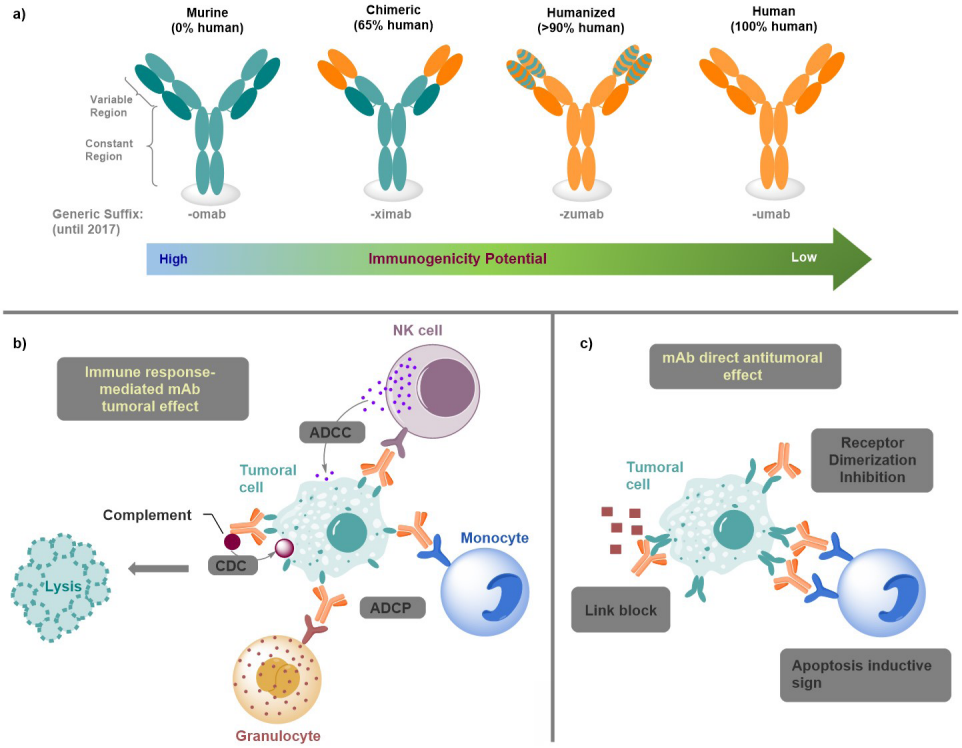

Figure 1. a) Structural and naming differences in the several mAb; **b** and **c)** Mechanisms of action of mAb used in cancer treatment.

Source: Adapted from Lythgoe[4], Weiner[5], Chiavenna SM, Jaworski JP, Vendrell A[6].

Captions: mAb = monoclonal antibodies; ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CDC = complement-dependent cytotoxicity.

website[8]. Only drugs that contained new mAb or mAb with new conjugated drugs were considered, excluding those with mAb associations already commercialized.

For mAb 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[9], 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[10], 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 mAb drugs available in Brazil that are not biosimilar but have the same mechanism of action or target cancer of mAb 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[11] 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 mAb were approved for cancer treatment by the FDA up to 2022 (Charts 1 to 3). Between 1997 and 2013, no more than two antineoplastic mAb 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 mAb were approved yearly for cancer treatment, with at least two antitumoral mAb being approved each year.

Among the 48 mAb, 8% are murine, 15% chimeric, 33% human and 44% humanized. A considerable portion of these drugs (13 mAb, 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 mAb were registered 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 mAb analyzed, the most common clinical indication was non-small cell lung carcinoma (NSCLC) with 11 mAb (23%) and hepatocellular carcinoma (HCC) with six mAb (12.5%). However, multiple myeloma (MM) had more drugs (five mAb, 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 mAb (20.8%) act on immunological/immune response modulation checkpoints, 16 mAb (33.4%) act on B-cells, 10 mAb (20.8%) label or bind to membrane antigens, and 12 mAb (25%) act in receptor tyrosine kinase (Figure 2).

DISCUSSION

Due to their highly specific and less prone to side effects nature, mAb 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[12].

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[13]. Specifically, over 70% (35 out of 48 by the FDA and 29 out of 35 by Anvisa) of antineoplastic mAb 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[14], necetumumab[15], alemtuzumab[16] and ofatumumab[17]. 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[18]. 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.[19].

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 mAb approved abroad to be approved in Brazil, this is not

Chart 1. Murine and chimeric monoclonal antibody-type antineoplastic drugs

Murine monoclonal antibodies				
Drug Name	**Commercial Name**	**FDA Approval**	**Anvisa Approval**	**Clinical Indication**
Ibritumomab Tiuxitan	Zevalin	2002	-	NHL
Tositumomab	Bexxar	2003	-	NHL
Blinatumomab	Blincyto	2014	2017	ALL
Moxetumomab pasudotox	Lumoxiti	2018	2020	HCL
Chimeric monoclonal antibodies				
Drug Name	**Commercial Name**	**FDA Approval**	**Anvisa Approval**	**Clinical Indication**
Rituximab	Mabthera	1997	1998	NHL, CLL
Cetuximab	Erbitux	2004	2006	mCRC, HNSCC
Brentuximab vedotin	Adcetris	2011	2014	cHL; sALCL; pcALCL; PTCL
Dinutuximab/ betadinutuximabe	Unituxin/ Qarziba*	2015	2021	NB
Isatuximab	Sarclisa	2020	2021	MM
Margetuximab	Margenza	2020	-	mBrC
Mirvetuximab soravtansine	Elahere	2022	-	OVC, FTC, PPC

Captions: NHL = non-Hodgkin lymphoma; ALL = acute lymphoblastic leukemia; HCL = hairy cell leukemia; CLL = chronic lymphocytic leukemia; mCRC = metastatic colorectal cancer; HNSCC = head and neck squamous cell carcinoma; cHL = classic Hodgkin lymphoma; sALCL = systemic anaplastic large cell lymphoma; pcALCL = primary cutaneous anaplastic large-cell lymphoma; PTCL = peripheral T cell lymphoma; NB = neuroblastoma; MM = multiple myeloma; mBrC = metastatic breast cancer; OVC = ovarian cancer, FTC = fallopian tube cancer; PPC = primary peritoneal cancer.

*In Brazil, the dinutuximab drug is sold as betadinutuximabe (Qarziba®).

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 *alfa* folate receptor (Frα) and cytotoxic activity of conjugated agent ravtansine (DM4)[20]. As an alternative for treating ovarian cancer, dostarlimab (Figure 2a)[21] 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[22]. 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[23].

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)[24]. For the treatment of triple-negative breast cancer only sacituzamab 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[25].

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)[26] (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)[27]. 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)[28]. 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

Drug Name	Commercial Name	FDA Approval	Anvisa Approval	Clinical Indication
Panitumumab	Vectibix	2006	2010	mCRC
Ofatumumab	Arzerra	2009	2015	CLL
Ipilimumab	Yervoy	2011	2012	RCC, mCRC, HCC, NSCLC, mMEL, MPM
Ramucirumab	Cyramza	2014	2016	mGC, NSCLC, mCRC, HCC
Nivolumab	Opdivo	2014	2016	MEL, NSCLC, MPM, RCC, CRC, HCC, ESCC, HNSCC, UC
Daratumumab	Darzalex/	2015	2017	MM
Dalinvi*	2015	2017	MM	NSCLC
Necitumumab	Portrazza	2015	-	NSCLC
Olaratumab	Lartruvo	2016	2017	STS
Avelumab	Bavencio	2017	2018	MCC, UC, RCC
Durvalumab	Imfinzi	2017	2017	NSCLC, BTC, SCLC
Cemiplimab	Libtayo	2018	2019	cSCC, BCC e NSCLC
Enfortumab vedotin	Padcev	2019	2022	mUC
Amivantamab	Rybrevant	2021	2021	NSCLC
Tisotumab vedotin	Tivdak	2021	-	CVC
Nivolumab + relatlimab	Opdualag	2022	-	mMEL
Tremelimumab	Imjudo	2022	2023	HCC, NSCLC

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 = urothelial carcinoma; mUC = metastatic urothelial carcinoma; HNSCC = head and neck squamous cell carcinoma; RCC = renal cell carcinoma; MM = multiple myeloma; BTC = biliary tract carcinoma; STS = soft tissue sarcoma; MCC = Merkel cell carcinoma; cSCC = cutaneous squamous cell carcinoma; BCC = basal cell carcinoma; CVC = cervical cancer; MPM = malignant pleural mesothelioma; ESCC = esophageal squamous cell carcinoma..

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

the first activating ADCC[29] and the second releasing their DNA intercalating agent (tesirine, SG3199) for inducing tumoral cell death[30].

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[31]. As to isatuximab and daratumumab (Figure 2c), they bind to the Cluster of Differentiation 38 (CD38) and trigger ADCC[32]. In addition to these two targets, MM mAb-based treatment can occur through B-cell maturation antigen (BCMA) bind[31]. 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[33], while teclistamab is bispecific, binding to CD3 of T-cells, then directing these cells to trigger lysis of BCMA-expressing tumoral cells[34].

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[35]. Though tisotumab is a first-line therapy, other mAb drugs can be used, such as pembrolizumab[36].

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[37]. 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[38]. The latter also prevents T-cell inhibition signal, through cytotoxic T-lymphocyte antigen-4 (CTLA-4) binding[39].

Among the mAb drugs approved for cancer treatment available in the market, their main clinical indication is

Chart 3. Humanized monoclonal antibody-type antineoplastic drugs

Drug Name	Commercial Name	FDA Approval	Anvisa Approval	Clinical Indication
Trastuzumab	Herceptin	1998	1999	BrC, mGC
Gentuzumab ozogamicin	Mylotarg	2000 and 2017	2001 and 2021	AML
Alemtuzumab	Campath	2001	2006	CLL
Bevacizumab	Avastin	2004	2005	mCRC, NSCLC, mBrC, mRCC, GBM
Pertuzumab	Perjeta	2012	2013	mBrC
Trastuzumab entansine	Kadcyla	2013	2014	mBrC
Obinutuzumab	Gazyva	2013	2015	CLL, FL
Pembrolizumab	Keytruda	2014	2016	MEL, SCLC, HL, NSCLC, HNSCC, PMBCL, CRC, GC, CVC, EC, TNBC, UC, MCC, HCC, RCC, cSCC, ESCA, MSI-H, dMMR, TMB-H
Elotuzumab	Empliciti	2015	2017	MM
Atezolizumab	Tecentriq	2016	2017	UC, NSCLC, SCLC, HCC, MEL
Inotuzumab ozogamicin	Besponsa	2017	2019	ALL
Polatuzumab vedotin	Polivy/	2019	2019	DLBCL
RoPolivy	2019	2019	DLBCL	BrC
Trastuzumab deruxtecan	Enhertu	2019	2021	BrC
Sacituzumab	Monjuvi	2020	-	DLBCL
govitecan	Trodelvy	2020	2022	TNBC, mUC
Tafasitamab	Monjuvi	2020	-	DLBCL
Belantamab mafodotin	Blenrep	2020	-	MM
Naxitamab	Danyelza	2020	2023	NB
Loncastuximab tesirine	Zynlonta	2021	-	DLBCL
Dostarlimab	Jemperli	2021	2022	EC
Teclistamab	Tecvayli	2022	2023	MM
Mosunetuzumab	Lunsumio	2022	-	FL

Captions: AML = acute myeloid leukemia; BrC = breast cancer; mBrC = metastatic breast cancer; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; mCRC = metastatic colorectal cancer; CRC = colorectal carcinoma; mGC = metastatic gastric cancer; GC = gastric cancer; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung carcinoma; SCLC = small cell lung carcinoma; MEL = melanoma; UC = urothelial carcinoma; mUC = metastatic urothelial carcinoma; HNSCC = head and neck squamous cell carcinoma; mRCC = metastatic renal cell carcinoma; RCC = renal cell carcinoma; ESCA = esophageal carcinoma; TNBC = triple-negative breast cancer; ALL = acute lymphoblastic leukemia; MM = multiple myeloma; HL = Hodgkin lymphoma; NB = neuroblastoma; MCC = Merkel cell carcinoma; cSCC = cutaneous squamous cell carcinoma; DLBCL = diffuse large B-cell lymphoma; EC = endometrial cancer; GBM = glioblastoma; PMBCL = primary mediastinal B-cell lymphoma, MSI-H = microsatellite instability-high solid tumors; dMMR = mismatch repair deficiency solid tumors; TMB-H = mutational burden-high solid tumors.

for NSCLC[40]. 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)[41]. Ramucirumab and bevacizumab are angiogenesis inhibitors (Figure 2c)[42]. There is also bispecific antibody amivantamab (Figure 2c), which blocks cellular division signaling[43].

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[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[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[46]. For hairy cell leukemia treatment, there is moxetumomab, which is also a conjugated antibody (pseudomonas exotoxin A, PE38) that binds to CD22[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)[48].

For cancers that target the genitourinary system, enfortumab (Figure 2c) and avelumab (initially approved for Merkel carcinoma[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[50], while avelumab acts on the PF-1/PD-L1 immunological checkpoint[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[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.

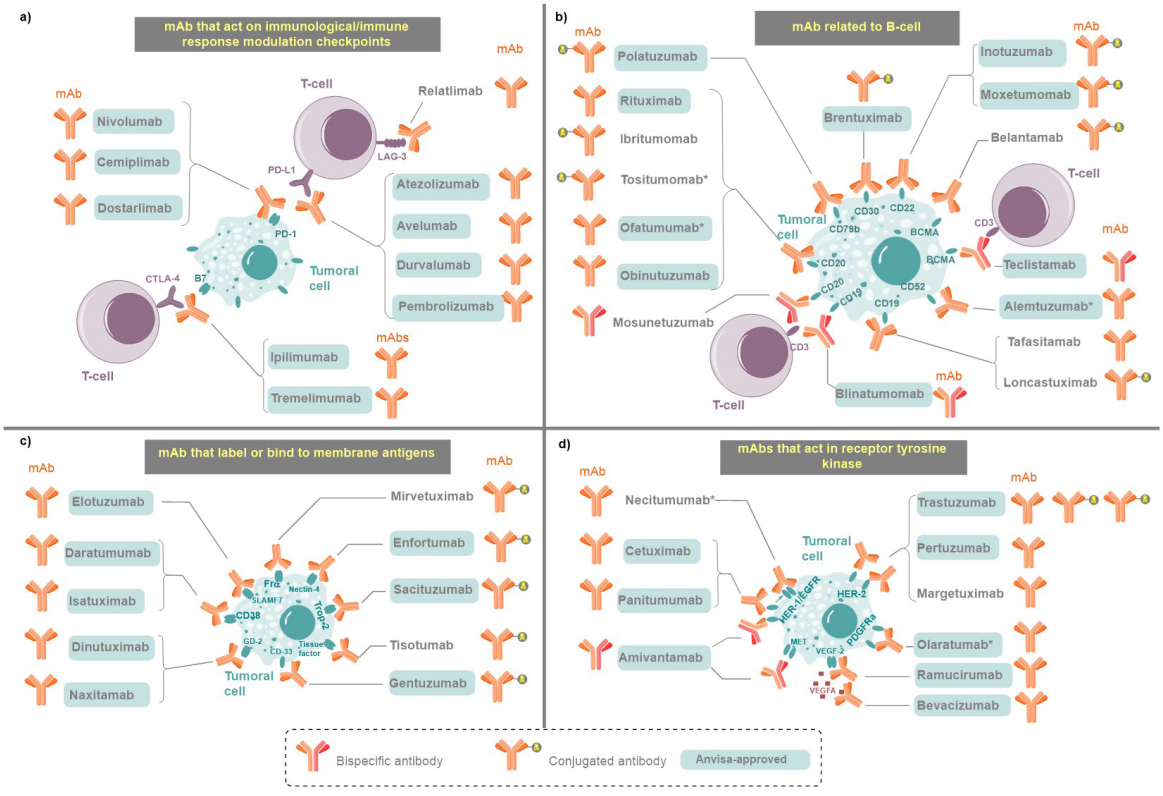

Figure 2. Representation of the mechanisms of action of mAb drugs used in cancer treatment

Captions: mAb = monoclonal antibodies.

*Drugs withdrawn from the market.

CONTRIBUTIONS

Júlia Teixeira de Menezes and Fernando Fumangli 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

1. Zahavi D, Weiner L. Monoclonal antibodies in cancer therapy. Antibodies. 2020;9(3):34. doi: https://doi.org/10.3390/antib9030034
2. Wang W, Wang E, Balthasar J. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008;84(5):548-58. doi: https://doi.org/10.1038/clpt.2008.170
3. Schumacher D, Hackenberger CPR, Leonhardt H, et al. Current status: site-specific antibody drug conjugates. J Clin Immunol. 2016;36(S1):100-7. doi: https://doi.org/10.1007/s10875-016-0265-6
4. Lythgoe MP. No New 'Mabs' in medicine - new nomenclature for monoclonal antibodies. British J Pharmacology. 2022;179(24):5338-9. doi: https://doi.org/10.1111/bph.15953
5. Weiner GJ. Building better monoclonal antibody-based therapeutics. Nat Rev Cancer. 2015:15(6):361-70. doi: https://doi.org/10.1038/nrc3930
6. Chiavenna SM, Jaworski JP, Vendrell A. State of the art in anti-cancer mabs. J Biomed Sci. 2017;24(1):15. doi: https://doi.org/10.1186/s12929-016-0311-y
7. Morin S, Segafredo G, Piccolis M, et al. Expanding access to biotherapeutics in low-income and middle-income countries through public health non-exclusive voluntary intellectual property licensing: considerations, requirements, and opportunities. Lancet Glob Health. 2023;11(1):e145-54. doi: https://doi.org/10.1016/S2214-109X(22)00460-0
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/new-drugs-fda-cders-new-molecular-entities-and-newtherapeutic-biological-products
9. FDA Label: FDALabel: Full-Text Search of Drug Product Labeling. Versão 2.8.1. Maryland: Departamento de Saúde e Serviços Humanos dos Estados Unidos; 2023. [acesso 2023 nov 13]. Disponível em: https://nctr-crs.fda.gov/fdalabel/ui/search
10. ANVISA: Agência Nacional de Vigilância Sanitária. Consulta Anvisa [sem versão]. Brasília, DF: Anvisa; [sem data]. [acesso 2023 nov 13]. Disponível em: https://consultas.anvisa.gov.br/#/medicamentos/
11. Conselho Nacional de Saúde (BR). Resolução nº 510, de 7 de abril de 2016. Dispõe sobre as normas aplicáveis a pesquisas em Ciências Humanas e Sociais cujos procedimentos metodológicos envolvam a utilização de dados diretamente obtidos com os participantes ou de informações identificáveis ou que possam acarretar riscos maiores do que os existentes na vida cotidiana, na forma definida nesta Resolução [Internet]. Diário Oficial da União, Brasília, DF. 2016 maio 24 [acesso 2023 ago 9]; Seção I:44. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/cns/2016/res0510_07_04_2016.html
12. Leonel RM, Reis FMD, Andolfatto D, et al. Assistência farmacêutica a pacientes oncológicos em uso de anticorpos monoclonais em um hospital de referência do Oeste de Santa Catarina. Rev Bras Cancerol. 2022;68(3):e152316. https://doi.org/10.32635/2176-9745.RBC.2022v68n3.2316
13. Mullard A. FDA approves 100th monoclonal antibody product. Nat Rev Drug Discov. 2021;20(7):491-5. doi: https://doi.org/10.1038/d41573-021-00079-7
14. Prasad V. The withdrawal of drugs for commercial reasons: the incomplete story of tositumomab. JAMA Intern Med. 2014;174(12):1887-8. https://doi.org/10.1001/jamainternmed.2014.5756
15. European Medicines Agency. Portrazza: termo de autorização de introdução no mercado na União Europeia. 2021 jul 9. [acesso 2023 nov 9]. Disponível em: https://www.ema.europa.eu/en/documents/public-statement/public-statement-portrazza-expiry-marketing-authorisation-european-union_en.pdf
16. European Medicines Agency. MabCampath (alemtuzumab): Retirada da autorização de introdução no mercado na União Europeia. 2012 ago 14. [acesso 2023 nov 9]. Disponível em: https://www.ema.europa.eu/en/documents/public-statement/public-statementmabcampath-alemtuzumab-withdrawal-marketingauthorisation-european-union_en.pdf
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

18. Bou Zerdan M, Bidikian AH, Alameh I, et al. Olaratumab's Failure in Soft Tissue Sarcoma. Rare Tumors 2021;13:203636132110341. doi: https://doi.org/10.1177/20363613211034115
19. Jin S, Sun Y, Liang X, et al. Emerging new therapeutic antibody derivatives for cancer treatment. Sig Transduct Target Ther. 2022;7(1):39. doi: https://doi.org/10.1038/s41392-021-00868-x
20. Moore KN, Martin LP, O'Malley DM, et al. A review of mirvetuximab soravtansine in the treatment of platinum-resistant ovarian cancer. Future Oncology. 2018;14(2):123-36. doi: https://doi.org/10.2217/fon-2017-0379
21. Singh V, Sheikh A, Abourehab MAS et al. Dostarlimab as a miracle drug: rising hope against cancer treatment. Biosensors. 2022;12(8):617. doi: https://doi.org/10.3390/bios12080617
22. Liao JB, Gwin WR, Urban RR, et al. Pembrolizumab with low-dose carboplatin for recurrent platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer: survival and immune correlates. J Immunother Cancer. 2021;9(9):e003122. doi: https://doi.org/10.3390/bios12080617
23. Oncology Times. FDA Approves Avastin Plus Chemotherapy for Ovarian Cancer. Oncol Times. 2014;36(23):10. doi: https://doi.org/10.1097/01.COT.0000459154.18451.1e
24. Alasmari MM. A Review of margetuximab-based therapies in patients with HER2-Positive metastatic breast cancer. Cancers. 2022;15:(1):38. doi: https://doi.org/10.3390/cancers15010038
25. Bardia A, Hurvitz AS, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021;384(16):1529-41. doi: https://doi.org/10.1056/NEJMoa2028485
26. Buske C, Weigert O, Dreyling M, et al. Current Status and Perspective of Antibody Therapy in Follicular Lymphoma. Hematológica. 2006;91(1):104-12.
27. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;23(8):1055-65. doi: https://doi.org/10.1016/S1470-2045(22)00335-7
28. Deeks ED. Polatuzumab vedotin: first global approval. Drugs. 2019;79(13):1467-75. doi: https://doi.org/10.1007/s40265-019-01175-0
29. Düll J, Topp M, Salles G. The use of tafasitamab in diffuse large b-cell lymphoma. Therapeut Advanc Hematol. 2021;12:204062072110274. doi: https://doi.org/10.1177/20406207211027458
30. Jain N, Stock W, Zeidan A, et al. Loncastuximab tesirine, an anti-cd19 antibody-drug conjugate, in relapsed/refractory b-cell acute lymphoblastic leukemia. Blood Advanc. 2020;4(3);449-57. doi: https://doi.org/10.1182/bloodadvances.2019000767
31. Romano A, Storti P, Marchica V, et al. Mechanisms of action of the new antibodies in use in multiple myeloma. Front Oncol. 2021;11:684561. doi: https://doi.org/10.3389/fonc.2021.684561
32. Moreno L, Perez C, Zabaleta A, et al. The mechanism of action of the anti-CD38 monoclonal antibody isatuximab in multiple myeloma. Clinic Cancer Res. 2019;25(10):3176-87. doi: https://doi.org/10.1158/1078-0432.CCR-18-1597
33. Lassiter G, Bergeron C, Guedry R, et al. Belantamab mafodotin to treat multiple myeloma: a comprehensive review of disease, drug efficacy and side effects. Current Oncolog. 2021;28(1):640-60. doi: https://doi.org/10.3390/curroncol28010063
34. Moreau P, Garfall AL, Van De Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387(6):495-505. doi: https://doi.org/10.1056/NEJMoa2203478
35. Markham A. Tisotumab vedotin: first approval. Drugs 2021;81(18):2141-7. doi: https://doi.org/10.1007/s40265-021-01633-8
36. Song Z, Zou K, Zou L. Immune checkpoint blockade for locally advanced or recurrent/metastatic cervical cancer: an update on clinical data. front Oncol. 2022;12:1045481. doi: https://doi.org/10.3389/fonc.2022.1045481
37. Tawbi HÁ, Schadendorf D, Lipson EJ, et. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24-34. doi: https://doi.org/10.1056/NEJMoa2109970
38. Bhandaru M, Rotte A. Monoclonal Antibodies for the Treatment of Melanoma: Present and Future Strategies. In: Steinitz M, editor. Human monoclonal antibodies: methods in molecular biology. New York: Springer New York; 2019. p 83-108. v.1904 doi: https://doi.org/10.1007/978-1-4939-8958-4_4
39. Tarhini A, Lo E, Minor DR. Releasing the brake on the immune system: ipilimumab in melanoma and other tumors. cancer biotherapy and radiopharmaceuticals. 2010;25(6):601-13. doi: https://doi.org/10.1089/cbr.2010.0865
40. Yang T, Xiong Y, Zeng Y, et al. Current status of immunotherapy for non-small cell lung cancer. Front Pharmacol. 2022;13:989461. doi: https://doi.org/10.3389/fphar.2022.989461
41. Dantoing E, Piton N, Salaün M, et al. Anti-PD1/PD-L1 immunotherapy for non-small cell lung cancer with actionable oncogenic driver mutations. IJMS. 2021;22(12):6288. doi: https://doi.org/10.3390/ijms22126288

42. Cheng WC, Shen YC, Chen CL, et al. Bevacizumab versus Ramucirumab in EGFR-mutated metastatic non-small-cell lung cancer patients: a real-world observational study. Cancers. 2023;15(3):642. doi: https://doi.org/10.3390/cancers15030642

43. Vyse S, Huang PH. Amivantamab for the treatment of EGFR Exon 20 insertion mutant non-small cell lung cancer. Expert Rev Anticancer Therap. 2022;22(1):3-16. doi: https://doi.org/10.1080/14737140.2022.2016397

44. Furman WL. Monoclonal antibody therapies for high risk neuroblastoma. BTT 2021;15:205-19. doi: https://doi.org/10.2147/BTT.S267278

45. Massumoto CM, Pinheiro RF, Pinheiro Júnior ED, et al. Gemtuzumab Ozogamicina: uma opção no tratamento de leucemia mielóide aguda CD33+. Rev Bras Hematol Hemoter. 2004;26(4):235-8. doi: https://doi.org/10.1590/S1516-84842004000400002

46. Contreras CF, Higham CS, Behnert A, et al. Clinical utilization of blinatumomab and inotuzumab immunotherapy in children with relapsed or refractory B-acute lymphoblastic leukemia. Pediatr Blood Cancer. 2021;68(1):e28718. doi: https://doi.org/10.1002/pbc.28718

47. Dhillon S. Moxetumomab pasudotox: first global approval. Drugs. 2018;78(16):1763-7. doi: https://doi.org/10.1007/s40265-018-1000-9

48. Younes A, Yasothan U, Kirkpatrick P. Brentuximab Vedotin. Nat Rev Drug Discov. 2012;11(1):19-20. doi: https://doi.org/10.1038/nrd3629

49. Shirley M. Avelumab: a review in metastatic merkel cell carcinoma. Targ Oncol. 2018;13(3)409-16. doi: https://doi.org/10.1007/s11523-018-0571-4

50. Alt M, Stecca C, Tobin S, et al. Enfortumab Vedotin in urothelial cancer. Therapeut Advanc Urol. 2020;12:175628722098019. doi: https://doi.org/10.1177/1756287220980192

51. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-30. doi: https://doi.org/10.1056/NEJMoa2002788

52. García-Foncillas J, Sunakawa Y, Aderka D, et al. Distinguishing features of cetuximab and panitumumab in colorectal cancer and other solid tumors. Front Oncol. 2019;9:849. doi: https://doi.org/10.3389/fonc.2019.00849

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