



Review

# Therapeutic Targets of Monoclonal Antibodies Used in the Treatment of Cancer: Current and Emerging

Brian Effer <sup>1,\*</sup> , Isabela Perez <sup>1</sup>, Daniel Ulloa <sup>1</sup> , Carolyn Mayer <sup>1</sup> , Francisca Muñoz <sup>1</sup>, Diego Bustos <sup>1</sup>, Claudio Rojas <sup>2,3</sup>, Carlos Manterola <sup>2,3</sup>, Luis Vergara-Gómez <sup>1</sup>, Camila Dappolonnio <sup>1</sup>, Helga Weber <sup>1</sup> and Pamela Leal <sup>1,4,\*</sup>

- <sup>1</sup> Center of Excellence in Translational Medicine (CEMT) and Scientific and Technological Bioresource Nucleus (BIOREN), Universidad de La Frontera, Temuco 4811230, Chile; pereznunezisabela@gmail.com (I.P.); d.ulloa09@ufromail.cl (D.U.); c.mayer01@ufromail.cl (C.M.); f.muñoz16@ufromail.cl (F.M.); d.bustos06@ufromail.cl (D.B.); lovg002@gmail.com (L.V.-G.); c.dappolonnio01@ufromail.cl (C.D.); hlaweber@gmail.com (H.W.)
- <sup>2</sup> Programa de Doctorado en Ciencias Médicas, Universidad de la Frontera, Temuco 4811230, Chile; crojas.vet@gmail.com (C.R.); carlos.manterola@ufrontera.cl (C.M.)
- <sup>3</sup> Centro de Estudios Morfológicos y Quirúrgicos de La, Universidad de La Frontera, Temuco 4811230, Chile
- <sup>4</sup> Department of Agricultural Sciences and Natural Resources, Faculty of Agricultural and Forestry Science, Universidad de La Frontera, Temuco 4810296, Chile
- \* Correspondence: breeiky@hotmail.com (B.E.); pamela.leal@ufrontera.cl (P.L.)

**Abstract:** Cancer is one of the leading global causes of death and disease, and treatment options are constantly evolving. In this sense, the use of monoclonal antibodies (mAbs) in immunotherapy has been considered a fundamental aspect of modern cancer therapy. In order to avoid collateral damage, it is indispensable to identify specific molecular targets or biomarkers of therapy and/or diagnosis (theragnostic) when designing an appropriate immunotherapeutic regimen for any type of cancer. Furthermore, it is important to understand the currently employed mAbs in immunotherapy and their mechanisms of action in combating cancer. To achieve this, a comprehensive understanding of the biology of cancer cell antigens, domains, and functions is necessary, including both those presently utilized and those emerging as potential targets for the design of new mAbs in cancer treatment. This review aims to provide a description of the therapeutic targets utilized in cancer immunotherapy over the past 5 years, as well as emerging targets that hold promise as potential therapeutic options in the application of mAbs for immunotherapy. Additionally, the review explores the mechanisms of action of the currently employed mAbs in immunotherapy.

**Keywords:** cancer; immunotherapy; monoclonal antibody; therapeutic targets



**Citation:** Effer, B.; Perez, I.; Ulloa, D.; Mayer, C.; Muñoz, F.; Bustos, D.; Rojas, C.; Manterola, C.; Vergara-Gómez, L.; Dappolonnio, C.; et al. Therapeutic Targets of Monoclonal Antibodies Used in the Treatment of Cancer: Current and Emerging. *Biomedicines* **2023**, *11*, 2086. <https://doi.org/10.3390/biomedicines11072086>

Academic Editor: Letizia Polito

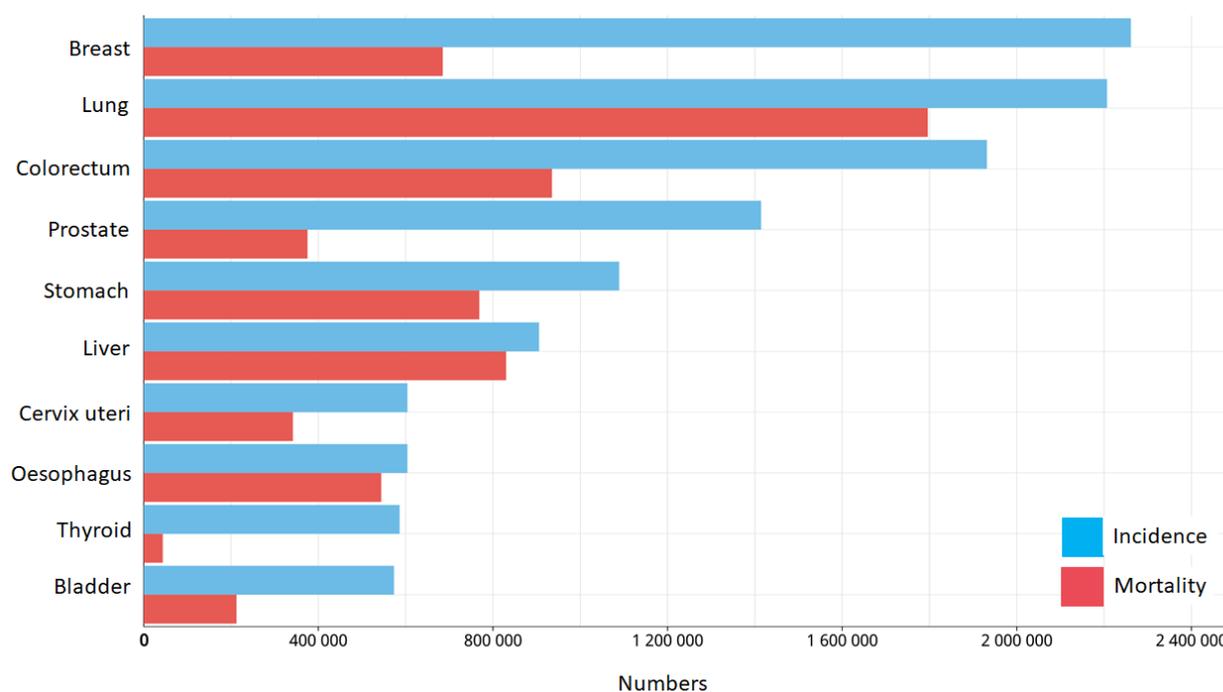
Received: 14 June 2023  
Revised: 14 July 2023  
Accepted: 17 July 2023  
Published: 24 July 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Cancer is one of the leading global causes of deceases. In 2020, about 10 million people died due to this condition [1]; by 2040, 29.5% and 16.6% increases are expected in new cases and deaths, respectively [2]. According to the World Health Organization (WHO), cancer is the result of an interaction between genetic factors and three types of external factors: (1) physical carcinogens such as UV and ionizing radiation, (2) chemical carcinogens such as aflatoxins, arsenic, benzopyrene, bisphenol, and tobacco smoke (which are associated with the modern lifestyle), and (3) biological carcinogens such as viruses (e.g., hepatitis B and C, human papillomavirus), bacteria (*Helicobacter pylori*), and parasites (*Schistosoma haematobium*, *Opisthorchis viverrini*, etc.) [3,4]. Recently, lung, colorectum, liver, stomach, and breast cancers (Figure 1) have been reported with the highest mortality rates, representing an alarming public health problem.



**Figure 1.** Estimated global number of new cancer cases in 2020, for both sexes and all age groups. Reproduced from Global Cancer Observatory (<http://gco.iarc.fr/> (accessed on 1 July 2023)); data source: GLOBOCAN 2020, International Agency for Research on Cancer 2022.

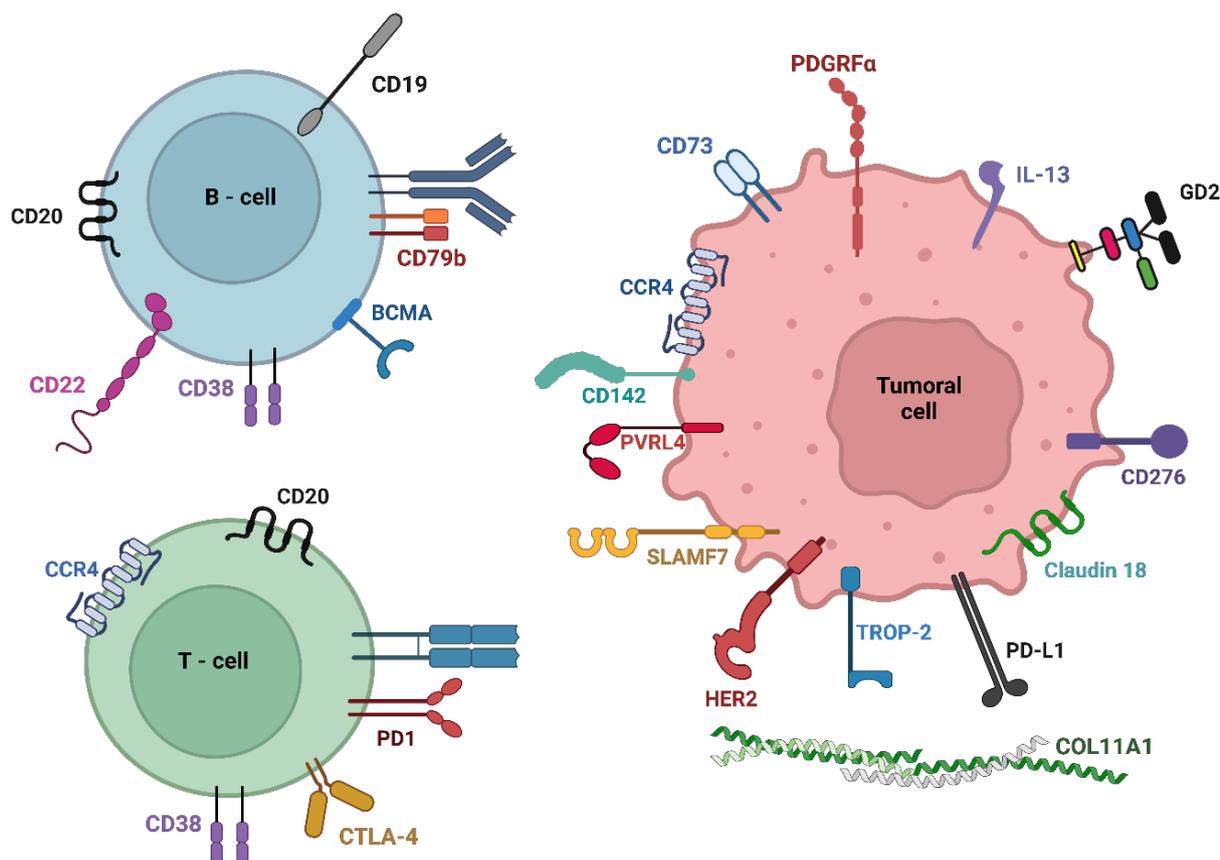
Cancer treatment options are constantly evolving and can be grouped into three categories: physical intervention (surgery), radiation therapy and pharmaceutical treatment, which includes chemotherapy, hormone therapy and immunotherapy [5]. The use of monoclonal antibodies (mAbs) in immunotherapy has been considered as the corner-stone of modern cancer therapy [6]. The mAbs have a high capacity to recognize and bind antigens (previously identified therapeutic targets) by its n-terminal extremes and then, coordinate both its inactivation and destruction by its c-terminal effector portion [7]; Moreover, mAbs can be applied alone or linked with drugs, enzymes, radionuclide or others antibodies [8–10]. In terms of mechanism of action [11,12], several characteristics make them an attractive therapeutic alternative, including specificity, potency, metabolic stability, malleability and versatility. This alternative enables the specific inhibition of cellular receptors and ligands, either extracellular domains of membrane proteins or secreted proteins [10] (cytokines), which play crucial roles in tumor development and angiogenesis [13]. As a result, out of the currently approved, one hundred and twenty four mAbs, forty-seven are designed for the treatment of cancer [14].

However, to design an appropriate immunotherapeutic regimen for any type of cancer, the identification of specific molecular targets or biomarkers of therapy and/or diagnosis (theragnostic) becomes indispensable in order to avoid collateral damage. Currently, there is an increasing number of established molecular targets for the treatment of diverse types of cancer. This review focuses on the therapeutic targets of mAbs utilized in cancer immunotherapy over the last 5 years and any new emerging targets that are being considered. It is necessary to understand the biological roles of these targets and the function of mAbs in antitumoral immunotherapies and immunotherapeutic treatments.

## 2. Current Immunotherapeutic Targets for Cancer Treatment

Therapeutic targets can be defined as individual molecules or sets of essential molecules involved in the development of one or several pathologies. These targets enable the identification and specific treatment of these diseases. Additionally, therapeutic targets should exhibit differential expression compared to the normal physiological condition, either

as soluble ligands or by being expressed on the surface of cells to be accessible to the therapeutic agent [6,15]. This section describes the main therapeutic targets identified in immunotherapy against various types of tumors, which are also represented in Figure 2.



**Figure 2.** Tumoral antigens and therapeutic targets currently utilized in cancer immunotherapy are primarily located in cells of the immune system and tumor cells.

### 2.1. Programmed Cell Death Protein 1 (PD1)/Programmed Cell Death Ligand 1 (PD-L1) Axis

PD1 (or CD279) (UniprotKB—Q15116), is a membrane protein weighing approximately 55 kDa, belonging to the immunoglobulin superfamily. It consists of 288 amino acids (aa) distributed in an extracellular domain (24–170 aa), transmembrane helical domain (171–191 aa), and cytoplasmic domain (192–288) [16]. This protein is commonly expressed on the surface of cells from immune system, particularly in tumor-specific T cells [17]. When it is activated by its ligands (PD-L1 or PD-L2), PD1 performs its regulatory function by inhibiting T cell-mediated immune responses [18]. This means that activated PD1 recruits the phosphatase SHP2 (UniprotKB—Q06124), which dephosphorylates and attenuates key molecules in the T-cell receptor (TCR) and CD28 pathways. This acts as a checkpoint to control the inhibition of overactive T cells, regulating their activation, killer functions, proliferation, cytokine production, and death [19]. Consequently, our organism is able to control the intensity and duration of T-cell responses in order to maintain self-tolerance and prevent autoimmune attacks [19].

However, several types of cancer cells have developed a strategy of overexpressing the PD1 ligand (PD-L1) on their surface. This allows them to mimic, slow down, and evade the immune response. PD-L1 (or CD274, B7-H1) (UniprotKB—Q9NZQ7) is a 33 kDa membrane protein that also belongs to the immunoglobulin subfamily, and it is the main ligand of PD1. It has 290 aa, which are mainly distributed in two extracellular domains (19–127 aa, Ig-like V-type; 133–225 aa, Ig-like C2-type), a transmembrane helical portion (239–259 aa), and a small cytoplasmic domain (260–290) [20]. It is expressed on the surface of regulatory

cells such as activated T and B cells, monocytes, keratinocytes, and dendritic cells [21]. It is also expressed by tumoral cells as a strategy to avoid immune response [19]. In fact, PD-L1 expression is observed in different types of human tumor [22], and its involvement in cancer progression has been established. For instance, in kidney cancer, the presence of PD-L1 has been found to induce epithelial-to-mesenchymal transition (EMT) and promote stem-cell-like phenotypes, which are indicative of renal cancer progression [23]. These findings highlight the role of the PD1/PD-L1 pathway in driving the progression of kidney cancer. However, the clinical efficacy of PD1/PD-L1-blocking antibodies has been demonstrated in patients with advanced melanoma, as well as lung and renal cancer. The discovery of the PD1/PD-L1 axis and its role in the control of T cells by Takuso Honjo represents a significant advancement in the actual fight against cancer. For this contribution, the Japanese scientist received the Nobel Prize in Physiology and Medicine in 2018 [24]. Due to these reasons, both PD1 and PD-L1 have been considered valuable therapeutic targets for the use of mAbs against different types of cancer [25–27]. Tislelizumab is an mAb that was approved in December 2019 in China for patients with relapsed or refractory classical Hodgkin's lymphoma after at least second-line chemotherapy [28]. penpulimab, a humanized and engineered mAb (designed to eliminate Fc-mediated effector functions), was approved in August 2021 in China for the treatment of adult patients with relapsed or refractory classic Hodgkin's lymphoma [29]. However, these two mAbs, along with three others, are currently under review for approval in EEUU and Europe for several types of cancer, such as esophageal squamous cell carcinoma (tislelizumab), metastatic nasopharyngeal carcinoma (penpulimab), non-small-cell lung cancer (sintilimab), nasopharyngeal carcinoma (toripalimab), and squamous cell carcinoma of the anal canal (retifanlimab) [14]. Retifanlimab was recently approved by the Food and Drug Administration (FDA) to be used in Merkel cell carcinoma [30]. Dostarlimab (Jemperli) is also one of the most recently mAbs approved (2021) by the FDA and the European Medicines Agency (EMA) for the treatment of endometrial cancer [14]. Furthermore, five other mAbs are currently under review for approval in several types of cancers.

## 2.2. B-Lymphocyte Antigen CD20 (CD20)

CD20 (UniprotKB—P11836) is a 33 kDa membrane protein that belongs to the membrane-spanning 4 domain family A (MS4A). It is expressed on the surface of B cells, although this expression is lost when B cells differentiate in plasmablasts or start secreting antibodies [31]. However, CD20 is found to be expressed in B-cell lymphomas, leukemias, Hodgkin's disease, and multiple sclerosis, among other conditions [32,33]. Furthermore, it is expressed in approximately 3–5% of CD3<sup>+</sup> T cells in human peripheral blood [31].

It is composed of N-terminal (1–56 aa) and C-terminal (210–297 aa) domains, along with a small cytosolic domain (106–120 aa), four transmembrane domains (57–78, 85–105, 121–141, and 189–209 aa), and two extracellular domains (79–84 and 142–188 aa). These extracellular domains contain epitopes recognized by most mAbs produced against CD20. However, alternative transcripts encoding truncated forms of CD20 have been identified in malignant B cells, allowing them to evade recognition by mAbs [34,35].

The function of CD20 is not yet fully understood, but is believed to play a crucial role in the optimal development of humoral immunity. It depends on a functional B-cell receptor (BCR) signaling pathway; apparently, CD20 works as a calcium channel that activates BCR [36]. Silencing CD20 in malignant B cells has been shown to affect the phosphorylation of several kinases and proteins associated with BCR [36], suggesting that CD20 is involved in BCR signaling [37].

Due to its prominent presence on the surface of B cells and some T cells, it is considered an important therapeutic target in hematological B-cell malignancies, such as leukemias and lymphomas [35,36], as well as autoimmune diseases, such as multiple sclerosis [32,38]. Two recently approved humanized and bispecific IgG1 mAbs targeting CD20 and CD3 are mosunetuzumab (approved in the European Union) and epcoritamab (approved in the USA), utilized for the treatment of follicular lymphoma and diffuse large B-cell lymphoma,

respectively [39,40]. Ublituximab, a chimeric IgG1 mAb against CD20, is currently under regulatory review for approval in the USA, for the treatment of chronic lymphocytic leukemia [14].

### 2.3. Human Epidermal Growth Factor Receptor 2 (Receptor Tyrosine Kinase) (HER2)

The human epidermal growth factor receptor 2 (HER2/ErbB2/Neu) (UniprotKB—P04626), encoded by the *ERBB2* gene, is a glycoprotein with a molecular weight of approximately 185 kDa. It belongs to the ErbB family of transmembrane receptor tyrosine kinases (RTKs), which play an important role in the signaling pathways involved in cell growth, proliferation, migration, differentiation, metabolism, survival, and regulation of intercellular communication during development [41]. It is composed of an extracellular ligand-binding domain (23–652 aa), a hydrophobic transmembrane domain (653–675 aa), and a cytoplasmic tyrosine kinase domain (676–1255 aa). This kind of RTK is activated when a ligand binds to the extracellular domain, leading to dimerization and autophosphorylation of the cytoplasmic tyrosine kinase domain. As a result, this initiates downstream signaling, influencing all processes mentioned above [42]. However, HER2 does not have a known ligand; instead, it is constitutively active and able to heterodimerize with other ErbB proteins, thereby becoming a powerful signal transducer [41,42]. HER2 is normally expressed in the epithelia of various organs, and its aberrant overexpression has been associated with adenocarcinomas, including breast, cervix, lung, ovary, endometrium, gastroesophageal junction, gastric, and bladder cancers [43]. Currently, HER2 serves as an important prognostic and therapeutic target for breast cancer. Approximately 15–30% of human breast cancers are HER2-positive or overexpress HER2 [44,45], which is associated with a poorer outcome compared to non-overexpressing cases [41]. To date, two monoclonal antibodies have been approved to treat HER2-positive breast cancer: margetuximab, approved on 2020 by the FDA, and trastuzumab deruxtecan, approved on 2019 in the United States (US) by the FDA and recently (2021) in Europe by the EMA [14].

### 2.4. B-Lymphocyte Antigen CD19 (CD19)

CD19 (UniprotKB—P15391) is a membrane protein with a molecular weight of approximately 95 kDa. It belongs to the immunoglobulin superfamily and is exclusively expressed on B cells [46]. This protein contains 556 aa distributed in an extracellular domain (20–113 aa, Ig-like C2-type1; 176–277 aa, Ig-like C2-type2), transmembrane domain (292–313), and most importantly, a cytoplasmic domain (314–556 aa). The cytoplasmic domain of CD19 contains conserved tyrosine residues that play an important role in the transduction of CD19-mediated signals [47,48]. It is a critical regulator coreceptor of BCR. Its functions include (a) mobilization of intracellular calcium, which is required for the activation of several transcription factors [49], (b) enhancement of mitogen-activated protein kinase (MAPK) activation, (c) amplification of Src protein tyrosine kinase (PTK) activation, which is involved in the initiation and propagation of BCR signaling, and (d) prolongation of BCR signaling in lipid rafts. For more details of these process, refer to the review by Li et al. [46]. Therefore, CD19 is essential for the primary activation of B cells by T-cell-dependent antigens, as well as for their differentiation into memory B cells [50]. Its abnormal expression, either decreased or not, can result in immune deficiency [46] such as chronic lymphocytic leukemia, follicular lymphoma, and diffuse large B-cell lymphoma, while its increased expression is correlated with systemic sclerosis [51,52]. Tafasitamab (Monjuvi) is an mAb against CD19 approved in 2020 by FDA to treat diffuse large B-cell lymphoma, and it is currently under review by EMA [14].

### 2.5. Disialoganglioside GD2 (GD2)

The GD2 antigen is a sphingolipid coated with five monosaccharides: glucose, galactose, N-acetylgalactosamine, and two N-acetylneuraminic acids [53]. It is synthesized in the Golgi apparatus, and its expression in normal tissues remains restricted to neurons, skin melanocytes, and peripheral pain fibers [54], but it also has been found expressed

in stem cells [55]. However, GD2 is overexpressed in several types of cancer such as neuroblastoma [56], small-cell lung cancer [57], melanoma [58], Ewing sarcoma [59], osteosarcoma [60], soft-tissue sarcoma [61], glioma [62], retinoblastoma [63], and breast [64] and bladder cancer [65]. GD2 can be detected in the plasma, peripheral blood, bone marrow, and tumor tissue [53]. Although the general role of GD2 in normal cells is not well defined [66], it is thought that GD2 possesses potent stemness ability [67] because it enhances proliferation, motility, migration, adhesion, and invasion of tumoral cells [68–70]. As GD2 overexpression is a signal of malignancy, it is considered an exceptionally promising therapeutic target. Naxitamab (Danyelza) is a humanized mAb against GD2. In 2020, it was approved by the FDA for the treatment of high-risk neuroblastoma and refractory osteomedullary disease [14].

#### 2.6. B-Cell Maturation Antigen (BCMA or CD269)

The BCMA (UniprotKB—Q02223) is a membrane protein with a molecular weight of approximately 20.2 kDa, encoded by the *TNFRSF17* gene. It belongs to the tumor necrosis factor receptor superfamily, and it is exclusively expressed on the surface of plasmablasts [71] and plasma cells [72]. This protein contains 184 aa distributed in an extracellular domain (1–54 aa), transmembrane domain (55–77 aa), and cytoplasmic domain (78–184 aa). This protein plays a crucial role in B-cell proliferation, survival, and differentiation into plasma cells [73]. The extracellular domain of BCMA is cleaved by  $\gamma$ -secretase to produce soluble BCMA, which regulates plasma cell in the bone marrow [74]. The BCMA has two ligands, a B-cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL). The interaction between APRIL and BCMA transmits differentiation and survival signals, leading to immunoglobulin isotype switching and viability of plasmablasts and plasma cells in the bone marrow [75,76]. BCMA is particularly highly expressed in pathogenic plasma cells from multiple myeloma, B-cell leukemias, and lymphomas [77,78]. It is an ideal target for treating malignancies of these cells types since BCM is elevated in the serum, plasma, and tissues suffering this disease [74,79]. Belantamab mafodotin is a humanized mAb conjugated with a synthetic antineoplastic agent, monomethyl auristatin F [80]. In 2020, it was approved by the FDA and EMA for the treatment of multiple myeloma [14].

#### 2.7. Trophoblast Cell-Surface Antigen 2 (TROP-2)

TROP-2, best known as tumor-associated calcium signal transducer 2, is a cell surface glycoprotein referred to by different names such as epithelial glycoprotein-1, membrane component surface marker-1 (M1S1), cell surface glycoprotein Trop-2, membrane component chromosome 1 surface marker 1, and gastrointestinal antigen 733-1 (GA733-1) [81–83] (UniprotKB—P09758). It is encoded by the *TACSTD2* gene, a transmembrane glycoprotein with a molecular weight of approximately 46 kDa. It is composed of an extracellular domain (27–274 aa), small transmembrane domain (275–297 aa), and cytoplasmic domain (298–323 aa). Due to its ability to be phosphorylated by protein kinase C [84], it is considered an important component of signal transduction across the cell membrane [85]. While its role in normal cells is not yet fully understood [81], TROP-2 has been found to be overexpressed in several solid epithelial cancers, and it is associated with proliferation, cell migration, and tumor growth [85]. The main pathway governing these processes is the PI3K/AKT pathway [86]. In gallbladder cancer, inhibition of TROP-2 was found to regulate the PI3K/AKT pathway by decreasing the expression and phosphorylation of Akt (known to induce oncogenesis [87]) and increasing the expression of the dual phosphatase PTEN [88], an enzyme that suppresses PI3K signaling and AKT activation [87]. Due to these findings, the extracellular domain of TROP-2 has been utilized as an antigen to produce mAbs for therapeutic purposes. Lin et al. isolated a Fab antibody fragment against TROP-2 utilizing phage display technology and successfully inhibited the growth of breast cancer in both in vitro and in vivo experiments [89]. This same Fab antibody fragment was further conjugated with doxorubicin (a commonly utilized in chemotherapy agent), and it

was able to inhibit the proliferation and growth of pancreatic cancer in both in vitro and in vivo experiments [90]. Additionally, this Fab fragment was converted into IgG through eukaryotic expression vectors and tested in ovarian cancer, where Liu et al. demonstrated its ability to inhibit tumor cell growth, migration, and invasion in both in vitro and in vivo experiments [91]. Recently, in 2020, sacituzumab govitecan was approved by the FDA for the treatment of triple-negative cancer [14].

### 2.8. *Adp-Ribosyl Cyclase/Cyclic Adp-Ribose Hydrolase 1 (CD38)*

CD38 encodes for a membrane glycoprotein, with a molecular weight of 34.33 kDa, composed of a cytoplasmatic domain (1–21 aa), transmembrane helix (22–42 aa), and extracellular domain (43–300 aa). This protein is expressed on plasma cells, natural killer cells, several subpopulations of B and T cells, prostatic epithelial cells, pancreatic islet cells, neurons, retinal ganglion cells and another subset of cells [92–95]. Its main function is the catabolism of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) to cyclic ADP-ribose (cADPR) and cADPR to ADPR [96], as well as the conversion of nicotinamide adenine dinucleotide phosphate (NADP) into nicotinic acid adenine dinucleotide phosphate (NAADP) [97]. Both cADPR and NAADP are considered potent Ca<sup>2+</sup>-releasing messengers implicated in various signaling pathways such as smooth muscle contraction, hormonal secretion, fertilization, immune responses, and other processes [98]. CD38 has been found highly expressed in a subset of hematological tumors, particularly multiple myeloma, compared to low levels on normal cells [99]. Its overexpression leads to a decline in intracellular NAD<sup>+</sup> and NADP levels, which is believed to disrupt the homeostasis of these important nucleotides, affecting normal metabolic processes and tissue integrity, as well as the tumor microenvironment [100]. Recently, it has been demonstrated that cancer-associated fibroblasts expressing CD38 in melanoma promote disease progression through the production of pro-tumoral factors that enhance tumor cell migration, invasion, and blood vessel formation [101]. In 2020, isatuximab, a chimeric mAb developed by Sanofi that binds CD38, was approved by the EMA and FDA for the treatment of relapsed/refractory multiple myeloma [102,103].

### 2.9. *Nectin-4 or Poliovirus Receptor-like 4 (PVRL4)*

Nectin-4 (UniprotKB—Q96NY8), also known as PVRL4, is a type of I transmembrane cell adhesion glycoprotein from with a molecular weight of approximately 66 kDa. It is composed of an extracellular domain (32–349 aa), transmembrane domain (350–370 aa), and cytoplasmatic domain (371–510 aa). It belongs to the immunoglobulin superfamily [104]. This protein is involved in the formation and maintenance of cell-to-cell adhesion junctions, and it participates in both homophilic and heterophilic interactions with cadherins. It regulates processes such as polarization, cellular adhesion, and movement [105,106]. In regular human tissue, Nectin-4 is predominantly expressed in the placenta and embryo [104,107,108]. However, under pathological conditions, it can be expressed in the skin, esophagus, stomach, bladder, breast, salivary gland, trachea, prostate, and lung [106,109]. Nectin-4 has been shown to be overexpressed in several types of cancer, leading to the activation of WNT-β catenin and Rac small protein pathways in the PI3K/AKT pathway [110]. While Nectin 4 mRNA expression is absent in healthy tissues, its presence in triple-negative breast cancer (TNBC) has been associated with a poor prognosis [111]. The serum levels of Nectin-4 in lung cancer patients and the expression in urothelial carcinoma cells are significantly higher compare to healthy patients and cells, respectively [112]. However, the interaction of Nectin-4 with tumor microenvironments and its predictive and prognostic role are still controversial [112,113]. Despite this and due to its overexpression, Nectin-4 was utilized to create enfortumab vedotin, a potent antibody conjugated to an antimetabolic agent, denominated monomethyl auristatin E (MMAE). This conjugate disrupts microtubules and induces apoptosis in multiple preclinical cancer models [109], particularly in urothelial carcinoma cells [112].

### 2.10. *Cd79b (ADC) Diffuse Large B-Cell Lymphoma*

CD79b (UniprotKB—P40259), also known as IgB, is a glycoprotein with a molecular weight of 26 kDa, encoded by the B29 gene [114]. It is part of the heterodimeric signaling component of the BCR [115], and it is exclusively expressed by the B-cell compartment. It is composed of an extracellular domain (29–159 aa, Ig-like V-type), transmembrane helix (160–180 aa), and small cytoplasmic domain (181–229 aa). The cytoplasmic region contains an immunoreceptor tyrosine-based activation motif (ITAM) [116], which is responsible for initiating BCR aggregation [114]. CD79b is responsible for mediating the surface expression and signaling of various BCR complexes at all stages of development, including immature precursor B cells and mature B cells [117,118]. Mutations in this protein have been associated with different types of bone marrow cancer. CD79B mutations in conjunction with MYD88L265P occur in approximately 8% of diffuse large B-cell lymphomas [119]. Moreover, the presence of the CD79b protein is commonly observed in patients with chronic lymphatic leukemia and in some cases of multiple myeloma. It also serves as a reliable pan-B-cell marker for the detection of neoplastic B-cells [120]. CD79b is expressed in non-Hodgkin's lymphomas about 90% of the time [121,122]. The ITAM domain enables the initiation of signaling cascades, leading the translocation of NF- $\kappa$ B members to the nucleus and subsequent transcription of pro-survival target genes. This promotes cell survival and proliferation, sustaining neoplastic proliferation [123]. Polatuzumab vedotin, a humanized mAb covalently conjugated with MMAE via a cleavable linker was developed by Genentech (a subsidiary of Roche) [124]. It was designed to bind CD79b. In 2019 and 2020, it was approved by the EMA and FDA, respectively, for the treatment of diffuse large B-cell lymphoma [14].

### 2.11. *CD22*

CD22 (UniprotKB—P20273) is also known as B-lymphocyte cell adhesion molecule (BL-CAM), sialic acid-binding Ig-like lectin 2 (Siglec-2), and T-cell surface antigen Leu-14. It is a 155 kDa protein that belongs to the SIGLEC family of lectins. It is a single-pass type I membrane protein, with an extracellular domain (20 to 687 aa), single transmembrane domain (688 to 706 aa), and cytoplasmic domain (707 to 847 aa). It is expressed during the early stages of ontogenesis of B cells in the spleen and bone marrow [125]. It is known to be an inhibitory receptor [126,127], and it is present exclusively on B cells, predominantly on mature B cells, where it regulates proliferation and function [128]. By associating with the BCR, CD22 inhibits B-cell response, preventing an overly aggressive B-cell reaction and autoimmunity [126]. One of its functions is to prevent the development of autoimmune diseases, although altered B cells can bypass the normal checkpoints and facilitate the development of autoimmune diseases [129], such as systemic sclerosis [130] and systemic lupus erythematosus [131]. By binding to sialo glycans, it reduces the regular inhibitory effects [126]. It is also known to promote cell proliferation and apoptosis via BCR [128]. It is often found alongside CD19 and CD20 on the surface of hyperactivated B cells in autoimmune diseases. Consequently, Medimmune (a parent company of AstraZeneca) has developed some therapeutic approaches, including naked antibodies [132], antibody–drug conjugates [133], radioimmunoconjugate antibodies [134], bispecific antibodies [135], and trispecific antibodies [136]. Moxetumomab pasudotox is a murine mAb conjugated with a toxic fragment of *Pseudomonas* exotoxin A that specifically targets CD22. It was approved by the FDA in the USA in 2018 and received approval by the EU in 2021 for the treatment of hairy cell leukemia [14,137].

### 2.12. *CC Chemokine Receptor Type 4 (CCR4)*

CCR4 (UniprotKB—P51679) is a chemokine receptor that can recognize CCL17 (thymus- and activation-regulated chemokine) and CCL22 (macrophage-derived chemokine) [138]. This antigen is composed of 360 aa distributed in four extracellular domains (1–39 aa, 99–111 aa, 176–206 aa, and 268–284 aa), seven transmembrane domains (40–67 aa, 78–98 aa, 112–133 aa, 151–175 aa, 207–226 aa, 243–267 aa, and 285–308 aa), and four cytoplasmic

domains (68–77 aa, 134–150 aa, 227–242 aa, and 309–360 aa). CCR4 is primarily expressed by Th2 lymphocytes and regulator T cells (Treg), and it is often overexpressed in mature T-cell cancers such as adult T-cell leukemia (ATL) and cutaneous T-cell lymphomas (CTCLs) [139]. In tumors, blocking of CCR4-dependent Treg recruitment is an important mechanism of tumor-extrinsic immune resistance [140]. Furthermore, accumulation of Treg cells in the tumoral microenvironment (TME) weakens the immune response of patients receiving immunotherapy [141]. The degree of infiltration of CCR4<sup>+</sup> Treg cells in prostate cancer is related to prognosis, with higher levels of expression of CCR4<sup>+</sup> T cells observed in specimens with higher Gleason scores ( $\geq 8$ ) ( $p = 0.041$ ) and associated with a faster progression to castration-resistant prostate cancer [142]. CCR4 has been identified as a tumor-initiating chemokine in cutaneous T-cell lymphoma [143], associated with migration and invasion of lung cancer cells [144], promoting metastasis (together with CCL17) in bladder cancer [145] and facilitating cell migration (together with CCL2) in head and neck squamous cell carcinoma [146]. The full therapeutic potential of CCR4 inhibition and Treg depletion is still to be defined [147]. However, mogamulizumab, a humanized anti-CCR4 mAb developed in Japan, was approved in 2018 by the FDA and EMA for the treatment of cutaneous T-cell lymphoma. This mAb has been used in combination with durvalumab (anti PD-L1) or tremelimumab (anti CTLA-4) for the treatment of solid tumors [138]. It has also been labeled with indium-111 for in vivo diagnostic imaging [148].

### 2.13. PDGFR $\alpha$

PDGFR $\alpha$  (platelet-derived growth factor subunit A) (UniprotKB—P04085) belongs to the type III transmembrane receptor tyrosine kinase (RTK) family, and it is a component of platelet-derived growth factor receptors (PDGFRs) [149]. Its structure is characterized by five extracellular domains named D1–D5, which are similar to immunoglobulins. It is also composed of a transmembrane portion and two intracellular tyrosine kinase domains with an adenosine triphosphate (ATP)-binding region and a phosphotransferase region [150,151]. Upon binding with its ligand, PDGFR $\alpha$  undergoes receptor dimerization, leading to autophosphorylation of the tyrosine kinase domain and subsequent activation of pathways involved in cell-cycle activation, cell proliferation, and apoptosis inhibition, such as PI3K/Akt, Ras/MAPK, JAK/STAT, and RaF/MEK/ERK [150,152,153]. This receptor plays a crucial role in the regulation of biological processes, including embryonic development, gastrulation, and organ development such as the lungs, intestine, skin, testicles, and kidneys [154,155]. It is responsible for the maintenance of mesenchymal stromal cell (MSC) and immune infiltration [156–158]. Moreover, it is involved in cell proliferation, migration, invasion, and tumor progression [155,156,159]. Errors in the activation of PDGFR $\alpha$  associated with malignant tumors by mutation, amplification, and gene fusion have been observed. Mutations commonly occur in gastrointestinal stromal tumor cells (5–10%) [160], as well as in non-small-cell lung cancer (6%) and colorectal cancer (5%). Gene amplification problems are frequently seen in glioblastoma (12%) [161,162]. Increased expression of PDGFR $\alpha$  has been shown to stimulate proliferation, metastasis, and invasive potential in papillary thyroid cancer cells. In addition, this high expression is associated with a lower probability of patient survival, highlighting its potential as a biomarker and pharmacological target in thyroid cancer therapy [163,164].

### 2.14. SLAMF7 (CD319)

SLAM (signaling lymphocytic activation molecule) is a family of receptors expressed exclusively at varying frequencies on immune cells, including CD8 T cells, natural killer cells, and activated B cells [165]. One member of this family is SLAMF7 (SLAM family member 7), which is also known as CD319, CRACC, CS1, and 19A. It is a protein encoded by the SLAMF7 gene (UniprotKB—Q9NQ25). Except for SLAMF2, SLAMF proteins are type I transmembrane glycoproteins [166]. They are composed of an extracellular domain (23–226 aa), helical transmembrane domain (227–247 aa), and cytoplasmic domain (248–335 aa). There are seven isoforms of SLAMF7 produced by alternative splicing which

differ in the extracellular (isoforms 2, 4, and 7), transmembrane (isoform 4, 6, and 7), and intracellular (isoforms 3, 5, and 7) domains. SLAMF7 functions as homotypic receptor, binding SLAM-associated proteins (e.g., EAT-2) through its cytoplasmic immunoreceptor tyrosine-based switch motifs [167]. This interaction leads to the activation of cellular immune responses [168], including natural killer cell activation [169]. However, SLAMF7 can also be activated in the absence of EAT-2, resulting in cellular inhibition [170]. In this context, SLAMF7 has been implicated as a regulator of T-cell inhibitory programs and a contributor to T-cell exhaustion [171]. Overexpression of SLAMF7 in clear-cell renal cell carcinoma (ccRCC) has been associated with poor patient survival due to T-cell exhaustion [171]. More than 95% of multiple myeloma patients express SLAMF7 [172], making it a promising therapeutic target in multiple myeloma. Elotuzumab, a humanized mAb, was approved in the USA in 2015 and EU in 2016 for the treatment of multiple myeloma [14].

#### 2.15. Tissue Factor/CD142

Tissue factor/CD142 (TF/CD142, UniprotKB—P13726), also known as coagulation factor III and thromboplastin, is a protein with a molecular weight of 33–27 kDa, encoded by the F3 gene in humans. There are two reported isoforms, P13726-1 and P13726-2. Isoform 1, also known as fTF, is a 33.07 kDa protein located on the cellular membrane. It is composed of an extracellular domain (33–251 aa), transmembrane domain (252–274 aa), and cytoplasmic domain (275–295 aa). Isoform 2 (UniprotKB—P13726-2), also known as asHTE, is a 27.145 kDa protein secreted from the cell. The amino-acid sequence of isoform 2 varies from the canonical sequence (isoform 1) from positions 199 to 238, and it is missing from positions 239 to 295. Its main function is to initiate normal blood coagulation by forming a complex with circulating factors VII or VIIa [173]. Additionally, it promotes maturation, cell growth, development, differentiation, migration, and cell mobility [174] by stimulating the production of chemokines such as interleukin-8 [175], CCL2 (C–C motif ligand 2) [176], and KC (keratinocyte-derived chemokine) [177]. CD142 has been reported to be expressed on the surface of multiple cancer cells, and it is also associated with the mobility of several tumors, including gastric adenocarcinoma [175], colorectal cancer [174], and ovarian cancer [178]. Although it has low tissue specificity, it has been identified as a marker in gastric adenocarcinoma [175], colorectal cancer [174], and prostate cancer [179]. It is also known to promote angiogenesis, endothelial cell proliferation, and other processes. The expression of CD142 is dependent on cell type and can be induced by interleukin-1 [180], interleukin-33 [181], and TNF $\alpha$  [182]. In 2021, the FDA approved an mAb denominated tisotumab vedotin (Tivdak<sup>TM</sup>). It is a human mAb conjugated with MMAE that binds tissue factors expressed in metastatic cervical cancer [183].

#### 2.16. CTLA-4

CTLA-4 (UniprotKB—P16410) is a membrane protein with a molecular weight of approximately 25 kDa, associated with T cytotoxic lymphocytes [184]. It is considered an immune checkpoint and an important negative regulator of T-cell responses [185]. It belongs to the immunoglobulin superfamily and contains 223 aa distributed in an extracellular domain (36–161 aa), transmembrane helical domain (162–182 aa), and cytoplasmic domain (183–223 aa). The CTLA-4 pathway is involved in regulating the immune response mediated by T cells during the priming phase [185]. CTLA-4 is constitutively expressed on regulatory T cells to exert immune suppression [185,186]. However, in the cell, 90% of CTLA-4 in early stages as inactive T-cells is located in the stimulating signals of CD28. The translocation of CTLA-4 is induced through exocytosis [186,187], thus regulating the level of expression of CD28 [188].

CTLA-4 plays an important role in tumorigenesis and tumor immunity. Therefore, it serves as a prognostic biomarker in different types of cancer [184,189]. Liu et al. observed increased levels of CTLA-4 in 13 tumor tissue types, including endometrial carcinoma cervix, cholangiocarcinoma, invasive breast carcinoma, head and neck carcinoma, esophageal carcinoma, renal papillary cell carcinoma, clear-cell carcinoma of the kidney, adenocar-

cinoma of the lung, hepatocellular carcinoma of the liver, adenocarcinoma of the liver, adenocarcinoma of the colon, squamous cell carcinoma of the lung, and adenocarcinoma of the prostate [184]. The levels of CTLA-4 were correlated with the degree of infiltration of cells such as T and B cells, macrophages, dendritic cells, and neutrophils in different types of cancer [184].

Usually, CTLA-4 therapy is combined with the marker PD-1, resulting in improved survival of patients with liver cancer [185]. However, the response rate to treatment in patients remains low (<50%) [190]. Currently, there are two anti-CTLA-4 human mAbs. The first is ipilimumab, developed by Bristol-Myers Squibb Pharmaceuticals (New York, NY, USA) and approved in the USA and EU, in 2011, for the treatment of metastatic melanoma [191]; it is used in gastro-esophageal cancer [192], colorectal cancer [193], and lung cancer [194]. The second is tremelimumab, developed by Pfizer and approved in the USA, in 2022, for the treatment of liver cancer and others cancers [195].

### 3. Emerging Immunotherapeutic Targets for Cancer Treatment

Thanks to advances in proteomics and the analysis of extracellular vesicles secreted in the blood plasma of patients with different types of cancer, the identification of potential protein biomarkers for immunotherapy treatment has become faster and more efficient. Some emerging proteins that play a crucial role in the progression and malignancy of various types of cancer are described below, which are also being considered for the design of mAbs for immunotherapy treatment.

#### 3.1. COL11A1

Alpha-1 collagen (XI) (UniprotKB—P12107) is a polypeptide chain encoded by the COL11a1 gene. It is composed of 1806 aa, and it is one of the alpha chains that make up alpha collagen XI [196], which is a heterotrimer composed of alpha chains encoded by the COL11a1, COL11a2, and COL2a1 genes [197]. This protein belongs to the cartilage family [198], and it is classified as a minor fibrillar collagen subgroup. It is composed of various domains but does not form triple-helical domains [199]. It has a globular amino-acid domain called TSPN (32–299 aa) [200] and a C-terminal propeptide, known as the COLFI domain (1575–1804 aa), which serves as a binding site for different proteins via calcium ions (UniprotKB, 2021).

COL11a1 is a critical protein involved in the regular formation of collagen fibrils and the regulation of type II collagen fibrillogenesis in different mammalian models [201]. It is predominantly expressed in the extracellular matrix [198], and it can be found in different tissues, including the articular cartilage, testicles, trachea, tendons, trabecular bone, skeletal muscle, placenta, and lung [201]. However, its expression in these tissues is relatively low. Interestingly, overexpression of COL11a1 is associated with different types of aggressive cancers, resistance to chemotherapy [198], and low prognosis [197]. This is particularly evident in mesenchymal tumors derived from scleroderma and keloids, as well as in gliomas/glioblastomas in humans, which exhibit high levels of COL11a1 expression [202].

Among the types of related cancers, lung cancer [203] is noteworthy, as COL11a1 has been associated with metastasis to lymph nodes and a poor prognosis. It promotes metastasis and resistance to cisplatin [204]. Similarly, overexpression of COL11a1 has been related to a poor prognosis in ovarian cancer [205]. This is related to increased level of metastasis and resistance to chemotherapy, primarily observed in stromal cells and, in particular, fibroblasts associated with cancers [206].

Furthermore, COL11a1, along with other proteins present in the extracellular matrix, is overexpressed in breast carcinoma. These proteins are released into the blood, enabling their detection in plasma using the ELISA technique [204,206]. Upon review, COL11a1 can be highlighted as a potential biomarker for different types of cancers. Its overexpression is associated with more aggressive cancers, poor prognosis and resistance to chemotherapy. However, there currently no specific alternatives designed to inhibit its function.

### 3.2. Claudin 18

Claudin 18 (UniprotKB—P56856), also called CLDN18, is a membrane protein that belongs to the claudin family. It is composed of 261 aa distributed across two extracellular domains (28–80 aa and 144–174 aa), four transmembrane domains (7–27 aa, 81–101 aa, 123–143 aa, and 175–195 aa), and three intracellular domains (1–6 aa and 102–122 aa). Its main function is associated with the maintenance of tight junctions, which regulate the exchange of molecules between cells [207]. Claudins are predominantly found in gastric [208], pancreatic [209], and pulmonary [210] tissues. Claudin 18 has two isoforms: CLDN18.1, mainly expressed in the lung; CLDN18.2, a specific isoform overexpressed in the stomach, which has emerged as an ideal biomarker [207] because it is widely expressed only in cancer cells, particularly gastric and gallbladder cancer [15]. CLDN18.2 is retained in the presence of a malignant transformation, making it an ideal candidate for monoclonal antibody binding [211]. Changes in claudins at tight junctions are associated with damage to tight adhesions and polarity in the epithelium [212]. These structural abnormalities can lead to increased cell proliferation, epithelial–mesenchymal transition, invasion, and metastasis [213]. Furthermore, the expression of CLDN18 is correlated with a common malignant Epstein–Barr virus-associated tumor known as EBV infection, specifically in gastric cancer (EBVaGC) [214]. This correlation is supported by the fact that the majority of EBVaGC cases exhibit high levels of CLDN18.2 expression. The CLDN18.2 expression in tumor cells is likely associated with key features of EBV12-mediated carcinogenesis [215]. On the contrary, low expression of CLDN18.2 is associated with changes in mucin expression, which is used to classify GC into different mucin phenotypes [216]. CLDN18.2 is not expressed in any healthy tissue, except for the gastric mucosa [216]. Recently, zolbetuximab, a chimeric IgG1 mAb, which binds to CLDN18.2 on the surface of tumor cells, was developed and investigated in clinical trials [217,218]. This mAb triggers antibody-dependent cellular cytotoxicity (ADCC) and induces apoptosis and inhibition of cell proliferation [207]. As a first-line treatment, it showed improved median survival in patients with CG expressing claudin 18.2 compared to chemotherapy alone [219,220]. For this reason, CLDN18.2 is being considered as a potential new target in several types of tumors, given the remarkable success of zolbetuximab against GC.

### 3.3. CD73

CD73, also known as ecto-5'-nucleotidase, is a protein composed of 574 aa and encoded by the NT5E gene (UniprotKB—P21589). It has a molecular weight of approximately 63.4 kDa and is found in the cell membrane with hydrolase activity. It is anchored to glycosylphosphatidylinositol (GPI). It is expressed at different levels in tissues, as well as cells such as endothelial cells, epithelial cells, and T and B lymphocytes. In these cases, it acts as an important factor in the differentiation of these two lines [221,222]. A soluble form of CD73 has been reported, which is responsible for transforming extracellular ATP into immunosuppressive adenosine. This process is correlated to CD39 and limits immune activity, leading to a rare disease denominated “arterial calcifications due to CD7 deficiency” [222].

Several studies have reported that CD73 is upregulated in various types of cancer, and that a higher level of CD73 is commonly associated with worse clinical outcomes [223]. When CD73 is overexpressed in cancer cells, they begin to generate high levels of adenosine, creating a microenvironment in the tumor area [224]. This adenosine-rich microenvironment promotes the growth and proliferation of cancer cells, angiogenesis, and immune suppression in the area [224]. Consequently, CD73 acts as an immunoinhibitory protein that promotes tumor metastasis [224,225]. Due to this role, CD73 is considered an important target for inhibiting tumor growth in many therapies.

CD73 can affect different tumorigenic characteristics, such as cell proliferation, by regulating the cell cycle. It also plays a role in apoptosis and other signaling pathways, including EGFR, beta-catenin/cyclin D1, VEGF, and AKT/ERK [225], via the Rap1/P110 $\beta$  pathway [226]. Additionally, it is also responsible for processes such as adhesion, migration,

stemness, angiogenesis, and metastasis [225]. It exhibits enzymatic activity related to CD39, as it utilizes AMP as a raw material for metabolic processes, resulting in the production of adenosine, which acts on extracellular receptors, regulates the activity of adenylyl cyclase (AC), and can be integrated into the cell through nucleoside transporters [225].

Adenosine functions as an immunomodulatory factor generated by the degradation of ATP by NTPDase1 [224]. While ATP mediates inflammatory responses, adenosine acts as an anti-inflammatory mediator, regulating the decline of immune cell function through its four receptors (A1, A2A, A2B, and A3) [222,224].

Due to its critical role in antitumor immunity, CD73 has been identified as a promising target for immunotherapies. Recent research has established effective models using strategies such as anti-CD73 mAb or inhibitors such as APCP, LY3475070, AB680, and CB-708. These approaches have demonstrated the antitumor effects of CD73 inhibition in preclinical trials tested in mice [227,228]. CD73 has also been found to contribute to chemoresistance against doxorubicin carboplatin, gemcitabine, and paclitaxel [229].

### 3.4. B7-H3 (CD276)

B7-H3 (UniprotKB—Q5ZPR3) antigen, also known as B7 homolog 3, is encoded by the CD276 gene, with a molecular weight of 45–66 kDa [230]. It is a type I transmembrane protein that belongs to the B7 ligand family, sharing 30% aa identity with PD-L1. Similar to PD-L1, it is also considered an immune-checkpoint protein [231].

B7-H3 is composed of an extracellular region (29 to 466 aa), short transmembrane domain (467 to 487 aa), and final cytoplasmic domain (488 to 534). It has two isoforms: 2IgB7-H3 (In soluble form) and 4IgB7-H3, which are caused by exon duplication [232].

Its primary biological function is the interaction with the CD28 receptor on T cells in order to co-stimulate deregulation, differentiation, and activation of T cells [232]. Normally, B7-H3 is expressed at low levels in fibroblasts, progenitor cells, and immune cells [233] to regulate the immune system and maintain self-tolerance.

Conversely, B7-H3 has been found to be overexpressed in several types of cancer, including ovarian [234], cervical [235], colorectal [236], breast, lung, brain [237], and neuroblastoma [238], associated with promoting tumor growth, metastasis, drug resistance, and poor survival rates [239–241].

The Memorial Sloan Kettering Cancer Center (MSKCC) has developed a murine monoclonal antibody that binds B7-H3 in neuroblastoma cells. Although it is still under review by the FDA and EMA, the FDA has granted it breakthrough therapy designation due to the lack of approved drugs for the treatment for neuroblastoma or targeting this emerging antigen [242].

### 3.5. Interleukin-13 (IL13)

IL-13 (UniprotKb—P35225) is a cytokine belonging to the group of lymphokines. It has a length of 146 aa and a molecular weight of 15.8 kDa. It is a structural cytokine highly related to IL-4, and both participate in immune regulation; they have also been found in pregnancy, fetal development, breast development in infancy, and important higher brain functions such as learning and memory [243].

Both interleukins regulate various cellular functions and activate the transcriptional machinery through cell surface receptors [244]. They are essential for the induction and persistence of the type 2 immune response, and they are associated with multiple atopic diseases [245]. Overexpression of IL-13 and its receptor IL-13R is correlated with the pathogenesis and progression of various malignancies [246]. These interleukins are primarily produced by immune cells, such as CD4 T cells, TH2 cells, basophils, eosinophils, and NKT cells [244].

IL-13 has three different types of receptors and shares two receptor chains with IL-4, allowing them to regulate both common and diverse biological functions [247]. The IL-13 receptors include the primary IL-13R (IL-13R $\alpha$ 1/IL-13R $\alpha$ 2) and the secondary receptor (IL-4R $\alpha$ /IL-13R $\alpha$ 1), which are expressed in nonhematopoietic cells [247]. The type III receptor

(IL-4R $\alpha$ /IL-13R $\alpha$ 1/  $\gamma$ c) is exclusively expressed on the surface of hemocytes, providing a wide range of complex signaling pathways regulated by IL-13 and IL-4 [247].

In the case of the alpha 2 receptor chain (IL-13R $\alpha$ 2), it interacts not only with interleukin-13 but also with other proteins, such as chitinase-3-like protein 1. However, it has high affinity for IL-13 [248].

IL-13R receptors have been found to be produced in various types of cancer, and their appearance is a result of altered cytokine signaling pathways, induced by the inflammation produced by cancer cells [249]. Furthermore, it has been observed that IL-13R receptors are overexpressed in several cell lines of solid human cancer, including pancreatic cancer and ovarian cancer [250].

IL-13 R $\alpha$ 2, one of the most commonly observed IL-13 receptors in cancer-related cell lines, has been directly related to metastasis in GC. Its overexpression is associated with increased invasion of tumor cells into other tissues [251,252], and it is considered a poor prognosis factor [253]. Another IL-13 receptor that has been observed is IL-13R $\alpha$ 1, which has been found in patients with colorectal and gallbladder cancer lesions [248].

A recent therapy targeting the overexpression of IL13R is the development of IL13 immunotoxins combined with highly cytotoxic truncated proteins. The aim is to reduce the amount of IL13R present in cancers [248], despite this form of therapy being highly cytotoxic to surrounding cells [248]. The most promising approach is the use of specific monoclonal antibodies against the IL-13R receptor chain to reduce its presence in cancerous tissues, thereby reducing metastasis and cell proliferation [248,250].

#### 4. Mechanisms of Action of the mAbs Currently Used in the Treatment of Cancer

The functional effect of an mAb in cancer treatment is dependent on the cancer antigen profile and the specific mechanisms of action of mAb. These mechanisms can include blocking the ligand or receptor, internalization of the mAb, activation of Fc $\gamma$  receptors (FCGR) on innate immune cells, activation of complement, or blocking receptor-mediated oncogenic signaling. This section provides a brief description of some of these processes, as observed in antibodies currently approved for the treatment of cancer.

##### 4.1. Blocking Ligand Binding

These mAbs bind to ligands or receptors on the cellular surface, preventing the ligand from binding to the receptor [254]. However, the mechanism can vary depending on whether the antibody is conjugated or not.

##### 4.1.1. Nonconjugated mAbs

Antibodies that are not conjugated can exert their function through several mechanisms:

- Steric hindrance: the antibody binds to the antigen receptor or ligand, occupying the region of interaction. By physically blocking the binding, it prevents the transmission of signals or the initiation of unwanted biological responses [255].
- Conformational changes: the antibody binds the antigen and induces conformational changes in the target cell. This alteration in structure prevents efficient interaction with ligand [255].
- Internalization of the complex: in some cases, once the antibody has bound to the antigen, the antibody–antigen complex undergoes internalization. The cell captures the complex through endocytosis, removing the receptor and ligand from contact with each other. This blocks the signaling or biological activity mediated by them [256].

##### 4.1.2. Conjugated mAbs

Conjugated mAbs are a class of therapies that combine the selective benefits of mAbs with the ability to transport and release specific therapeutic agents. These therapeutic agents can include cytotoxic molecules, radioisotopes, drugs, cytotoxic payloads, or even other therapeutic proteins [256,257]. The working mechanism of mAbs conjugated involves the following steps: selective mating, internalization, and release of the therapeutic agent.

Once the conjugated mAb has bound to the specific antigen or receptor on the surface of the target cell, it can be internalized by the cell through endocytosis. Once inside the cell, the antibody targets specific intracellular compartments, such as endosomes or lysosomes [258,259]. Within these compartments, the therapeutic agent bound to mAb is released. It can occur through various mechanisms, such as enzymatic degradation, pH changes, or the action of proteases. The release of the therapeutic agent enables its specific activity within the target cell [257,259].

#### Action of the Therapeutic Agent

Once released within the cell, the therapeutic agent can exert its specific effect. For instance, if the therapeutic agent is a cytotoxic molecule, it can induce programmed cell death (apoptosis) or interfere with vital cellular processes required for cell survival. On the other hand, if the therapeutic agent is a drug, it can obstruct specific signaling pathways or disrupt metabolic processes necessary for cell proliferation or survival [258].

#### 4.2. Blocking Signaling Pathway

Furthermore, mAbs can induce the death of tumor cells by blocking the signaling pathways associated with growth factor receptors. This can be achieved when the Fab region of the mAb recognizes the receptors for the growth factors, resulting in the inactivation of signaling pathways or blocking the binding of the ligand [260]. The mAb impedes tumor cell survival cascades, interfering with cell proliferation, adhesion, and angiogenesis, eluding programmed cell death, and evading immune checkpoints [261,262]. Tumor signaling can be perturbed when targeted antibodies disrupt growth signaling pathways by neutralizing cytokines that are critical to cellular growth and proliferation [263].

While the mechanisms of action (MOAs) for these types of mAbs are similar, the subsequent effects vary due to a range of intrinsic properties. These properties include the mAb-binding epitope, affinity, and serum half-life [264]. The mAb can alter dimerization properties, resulting in different signaling properties depending on whether it is targeting a homodimer or a heterodimer receptor. Understanding this complexity is crucial as it has a significant impact on the development and clinical testing of novel therapeutics, particularly those involving mAb combinations [265].

The majority of FDA-approved mAbs target two members of the ERBB family, HER2 and EGFR. Both EGFR and HER2 are cell surface membrane-spanning Type I receptors, highly expressed on different solid cancers and capable of triggering a wide range of oncogenic signaling through homo- and heterodimerization [259,261,266]. Although HER2-targeted mAbs were initially described as inhibitors of HER2-mediated signaling, multiple studies have demonstrated that these mAbs also inhibit the downstream PI3K/Akt signaling pathway, resulting in p27 upregulation and inhibition of cellular proliferation [259,267]. Subsequent studies have revealed that HER2 mAbs primarily exert immunologic MOAs by engaging Fc receptors to activate innate immune effector functions and complement activity [259,268].

Trastuzumab and pertuzumab are examples of HER2 mAbs. Trastuzumab recognizes domain 4 of HER2, while pertuzumab binds to domain 2. Pertuzumab specifically prevents both hetero- and homodimerization of HER2 with EGFR. This blocking of receptor tyrosine kinase dimerization results in the shutdown of signaling, leading to the inhibition of cell proliferation, which is a consequence of activated signaling [264].

EGFR is a transmembrane glycoprotein. It is composed of an extracellular ligand-binding domain and a cytoplasmic domain housing a tyrosine kinase. Cetuximab is the most studied anti-EGFR agent, which exerts its effects by blocking ligand binding and receptor dimerization, leading to cell-cycle arrest and apoptosis in tumor cells [263]. On the other hand, panitumumab acts as an antagonist and induces the internalization of EGFR. By preventing intracellular processes triggered by EGFR activation (e.g., dimerization, autophosphorylation, and signal transduction), panitumumab promotes an increase in the apoptotic rate and reduces the proliferation and angiogenesis of tumor cells [260,269].

The mAb targets inhibitory immunologic checkpoint signals, thereby enhancing the antitumoral cellular immune response [265]. Therapeutic mAbs that target coinhibitory receptor pathways (e.g., CTLA-4 or PD-1/PD-L1) have been shown to limit T-cell exhaustion, enhance CD8<sup>+</sup> T cell antitumor activity, and increase the ratio of effector T cells (Teff) to regulatory T cells (Treg) within tumors [270].

#### 4.3. Depletion of Target by Fc Interaction

As we know, mAbs can perform their function in multiple ways, particularly in the treatment of cancer. One of these mechanisms involves the interaction between the Fc domain of immunoglobulins and Fc receptors (FcRs) present on effector cells [271], such as natural killer (NK) cells, cytotoxic T cells, dendritic cells, monocytes, neutrophils, and macrophages. Through this interaction, mAbs can mediate antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP), and complement-dependent cytotoxicity (CDC) [258,272].

ADCC occurs mainly when the antibody binds to FcRs on NK cells. It initiates multiple signals that lead to release of lytic compounds from the effector cell, resulting in lysis of the target cell [271]. ADP take place when antibodies opsonize a cell, facilitating its recognition and internalization by phagocytic cells such as macrophages, neutrophils, dendritic cells, and monocytes. Within the phagolysosomes of these cells, the opsonized pathogens or malignant cells are internalized and degraded [271]. CDC begins when the immunoglobulin binds to the antigen on the target cell.

Subsequently, the Fc region of the antibody recruits protein such as C1q, C1r, C1s, and serine proteases, initiating a proteolytic cascade that generates cell death [273,274].

For this reason, immunoglobulins IgG are the most commonly used for treatment of cancer. There are four subtypes of IgG: IgG<sub>1</sub>, which is the most abundant in the plasma and can induce strong ADCC, ADP, and CDC [275]; IgG<sub>2</sub>, which self-aggregates, becoming less useful when linked to drugs [276]; IgG<sub>3</sub>, which is not widely used due to its shorter half-life (around 7 days) compared to the other subtypes with a half-life of 21 days [277]; IgG<sub>4</sub>, which is used in some cancer treatments due to its unique dynamism [278].

In Table 1, the antibodies used in the treatment of cancer in the last 5 years are listed and described.

**Table 1.** Monoclonal antibodies (mAbs) approved for the use in the actual immunotherapy against cancer in both the United States (US) and Europe.

mAbs	Antigen that Recognizes	Format	Cancer for It Was Approved	Mechanism of Action	Reference
Dostarlimab	PD1	IgG4-humanized	Endometrial Cancer	Produced from a mouse hybridoma that acts as a PD-1 blocker via steric impediment with PD-L1 and PD-L2, thereby normalizing the immune response.	[279]
Cemiplimab	PD1	IgG4-humanized	Cutaneous squamous cell carcinoma	This mAb binds to PD1 on T-cells, blocking the interaction with PDL-1 and PDL-2 ligands and activating the immune response.	[280]
Durvalumab	PD-L1	IgG1-human	Bladder cancer	This is a human mAb with high affinity by PD-L1 and CD80.	[281]
Avelumab	PD-L1	IgG1-human	Merkel cell carcinoma	Regulates cytotoxicity mediated by antibody-dependent cells, due to the fact that it presents a native Fc region.	[282,283]
Atezolizumab	PD-L1	IgG1-humanized	Bladder cancer	Inhibits the interaction between PD-1 and B7.1, restoring the antitumor function of T cells.	[284]
Retifanlimab	PD-L1	IgG4-humanized	Merkel cell carcinoma	Blocks PD-1 interaction with its PD-L1 and PD-L2 ligands.	[30]

Table 1. Cont.

mAbs	Antigen that Recognizes	Format	Cancer for It Was Approved	Mechanism of Action	Reference
Mosunetuzumab	CD20-CD3	IgG1-humanized bispecific	Follicular lymphoma	Simultaneously binds to CD20 on malignant B cells and CD3 on T cells, causing T-cell activation and B-cell elimination.	[39,285]
Epcoritamab	CD20-CD3	IgG1-humanized bispecific	Diffuse large B-cell lymphoma	Induces T cells to kill CD20 <sup>+</sup> tumor cells through a unique mechanism of action (MOA).	[40,286]
Margetuximab	HER2	IgG1-chimeric	HER2 <sup>+</sup> breast cancer	Designed against HER2 to decrease binding to the inhibitory receptor Fcγ IIB (CD32B) and to increase binding to the receptor Fcγ activation IIA (CD16A).	[287]
Fam-Trastuzumab Deruxtecan	HER2	IgG1-humanized antibody–drug conjugate	HER2 <sup>+</sup> breast cancer	Designed against HER2 and conjugated to a cytotoxic topoisomerase 1 inhibitor	[80,288]
Loncastuximab Tesirine	CD19	IgG1-humanized antibody–drug conjugate	Diffuse large B-cell lymphoma	Designed to target CD19 and conjugated to a pyrrolobenzodiazepine DNA-alkylating warhead. It produces DNA interstrand crosslinks with high efficiency, leading to triggering of cell death.	[289,290]
Tafasitamab	CD19	IgG1-humanized	Diffuse large B-cell lymphoma	Produces antibody-dependent cellular cytotoxicity and antibody-dependent cell-mediated phagocytosis.	[291,292]
Naxitamab	GD2	IgG1-humanized	Neuroblastoma	Induces complement-dependent and cell-mediated antibody-dependent cytotoxicity	[293]
Teclistamab	BCMA-CD3	IgG4-humanized bispecific	Multiple myeloma	Redirects CD3-positive cells to BCMA-expressing tumor cells, inducing cytotoxicity and apoptosis.	[294]
Belantamab mafodotin	BCMA	IgG1-humanized antibody–drug conjugate	Multiple myeloma	Composed of an antibody that targets B-cell maturation antigen (BCMA), conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF). The other part of the antibody binds to BCMA on the surface of the tumor cell, delivering the cytotoxic microtubule inhibitor MMAF to the therapeutic target.	[295]
Sacituzumab govitecan	TROP-2	IgG1-humanized antibody–drug conjugate	Triple-negative breast cancer	This mAb acts against TROP-2 conjugate with the active metabolite of irinotecan and topoisomerase 1 inhibitor.	[296,297]
Isatuximab	CD38	IgG1-chimeric	Multiple myeloma	By binding to CD38, this mAb causes apoptosis via multiple mechanisms such as antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity, and effects that depend on the Fc region.	[298–300]
Enfortumab vedotin	Nectin-4	IgG1-human antibody–drug conjugate	Urothelial cancer	Works by releasing monomethyl auristatin E (MMAE) into cells that express nectin-4, causing apoptosis.	[301]
Polatuzumab vedotin	CD79b	IgG1-humanized antibody–drug conjugate	Diffuse large B-cell lymphoma	Works by binding to CD79b upon entering the cell, releasing MMAE, inhibiting cell division, and inducing apoptosis.	[124]
Moxetumomab pasudotox	CD22	IgG1-murine dsFv	Hairy cell leukemia	This mAb is conjugated with a toxic fragment of A exotoxin from <i>Pseudomonas aeruginosa</i> , which is internalized, resulting in apoptotic cell death.	[137,302]

Table 1. Cont.

mAbs	Antigen that Recognizes	Format	Cancer for It Was Approved	Mechanism of Action	Reference
Inotuzumab ozogamicin	CD22	IgG4-humanized antibody–drug conjugate	Hematological malignancy	By binding to CD22, the cytotoxic derivative of calicheamicin enters the cell, causing apoptosis.	[303]
Mogamulizumab	CCR4	IgG1-humanized	Cutaneous T-cell lymphoma	Has a defucosylated Fc region that enhances its antibody-dependent cellular cytotoxicity.	[304,305]
Olaratumab	PDGFR $\alpha$	IgG1-human	Soft-tissue sarcoma	Blocks PDGF ligand binding and inhibits PDGFR $\alpha$ .	[306]
Elotuzumab	SLAMF7	IgG1-humanized	Multiple myeloma	Induces antibody-dependent cellular cytotoxicity and the activation of natural killer cells.	[307]
Tisotumab vedotin	CD142	IgG1-human antibody–drug conjugate	Cervical cancer	This is a human mAb conjugated with an antimetabolic monomethyl auristatin E, which inhibits cell division by blocking polymerization of tubulin.	[183]
Tremelimumab	CTLA-4	IgG2A-human	Liver cancer	Blocks the union of B7-1 and B7-2 to CTLA4.	[308,309]

## 5. Perspectives

It is evident that the emergence of immunotherapy has significantly improved the prognosis and life expectancy of patients with various diseases, particularly cancers. Immunotherapeutic strategies encompass cancer vaccines, oncolytic viruses, adoptive transfer of ex vivo activated T and natural killer cells, and administration of recombinant proteins and primarily mAbs that either co-stimulate cells or block checkpoint pathways [310]. Despite the benefits of mAbs in cancer treatment, accessibility remains an issue in underdeveloped countries and even in developed ones due to the high cost.

For instance, the humanized mAb dostarlimab (Jemperli), which targets the PD-1 receptor, shows promise in treating colon cancer, eradicating all tumor cells within 6 months of treatment in a small yet promising clinical trial involving colorectal cancer patients. The treatment involves one dose every 3 weeks for 6 months [311]. However, each dose costs just over 11,000 USD, making the total treatment cost around 88,000 USD. Consequently, strategies that enable more affordable production of therapeutic antibodies are crucial. The widespread implementation of directed evolution techniques, such as phage display, can help reduce production costs and facilitate the production of fully human antibodies. However, to effectively apply this technology, it is essential to identify and validate the different overexpressed antigens as cancer biomarkers, determining their biological functions, topology, and the extracellular regions or the most exposed areas susceptible to antibody recognition, as proposed in this study. Subsequently, a panel of these extracellular regions or areas that are prone to antibody recognition can be recombinantly produced. These antigens can be used for the selection and isolation of full human variable domains of mAb from recombinant naïve [312], synthetic [313], or immune [314] libraries, which contain the repertoire of human V genes. These libraries can be expanded utilizing display systems, such as yeast [315], ribosome [316], cDNA [317], and phage display [318]. Finally, the recovered sequence, that belongs to the most optimal monoclonal antibody can be cloned into the commercial plasmid that contains the desired Fc fragment. This cloned antibody can then undergo subsequent recombinant production, characterization, and validation.

In conclusion, this study provided a comprehensive description of significant cancer biomarkers and mechanisms of action of antibodies currently utilized in therapy. It offered an overview aimed at guiding future research toward potential approaches for the development of more accessible antibodies applied in immunotherapy, as well as various biotechnological applications.

**Author Contributions:** Conceptualization, B.E.; investigation, B.E.; writing—original draft preparation, B.E., I.P., D.U., C.M. (Carolyn Mayer), F.M., D.B., C.R., C.M. (Carlos Manterola), L.V.-G. and C.D.; project administration, B.E.; writing—review and editing, B.E. and H.W.; funding acquisition, B.E. and P.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Agencia Nacional de Investigación y Desarrollo (ANID) from Chile, Grands, the Fondecyt de Posdoctorado Folio 3210142, the Fondecyt de Iniciación Folio 11180987, and the Fondecyt Regular Folio 1201734.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data Sharing not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Ferlay, J.; Ervik, M.; Lam, F.; Colombet, M.; Mery, L.; Piñeros, M.; Znaor, A.; Soerjomataram, I.; Bray, F. Global Cancer Observatory: Cancer Today; International Agency for Research on Cancer: Lyon, Franc. Available online: <https://gco.iarc.fr/today> (accessed on 20 March 2021).
2. Cancer Statistics. Available online: <https://www.cancer.gov/about-cancer/understanding/statistics> (accessed on 20 March 2021).
3. WHO. Cáncer. Available online: <https://www.who.int/es/news-room/fact-sheets/detail/cancer> (accessed on 20 March 2021).
4. Botelho, M.C.; Richter, J. Editorial: Parasites and Cancer. *Front. Med.* **2019**, *6*, 55. [CrossRef] [PubMed]
5. Cao, G.; He, X.; Sun, Q.; Chen, S.; Wan, K.; Xu, X.; Feng, X.; Li, P.; Chen, B.; Xiong, M. The Oncolytic Virus in Cancer Diagnosis and Treatment. *Front. Oncol.* **2020**, *10*, 1786. [CrossRef] [PubMed]
6. Carvalho, S.; Levi-Schaffer, F.; Sela, M.; Yarden, Y. Immunotherapy of Cancer: From Monoclonal to Oligoclonal Cocktails of Anti-Cancer Antibodies: IUPHAR Review 18. *Br. J. Pharmacol.* **2016**, *173*, 1407–1424. [CrossRef] [PubMed]
7. Merino, G. Monoclonal Antibodies. Basic Features. *Neurologia* **2011**, *26*, 301–306. [CrossRef]
8. Newsome, B.W.; Ernstoff, M.S. The Clinical Pharmacology of Therapeutic Monoclonal Antibodies in the Treatment of Malignancy; Have the Magic Bullets Arrived? *Br. J. Clin. Pharmacol.* **2008**, *66*, 6–19. [CrossRef]
9. Marrocco, I.; Romaniello, D.; Yarden, Y. Cancer Immunotherapy: The Dawn of Antibody Cocktails. In *Human Monoclonal Antibodies: Methods and Protocols*; Steinitz, M., Ed.; Springer: Berlin/Heidelberg, Germany, 2019; pp. 11–51.
10. Mullard, A. FDA Approves 100th Monoclonal Antibody Product. *Nat. Rev. Drug Discov.* **2021**, *20*, 491–495. [CrossRef]
11. Goulet, D.R.; Atkins, W.M. Considerations for the Design of Antibody-Based Therapeutics. *J. Pharm. Sci.* **2020**, *109*, 74–103. [CrossRef]
12. Ramaswami, R.; Longo, D. Monoclonal Antibodies. In *Cancer Chemotherapy, Immunotherapy and Biotherapy: Principles and Practice*; Chabner, B., Longo, D., Eds.; Wolters Kluwer: Alphen aan den Rijn, The Netherlands, 2019; pp. 782–812.
13. Karpuz, M.; Silindir-Gunay, M.; Ozer, A.Y. Current and Future Approaches for Effective Cancer Imaging and Treatment. *Cancer Biother. Radiopharm.* **2018**, *33*, 39–51. [CrossRef]
14. Therapeutic Monoclonal Antibodies Approved or in Review in the EU or US. Available online: [www.antibodysociety.org](http://www.antibodysociety.org) (accessed on 12 December 2022).
15. Espinoza, J.A.; Riquelme, I.; Sagredo, E.A.; Rosa, L.; García, P.; Bizama, C.; Apud-Bell, M.; Leal, P.; Weber, H.; Benavente, F.; et al. Mucin 5B, Carbonic Anhydrase 9 and Claudin 18 Are Potential Theranostic Markers of Gallbladder Carcinoma. *Histopathology* **2019**, *74*, 597–607. [CrossRef]
16. Han, Y.; Liu, D.; Li, L. PD-1/PD-L1 Pathway: Current Researches in Cancer. *Am. J. Cancer Res.* **2020**, *10*, 727–742.
17. Ahmadzadeh, M.; Johnson, L.A.; Heemskerk, B.; Wunderlich, J.R.; Dudley, M.E.; White, D.E.; Rosenberg, S.A. Tumor Antigen-Specific CD8 T Cells Infiltrating the Tumor Express High Levels of PD-1 and Are Functionally Impaired. *Blood* **2009**, *114*, 1537–1544. [CrossRef]
18. Goodsell, D.S. PD-1 (Programmed Cell Death Protein 1). *RCSB Protein Data Bank* **2016**. [CrossRef]
19. Ai, L.; Xu, A.; Xu, J. Roles of PD-1/PD-L1 Pathway: Signaling, Cancer, and Beyond. In *Advances in Experimental Medicine and Biology 1248—Regulation of Cancer Immune Checkpoints—Molecular and Cellular Mechanisms and Therapy*; Xu, J., Ed.; Springer: Berlin/Heidelberg, Germany, 2020; pp. 33–59.
20. UniProtKB UniProtKB-Q9NZQ7 (PD1L1\_HUMAN). Available online: <https://www.uniprot.org/uniprot/Q9NZQ7> (accessed on 29 May 2021).
21. Sharpe, A.H.; Wherry, E.J.; Ahmed, R.; Freeman, G.J. The Function of Programmed Cell Death 1 and Its Ligands in Regulating Autoimmunity and Infection. *Nat. Immunol.* **2007**, *8*, 239–245. [CrossRef]
22. Zou, W.; Chen, L. Inhibitory B7-Family Molecules in the Tumour Microenvironment. *Nat. Rev. Immunol.* **2008**, *8*, 467–477. [CrossRef]

23. Nunes-Xavier, C.E.; Angulo, J.C.; Pulido, R.; López, J.I. A Critical Insight into the Clinical Translation of PD-1/PD-L1 Blockade Therapy in Clear Cell Renal Cell Carcinoma. *Curr. Urol. Rep.* **2019**, *20*, 1. [CrossRef]
24. The Nobel Assembly at Karolinska Institutet. *The Nobel Assembly at Karolinska Institutet Has Today Decided to Award the 2018 Nobel Prize in Physiology or Medicine Jointly to James P. Allison and Tasuku Honjo*; 2018; pp. 1–5.
25. Topalian, S.L.; Sznol, M.; McDermott, D.F.; Kluger, H.M.; Carvajal, R.D.; Sharfman, W.H.; Brahmer, J.R.; Lawrence, D.P.; Atkins, M.B.; Powderly, J.D.; et al. Survival, Durable Tumor Remission, and Long-Term Safety in Patients with Advanced Melanoma Receiving Nivolumab. *J. Clin. Oncol.* **2014**, *32*, 1020–1030. [CrossRef]
26. Sundar, R.; Cho, B.C.; Brahmer, J.R.; Soo, R.A. Nivolumab in NSCLC: Latest Evidence and Clinical Potential. *Ther. Adv. Med. Oncol.* **2015**, *7*, 85–96. [CrossRef]
27. Choueiri, T.K.; Fishman, M.N.; Escudier, B.; McDermott, D.F.; Drake, C.G.; Kluger, H.; Stadler, W.M.; Perez-Gracia, J.L.; McNeel, D.G.; Curti, B.; et al. Immunomodulatory Activity of Nivolumab in Metastatic Renal Cell Carcinoma. *Clin. Cancer Res.* **2016**, *22*, 5461–5471. [CrossRef]
28. Lee, A.; Keam, S.J. Tislelizumab: First Approval. *Drugs* **2020**, *80*, 617–624. [CrossRef]
29. Dhillon, S. Penpulimab: First Approval. *Drugs* **2021**, *81*, 2159–2166. [CrossRef]
30. FDA Wwww.Fda.Gov. Available online: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-retifanlimab-dlwr-metastatic-or-recurrent-locally-advanced-merkel#:~:text=OnMarch22%2C2023%2CtheFoodandDrug,carcinoma%28MCC%29> (accessed on 13 June 2023).
31. Chen, Q.; Yuan, S.; Sun, H.; Peng, L. CD3<sup>+</sup> CD20<sup>+</sup> T Cells and Their Roles in Human Diseases. *Hum. Immunol.* **2019**, *80*, 191–194. [CrossRef] [PubMed]
32. Florou, D.; Katsara, M.; Feehan, J.; Dardiotis, E.; Apostolopoulos, V. Anti-Cd20 Agents for Multiple Sclerosis: Spotlight on Ocrelizumab and Ofatumumab. *Brain Sci.* **2020**, *10*, 758. [CrossRef] [PubMed]
33. Uchida, J.; Lee, Y.; Hasegawa, M.; Liang, Y.; Bradney, A.; Oliver, J.A.; Bowen, K.; Steeber, D.A.; Haas, K.M.; Poe, J.C.; et al. Mouse CD20 Expression and Function. *Int. Immunol.* **2004**, *16*, 119–129. [CrossRef] [PubMed]
34. Henry, C.; Deschamps, M.; Rohrllich, P.S.; Pallandre, J.R.; Rémy-Martin, J.P.; Callanan, M.; Traverse-Glehen, A.; GrandClément, C.; Garnache-Ottou, F.; Gressin, R.; et al. Identification of an Alternative CD20 Transcript Variant in B-Cell Malignancies Coding for a Novel Protein Associated to Rituximab Resistance. *Blood* **2010**, *115*, 2420–2429. [CrossRef] [PubMed]
35. Gamonet, C.; Bole-Richard, E.; Delherme, A.; Aubin, F.; Toussiro, E.; Garnache-Ottou, F.; Godet, Y.; Ysebaert, L.; Tournilhac, O.; Caroline, D.; et al. New CD20 Alternative Splice Variants: Molecular Identification and Differential Expression within Hematological B Cell Malignancies. *Exp. Hematol. Oncol.* **2016**, *5*, 7. [CrossRef]
36. Pavlasova, G.; Borsky, M.; Svobodova, V.; Oppelt, J.; Cerna, K.; Novotna, J.; Seda, V.; Fojtova, M.; Fajkus, J.; Brychtova, Y.; et al. Rituximab Primarily Targets an Intra-Clonal BCR Signaling Proficient CLL Subpopulation Characterized by High CD20 Levels. *Leukemia* **2018**, *32*, 2028–2031. [CrossRef]
37. Pavlasova, G.; Mraz, M. The Regulation and Function of CD20: An “Enigma” of B-Cell Biology and Targeted Therapy. *Haematologica* **2020**, *105*, 1494–1506. [CrossRef]
38. Schuh, E.; Berer, K.; Mulazzani, M.; Feil, K.; Meinel, I.; Lahm, H.; Krane, M.; Lange, R.; Pfannes, K.; Subklewe, M.; et al. Features of Human CD3<sup>+</sup> CD20<sup>+</sup> T Cells. *J. Immunol.* **2016**, *197*, 1111–1117. [CrossRef]
39. Kang, C. Mosunetuzumab: First Approval. *Drugs* **2022**, *82*, 1229–1234. [CrossRef]
40. Fischer, L. Oncology Nursing News. Available online: <https://www.oncnursingnews.com/view/epcoritamab-obtains-accelerated-approval-for-relapsed-refractory-dlbcl> (accessed on 19 May 2023).
41. Faloso, A.; Gianni, L. Introduction and Background Biology. In *Handbook of HER2-Targeted Agents in Breast Cancer*; Alvarez, R., Cortés, J., Falzon, M., Gandy, M., Gianni, L., Harbeck, N., Piccart, M., Eds.; Springer International Publishing: Cham, Switzerland, 2016; pp. 1–13.
42. Connell, C.M.; Doherty, G.J. Activating HER2 Mutations as Emerging Targets in Multiple Solid Cancers. *ESMO Open* **2017**, *2*, e000279. [CrossRef]
43. Albagoush, S.A.; Limaiem, F. *HER2*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
44. Slamon, D.J.; Clark, G.M.; Wong, S.G.; Levin, W.J.; McGuire, W.L. American Association for the Advancement of Science. *Science* **1987**, *os-2*, 341–342. [CrossRef]
45. Sjögren, S.; Inganäs, M.; Lindgren, A.; Holmberg, L.; Bergh, J. Prognostic and Predictive Value of C-ErbB-2 Overexpression in Primary Breast Cancer, Alone and in Combination with Other Prognostic Markers. *J. Clin. Oncol.* **1998**, *16*, 462–469. [CrossRef]
46. Li, X.; Ding, Y.; Zi, M.; Sun, L.; Zhang, W.; Chen, S.; Xu, Y. CD19, from Bench to Bedside. *Immunol. Lett.* **2017**, *183*, 86–95. [CrossRef]
47. Bradbury, L.E.; Goldmacher, V.S.; Tedder, T.F. The CD19 Signal Transduction Complex of B Lymphocytes. Deletion of the CD19 Cytoplasmic Domain Alters Signal Transduction but Not Complex Formation with TAPA-1 and Leu 13. *J. Immunol.* **1993**, *151*, 2915–2927. [CrossRef]
48. Zhou, L.J.; Ord, D.C.; Hughes, A.L.; Tedder, T.F. Structure and Domain Organization of the CD19 Antigen of Human, Mouse, and Guinea Pig B Lymphocytes. Conservation of the Extensive Cytoplasmic Domain. *J. Immunol.* **1991**, *147*, 1424–1432. [CrossRef]
49. Baba, Y.; Kurosaki, T. Impact of Ca<sup>2+</sup> Signaling on B Cell Function. *Trends Immunol.* **2011**, *32*, 589–594. [CrossRef]
50. Rickert, R.C.; Rajewsky, K.; Roes, J. Impairment of T-Cell-Dependent B-Cell Responses and B-1 Cell Development in CD19-Deficient Mice. *Nature* **1995**, *376*, 352–355. [CrossRef]

51. Yoshizaki, A.; Iwata, Y.; Komura, K.; Ogawa, F.; Hara, T.; Muroi, E.; Takenaka, M.; Shimizu, K.; Hasegawa, M.; Fujimoto, M.; et al. CD19 Regulates Skin and Lung Fibrosis via Toll-like Receptor Signaling in a Model of Bleomycin-Induced Scleroderma. *Am. J. Pathol.* **2008**, *172*, 1650–1663. [[CrossRef](#)]
52. Sato, S.; Hasegawa, M.; Fujimoto, M.; Tedder, T.F.; Takehara, K. Quantitative Genetic Variation in CD19 Expression Correlates with Autoimmunity. *J. Immunol.* **2000**, *165*, 6635–6643. [[CrossRef](#)]
53. Nazha, B.; Inal, C.; Owonikoko, T.K. Disialoganglioside GD2 Expression in Solid Tumors and Role as a Target for Cancer Therapy. *Front. Oncol.* **2020**, *10*, 1000. [[CrossRef](#)]
54. Svennerholm, L.; Bostrom, K.; Fredman, P.; Jungbjer, B.; Lekman, A.; Jan-eric, M.; Rynmark, B. Gangliosides and Allied Glycosphingolipids in Human Peripheral Nerve and Spinal Cord. *Biochim. Et Biophys. Acta* **1994**, *1214*, 115–123. [[CrossRef](#)] [[PubMed](#)]
55. Yanagisawa, M.; Yoshimura, S.; Yu, R.K. Expression of GD2 and GD3 Gangliosides in Human Embryonic Neural Stem Cells. *ASN Neuro* **2011**, *3*, AN20110006. [[CrossRef](#)] [[PubMed](#)]
56. Schulz, G.; Cheresch, D.A.; Varki, N.M.; Staffilano, L.K.; Reisfeld, R.A.; Yu, A. Detection of Ganglioside GD2 in Tumor Tissues and Sera of Neuroblastoma Patients. *Cancer Res.* **1984**, *44*, 5914–5920. [[PubMed](#)]
57. Chen, L.C.; Brown, A.B.; Cheung, I.Y.; Cheung, N.K.V.; Kris, M.G.; Krug, L.M. Analysis of GD2/GM2 Synthase MRNA as a Biomarker for Small Cell Lung Cancer. *Lung Cancer* **2010**, *67*, 216–220. [[CrossRef](#)]
58. Tsuchida, T.; Irie, R.F.; Ishibashi, Y. Gangliosides of Human Melanoma. *Pigment. Cell Res.* **1987**, *3*, 147–150. [[CrossRef](#)]
59. Casey, D.L.; Lin, T.Y.; Cheung, N.K.V. Exploiting Signaling Pathways and Immune Targets beyond the Standard of Care for Ewing Sarcoma. *Front. Oncol.* **2019**, *9*, 537. [[CrossRef](#)]
60. Roth, M.; Linkowski, M.; Tarim, J.; Piperdi, S.; Sowers, R.; Geller, D.; Gill, J.; Gorlick, R. Ganglioside GD2 as a Therapeutic Target for Antibody-Mediated Therapy in Patients with Osteosarcoma. *Cancer* **2014**, *120*, 548–554. [[CrossRef](#)]
61. Chang, H.; Cordon-Cardo, C.; Houghton, A.; Cheung, N.; Brennan, M. Expression of Disialogangliosides GD2 and GD3 on Human Soft Tissue Sarcomas. *Cancer* **1992**, *70*, 633–638. [[CrossRef](#)]
62. Longee, D.C.; Wikstrand, C.J.; Månsson, J.E.; He, X.; Fuller, G.N.; Bigner, S.H.; Fredman, P.; Svennerholm, L.; Bigner, D.D. Disialoganglioside GD2 in Human Neuroectodermal Tumor Cell Lines and Gliomas. *Acta Neuropathol.* **1991**, *82*, 45–54. [[CrossRef](#)]
63. Andersch, L.; Radke, J.; Klaus, A.; Schwiebert, S.; Winkler, A.; Schumann, E.; Grunewald, L.; Zirngibl, F.; Flemmig, C.; Jensen, M.C.; et al. CD171- and GD2-Specific CAR-T Cells Potently Target Retinoblastoma Cells in Preclinical in Vitro Testing. *BMC Cancer* **2019**, *19*, 895. [[CrossRef](#)]
64. Orsi, G.; Barbolini, M.; Ficarra, G.; Tazzioli, G.; Manni, P.; Petrachi, T.; Mastrolia, I.; Orvieto, E.; Spano, C.; Prapa, M.; et al. GD2 Expression in Breast Cancer. *Oncotarget* **2017**, *8*, 31592–31600. [[CrossRef](#)]
65. Vantaku, V.; Donepudi, S.R.; Ambati, C.R.; Jin, F.; Putluri, V.; Nguyen, K.; Rajapakshe, K.; Coarfa, C.; Battula, V.L.; Lotan, Y.; et al. Expression of Ganglioside GD2, Reprogram the Lipid Metabolism and EMT Phenotype in Bladder Cancer. *Oncotarget* **2017**, *8*, 95620–95631. [[CrossRef](#)]
66. Dobrenkov, K.; Cheung, N.-K.V. GD2-Targeted Immunotherapy and Radioimmunotherapy. *Semin. Oncol.* **2014**, *41*, 589–612. [[CrossRef](#)]
67. Hung, J.; Yu, A. GD2-Targeted Immunotherapy of Neuroblastoma. In *Neuroblastoma: Molecular Mechanisms and Therapeutic Interventions*; Swapan, R., Ed.; Elsevier Academic Press: Amsterdam, The Netherlands, 2019; pp. 62–78.
68. Cavdarli, S.; Groux-Degroote, S.; Delannoy, P. Gangliosides: The Double-Edge Sword of Neuro-Ectodermal Derived Tumors. *Biomolecules* **2019**, *9*, 311. [[CrossRef](#)]
69. Esaki, N.; Ohkawa, Y.; Hashimoto, N.; Tsuda, Y.; Ohmi, Y.; Bhuiyan, R.H.; Kotani, N.; Honke, K.; Enomoto, A.; Takahashi, M.; et al. ASC Amino Acid Transporter 2, Defined by Enzyme-Mediated Activation of Radical Sources, Enhances Malignancy of GD2-Positive Small-Cell Lung Cancer. *Cancer Sci.* **2018**, *109*, 141–153. [[CrossRef](#)]
70. Liu, Y.; Wondimu, A.; Yan, S.; Bobb, D.; Ladisch, S. Tumor Gangliosides Accelerate Murine Tumor Angiogenesis. *Angiogenesis* **2014**, *17*, 563–571. [[CrossRef](#)]
71. Avery, D.T.; Kalled, S.L.; Ellyard, J.I.; Ambrose, C.; Bixler, S.A.; Thien, M.; Brink, R.; Mackay, F.; Hodgkin, P.D.; Tangye, S.G. BAFF Selectively Enhances the Survival of Plasmablasts Generated from Human Memory B Cells. *J. Clin. Investig.* **2003**, *112*, 286–297. [[CrossRef](#)]
72. O'Connor, B.P.; Raman, V.S.; Erickson, L.D.; Cook, W.J.; Weaver, L.K.; Ahonen, C.; Lin, L.-L.; Mantchev, G.T.; Bram, R.J.; Noelle, R.J. BCMA Is Essential for the Survival of Long-Lived Bone Marrow Plasma Cells. *J. Exp. Med.* **2004**, *199*, 91–98. [[CrossRef](#)]
73. Tai, Y.T.; Anderson, K.C. B Cell Maturation Antigen (BCMA)-Based Immunotherapy for Multiple Myeloma. *Expert Opin. Biol. Ther.* **2019**, *19*, 1143–1156. [[CrossRef](#)]
74. Dogan, A.; Siegel, D.; Tran, N.; Fu, A.; Fowler, J.; Belani, R.; Landgren, O. B-Cell Maturation Antigen Expression across Hematologic Cancers: A Systematic Literature Review. *Blood Cancer J.* **2020**, *10*, 73. [[CrossRef](#)]
75. Guadagnoli, M.; Kimberley, F.C.; Phan, U.; Cameron, K.; Vink, P.M.; Rodermond, H.; Eldering, E.; Kater, A.P.; van Eenennaam, H.; Medema, J.P. Development and Characterization of APRIL Antagonistic Monoclonal Antibodies for Treatment of B-Cell Lymphomas. *Blood* **2011**, *117*, 6856–6865. [[CrossRef](#)] [[PubMed](#)]
76. Belnoue, E.; Pihlgren, M.; McGaha, T.L.; Tougne, C.; Rochat, A.-F.; Bossen, C.; Schneider, P.; Huard, B.; Lambert, P.-H.; Siegrist, C.-A. APRIL Is Critical for Plasmablast Survival in the Bone Marrow and Poorly Expressed by Early-Life Bone Marrow Stromal Cells. *Blood* **2008**, *111*, 2755–2764. [[CrossRef](#)] [[PubMed](#)]

77. Khattar, P.; Pichardo, J.; Jungbluth, A.; Gao, Q.; Smith, E.; Roshal, M.; Dogan, A. B-Cell Maturation Antigen Is Exclusively Expressed in a Wide Range of B-Cell and Plasma Cell Neoplasm and in a Potential Therapeutic Target for Bcma Directed Therapies. In *Proceedings of the Lymphoma Biology Non Genetic Studies: Poster II*; Elsevier: Amsterdam, The Netherlands, 2017.
78. Maia, S.; Pelletier, M.; Ding, J.; Hsu, Y.-M.; Sallan, S.E.; Rao, S.P.; Nadler, L.M.; Cardoso, A.A. Aberrant Expression of Functional BAFF-System Receptors by Malignant B-Cell Precursors Impacts Leukemia Cell Survival. *PLoS ONE* **2011**, *6*, e20787. [[CrossRef](#)]
79. Sanchez, E.; Tanenbaum, E.J.; Patil, S.; Li, M.; Soof, C.M.; Vidisheva, A.; Waterman, G.N.; Hekmati, T.; Tang, G.; Wang, C.S.; et al. The Clinical Significance of B-Cell Maturation Antigen as a Therapeutic Target and Biomarker. *Expert Rev. Mol. Diagn.* **2018**, *18*, 319–329. [[CrossRef](#)] [[PubMed](#)]
80. Kaplon, H.; Muralidharan, M.; Schneider, Z.; Reichert, J.M. Antibodies to Watch in 2020. *mAbs* **2020**, *12*, 1703531. [[CrossRef](#)]
81. Zaman, S.; Jadid, H.; Denson, A.C.; Gray, J.E. Targeting Trop-2 in Solid Tumors: Future Prospects. *OncoTargets Ther.* **2019**, *12*, 1781–1790. [[CrossRef](#)]
82. Cubas, R.; Li, M.; Chen, C.; Yao, Q. Trop2: A Possible Therapeutic Target for Late Stage Epithelial Carcinomas. *Biochim. Biophys. Acta (BBA)-Rev. Cancer* **2009**, *1796*, 309–314. [[CrossRef](#)]
83. Shvartsur, A.; Bonavida, B. Trop2 and Its Overexpression in Cancers: Regulation and Clinical/Therapeutic Implications. *Genes Cancer* **2014**, *6*, 84–105. [[CrossRef](#)]
84. Basu, A.; Goldenberg, D.M.; Stein, R. The Epithelial/Carcinoma Antigen EGP-1, Recognized by Monoclonal Antibody RS7-3G11, Is Phosphorylated on Serine 303. *Int. J. Cancer* **1995**, *62*, 472–479. [[CrossRef](#)]
85. Goldenberg, D.M.; Stein, R.; Sharkey, R.M. The Emergence of Trophoblast Cell-Surface Antigen 2 (TROP-2) as a Novel Cancer Target. *Oncotarget* **2018**, *9*, 28989–29006. [[CrossRef](#)]
86. Martini, M.; De Santis, M.C.; Braccini, L.; Gulluni, F.; Hirsch, E. PI3K/AKT Signaling Pathway and Cancer: An Updated Review. *Ann. Med.* **2014**, *46*, 372–383. [[CrossRef](#)]
87. Lim, H.J.; Crowe, P.; Yang, J.L. Current Clinical Regulation of PI3K/PTEN/Akt/MTOR Signalling in Treatment of Human Cancer. *J. Cancer Res. Clin. Oncol.* **2015**, *141*, 671–689. [[CrossRef](#)]
88. Li, X.; Teng, S.; Zhang, Y.; Zhang, W.; Zhang, X.; Xu, K.; Yao, H.; Yao, J.; Wang, H.; Liang, X.; et al. TROP2 Promotes Proliferation, Migration and Metastasis of Gallbladder Cancer Cells by Regulating PI3K/AKT Pathway and Inducing EMT. *Oncotarget* **2017**, *8*, 47052–47063. [[CrossRef](#)]
89. Lin, H.; Zhang, H.; Wang, J.; Lu, M.; Zheng, F.; Wang, C.; Tang, X.; Xu, N.; Chen, R.; Zhang, D.; et al. A Novel Human Fab Antibody for Trop2 Inhibits Breast Cancer Growth in Vitro and in Vivo. *Int. J. Cancer* **2014**, *134*, 1239–1249. [[CrossRef](#)]
90. Mao, Y.; Wang, X.; Zheng, F.; Wang, C.; Tang, Q.; Tang, X.; Xu, N.; Zhang, H.; Zhang, D.; Xiong, L.; et al. The Tumor-Inhibitory Effectiveness of a Novel Anti-Trop2 Fab Conjugate in Pancreatic Cancer. *Oncotarget* **2016**, *7*, 24810–24823. [[CrossRef](#)]
91. Liu, J.; Yang, D.; Yin, Z.; Gao, M.; Tong, H.; Su, Y.; Zhu, J.; Ye, C.; Zhang, H. A Novel Human Monoclonal Trop2-IgG Antibody Inhibits Ovarian Cancer Growth in Vitro and in Vivo. *Biochem. Biophys. Res. Commun.* **2019**, *512*, 276–282. [[CrossRef](#)]
92. Crowell, P.D.; Goldstein, A.S. Functional Evidence That Progenitor Cells near Sites of Inflammation Are Precursors for Aggressive Prostate Cancer. *Mol. Cell. Oncol.* **2017**, *4*, e1279723. [[CrossRef](#)]
93. Krejcik, J.; Casneuf, T.; Nijhof, I.S.; Verbist, B.; Bald, J.; Plesner, T.; Syed, K.; Liu, K.; Van De Donk, N.W.C.J.; Weiss, B.M.; et al. Daratumumab Depletes CD38<sup>+</sup> Immune Regulatory Cells, Promotes T-Cell Expansion, and Skews T-Cell Repertoire in Multiple Myeloma. *Blood* **2016**, *128*, 384–394. [[CrossRef](#)]
94. Kotlikoff, M.I.; Kannan, M.S.; Solway, J.; Deng, K.Y.; Deshpande, D.A.; Dowell, M.; Feldman, M.; Green, K.S.; Ji, G.; Johnston, R.; et al. Methodologic Advancements in the Study of Airway Smooth Muscle. *J. Allergy Clin. Immunol.* **2004**, *114*, 18–31. [[CrossRef](#)]
95. Horenstein, A.L.; Sizzano, F.; Lusso, R.; Besso, F.G.; Ferrero, E.; Deaglio, S.; Corno, F.; Malavasi, F. CD38 and CD157 Ectoenzymes Mark Cell Subsets in the Human Corneal Limbus. *Mol. Med.* **2009**, *15*, 76–84. [[CrossRef](#)]
96. Chini, E. CD38 as a Regulator of Cellular NAD: A Novel Potential Pharmacological Target for Metabolic Conditions. *Curr. Pharm. Des.* **2009**, *15*, 57–63. [[CrossRef](#)] [[PubMed](#)]
97. Kar, A.; Mehrotra, S.; Chatterjee, S. CD38: T Cell Immuno-Metabolic Modulator. *Cells* **2020**, *9*, 1716. [[CrossRef](#)] [[PubMed](#)]
98. Lin, W.K.; Bolton, E.L.; Cortopassi, W.A.; Wang, Y.; O'Brien, F.; Maciejewska, M.; Jacobson, M.P.; Garnham, C.; Ruas, M.; Parrington, J.; et al. Synthesis of the Ca<sup>2+</sup>-Mobilizing Messengers NAADP and CADPR by Intracellular CD38 Enzyme in the Mouse Heart: Role in -Adrenoceptor Signaling. *J. Biol. Chem.* **2017**, *292*, 13243–13257. [[CrossRef](#)] [[PubMed](#)]
99. Van De Donk, N.W.C.J.; Richardson, P.G.; Malavasi, F. CD38 Antibodies in Multiple Myeloma: Back to the Future. *Blood* **2018**, *131*, 13–29. [[CrossRef](#)]
100. Hogan, K.A.; Chini, C.C.S.; Chini, E.N. The Multi-Faceted Ecto-Enzyme CD38: Roles in Immunomodulation, Cancer, Aging, and Metabolic Diseases. *Front. Immunol.* **2019**, *10*, 1187. [[CrossRef](#)]
101. Ben Baruch, B.; Mantsur, E.; Franco-Barraza, J.; Blacher, E.; Cukierman, E.; Stein, R. CD38 in Cancer-Associated Fibroblasts Promotes pro-Tumoral Activity. *Lab. Investig.* **2020**, *100*, 1517–1531. [[CrossRef](#)]
102. Sanofi. *Phase 3 Trial of Isatuximab Combination Therapy Showed 40% Reduction in the Risk of Disease Progression or Death for Patients with Relapsed/Refractory Multiple Myeloma*; Sanofi: Paris, France, 2019.
103. Sanofi. *FDA to Review Isatuximab as a Potential Treatment for Relapsed/Refractory Multiple Myeloma July 10, 2019 Press Release*; Sanofi: Paris, France, 2019.

104. Reymond, N.; Fabre, S.; Lecocq, E.; Adelaide, J.; Dubreuil, P.; Lopez, M. Nectin4/PRR4, a New Afadin-Associated Member of the Nectin Family That Trans-Interacts with Nectin1/PRR1 through V Domain Interaction. *J. Biol. Chem.* **2001**, *276*, 43205–43215. [[CrossRef](#)]
105. Takai, Y.; Miyoshi, J.; Ikeda, W.; Ogita, H. Nectins and Nectin-like Molecules: Roles in Contact Inhibition of Cell Movement and Proliferation. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 603–615. [[CrossRef](#)]
106. Brancati, F.; Fortugno, P.; Bottillo, I.; Lopez, M.; Josselin, E.; Boudghene-Stambouli, O.; Agolini, E.; Bernardini, L.; Bellacchio, E.; Iannicelli, M.; et al. Mutations in PVRL4, Encoding Cell Adhesion Molecule Nectin-4, Cause Ectodermal Dysplasia-Syndactyly Syndrome. *Am. J. Hum. Genet.* **2010**, *87*, 265–273. [[CrossRef](#)]
107. Fabre, S.; Reymond, N.; Cocchi, F.; Menotti, L.; Dubreuil, P.; Campadelli-Fiume, G.; Lopez, M. Prominent Role of the Ig-like V Domain in Trans-Interactions of Nectins. Nectin3 and Nectin4 Bind to the Predicted C-C'-C''-D  $\beta$ -Strands of the Nectin1 V Domain. *J. Biol. Chem.* **2002**, *277*, 27006–27013. [[CrossRef](#)]
108. Nakanishi, H.; Takai, Y. Roles of Nectins in Cell Adhesion, Migration and Polarization. *Biol. Chem.* **2004**, *385*, 885–892. [[CrossRef](#)]
109. Challita-Eid, P.M.; Satpayev, D.; Yang, P.; An, Z.; Morrison, K.; Shostak, Y.; Raitano, A.; Nadell, R.; Liu, W.; Lortie, D.R.; et al. Enfortumab Vedotin Antibody-Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models. *Cancer Res.* **2016**, *76*, 3003–3013. [[CrossRef](#)]
110. Zhang, Y.; Chen, P.; Yin, W.; Ji, Y.; Shen, Q.; Ni, Q. Nectin-4 Promotes Gastric Cancer Progression via the PI3K/AKT Signaling Pathway. *Hum. Pathol.* **2018**, *72*, 107–116. [[CrossRef](#)]
111. M-Rabet, M.; Cabaud, O.; Josselin, E.; Finetti, P.; Castellano, R.; Farina, A.; Agavniac-Couquiaud, E.; Saviane, G.; Collette, Y.; Viens, P.; et al. Nectin-4: A New Prognostic Biomarker for Efficient Therapeutic Targeting of Primary and Metastatic Triple-Negative Breast Cancer. *Ann. Oncol.* **2017**, *28*, 769–776. [[CrossRef](#)]
112. Heath, E.I.; Rosenberg, J.E. The Biology and Rationale of Targeting Nectin-4 in Urothelial Carcinoma. *Nat. Rev. Urol.* **2021**, *18*, 93–103. [[CrossRef](#)]
113. Erturk, K.; Karaman, S.; Dagoglu, N.; Serilmez, M.; Duranyildiz, D.; Tas, F. Serum Nectin-2 and Nectin-4 Are Diagnostic in Lung Cancer: Which Is Superior? *Wien. Klin. Wochenschr.* **2019**, *131*, 419–426. [[CrossRef](#)]
114. Johnson, S.A.; Pleiman, C.M.; Pao, L.; Schneringer, J.; Hippen, K.; Cambier, J.C. Phosphorylated Immunoreceptor Signaling Motifs (ITAMs) Exhibit Unique Abilities to Bind and Activate Lyn and Syk Tyrosine Kinases. *J. Immunol.* **1995**, *155*, 4596–4603. [[CrossRef](#)]
115. Bourbon, E.; Salles, G. Polatuzumab Vedotin: An Investigational Anti-CD79b Antibody Drug Conjugate for the Treatment of Diffuse Large B-Cell Lymphoma. *Expert Opin. Investig. Drugs* **2020**, *29*, 1079–1088. [[CrossRef](#)]
116. RETH, M. Antigen Receptor Tail Clue. *Nature* **1989**, *338*, 383–384. [[CrossRef](#)]
117. Hombach, J.; Tsubata, T.; Leclercq, L.; Stappert, H.; Reth, M. Molecular Components of the B-Cell Antigen Receptor Complex of the IgM Class. *Nature* **1990**, *343*, 760–762. [[CrossRef](#)]
118. Pelanda, R.; Braun, U.; Hobeika, E.; Nussenzweig, M.C.; Reth, M. B Cell Progenitors Are Arrested in Maturation but Have Intact VDJ Recombination in the Absence of Ig- $\alpha$  and Ig- $\beta$ . *J. Immunol.* **2002**, *169*, 865–872. [[CrossRef](#)] [[PubMed](#)]
119. Schmitz, R.; Wright, G.W.; Huang, D.W.; Johnson, C.A.; Phelan, J.D.; Wang, J.Q.; Roulland, S.; Kasbekar, M.; Young, R.M.; Shaffer, A.L.; et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *N. Engl. J. Med.* **2018**, *378*, 1396–1407. [[CrossRef](#)] [[PubMed](#)]
120. Naeim, F.; Nagesh Rao, P.; Song, S.X.; Phan, R.T. Principles of Immunophenotyping. In *Atlas of Hematopathology*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 29–56.
121. Young, R.M.; Shaffer, A.L.; Phelan, J.D.; Staudt, L.M. B-Cell Receptor Signaling in Diffuse Large B-Cell Lymphoma. *Semin. Hematol.* **2015**, *52*, 77–85. [[CrossRef](#)]
122. Pfeifer, M.; Zheng, B.; Erdmann, T.; Koeppen, H.; McCord, R.; Grau, M.; Staiger, A.; Chai, A.; Sandmann, T.; Madle, H.; et al. Anti-CD22 and Anti-CD79B Antibody Drug Conjugates Are Active in Different Molecular Diffuse Large B-Cell Lymphoma Subtypes. *Leukemia* **2015**, *29*, 1578–1586. [[CrossRef](#)] [[PubMed](#)]
123. Visco, C.; Tanasi, I.; Quaglia, F.M.; Ferrarini, I.; Fraenza, C.; Krampera, M. Oncogenic Mutations of MYD88 and CD79B in Diffuse Large B-Cell Lymphoma and Implications for Clinical Practice. *Cancers* **2020**, *12*, 2913. [[CrossRef](#)]
124. Deeks, E.D. Polatuzumab Vedotin: First Global Approval. *Drugs* **2019**, *79*, 1467–1475. [[CrossRef](#)]
125. Lanza, F.; Maffini, E.; Rondoni, M.; Massari, E.; Faini, A.C.; Malavasi, F. CD22 Expression in B-Cell Acute Lymphoblastic Leukemia: Biological Significance and Implications for Inotuzumab Therapy in Adults. *Cancers* **2020**, *12*, 303. [[CrossRef](#)]
126. Gonzalez-Gil, A.; Schnaar, R.L. Siglec Ligands. *Cells* **2021**, *10*, 1260. [[CrossRef](#)]
127. Clark, E.A.; Giltiy, N.V. CD22: A Regulator of Innate and Adaptive B Cell Responses and Autoimmunity. *Front. Immunol.* **2018**, *9*, 2235. [[CrossRef](#)]
128. Shah, N.N.; Sokol, L. Targeting CD22 for the Treatment of B-Cell Malignancies. *ImmunoTargets Ther.* **2021**, *10*, 225–236. [[CrossRef](#)]
129. Tedder, T.F.; Sato, S.; Poe, J.C.; Fujimoto, M. CD19 and CD22 Regulate a B Lymphocyte Signal Transduction Pathway That Contributes to Autoimmunity. *Keio J. Med.* **2000**, *49*, 1–13. [[CrossRef](#)]
130. Melissaropoulos, K.; Liossis, S.-N. Decreased CD22 Expression and Intracellular Signaling Aberrations in B Cells of Patients with Systemic Sclerosis. *Rheumatol. Int.* **2018**, *38*, 1225–1234. [[CrossRef](#)]
131. Lee, W.S.; Amengual, O. B Cells Targeting Therapy in the Management of Systemic Lupus Erythematosus. *Immunol. Med.* **2020**, *43*, 16–35. [[CrossRef](#)]

132. Yurkiewicz, I.R.; Muffly, L.; Liedtke, M. Inotuzumab Ozogamicin: A CD22 MAB&ndash;Drug Conjugate for Adult Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia. *Drug Des. Dev. Ther.* **2018**, *12*, 2293–2300. [[CrossRef](#)]
133. Sun, Z.; Li, W.; Mellors, J.W.; Orentas, R.; Dimitrov, D.S. Construction of a Large Size Human Immunoglobulin Heavy Chain Variable (VH) Domain Library, Isolation and Characterization of Novel Human Antibody VH Domains Targeting PD-L1 and CD22. *Front. Immunol.* **2022**, *13*, 869825. [[CrossRef](#)]
134. Rousseau, J.; Lau, J.; Bénard, F. Radiolabeled Antibodies for Cancer Radioimmunotherapy. In *Nuclear Medicine and Immunology*; Springer International Publishing: Cham, Switzerland, 2022; pp. 297–345.
135. Spiegel, J.Y.; Patel, S.; Muffly, L.; Hossain, N.M.; Oak, J.; Baird, J.H.; Frank, M.J.; Shiraz, P.; Sahaf, B.; Craig, J.; et al. CAR T Cells with Dual Targeting of CD19 and CD22 in Adult Patients with Recurrent or Refractory B Cell Malignancies: A Phase 1 Trial. *Nat. Med.* **2021**, *27*, 1419–1431. [[CrossRef](#)]
136. Schneider, D.; Xiong, Y.; Wu, D.; Hu, P.; Alabanza, L.; Steimle, B.; Mahmud, H.; Anthony-Gonda, K.; Krueger, W.; Zhu, Z.; et al. Trispecific CD19-CD20-CD22-Targeting DuoCAR-T Cells Eliminate Antigen-Heterogeneous B Cell Tumors in Preclinical Models. *Sci. Transl. Med.* **2021**, *13*, eabc6401. [[CrossRef](#)]
137. Dhillon, S. Moxetumomab Pasudotox: First Global Approval. *Drugs* **2018**, *78*, 1763–1767. [[CrossRef](#)]
138. Zamarin, D.; Hamid, O.; Nayak-Kapoor, A.; Sahebjam, S.; Sznol, M.; Collaku, A.; Fox, F.E.; Marshall, M.A.; Hong, D.S. Mogamulizumab in Combination with Durvalumab or Tremelimumab in Patients with Advanced Solid Tumors: A Phase I Study. *Clin. Cancer Res.* **2020**, *26*, 4531–4541. [[CrossRef](#)]
139. Yoshie, O.; Matsushima, K. CCR4 and Its Ligands: From Bench to Bedside. *Int. Immunol.* **2015**, *27*, 11–20. [[CrossRef](#)]
140. Marshall, L.A.; Marubayashi, S.; Jorapur, A.; Jacobson, S.; Zibinsky, M.; Robles, O.; Hu, D.X.; Jackson, J.J.; Pookot, D.; Sanchez, J.; et al. Tumors Establish Resistance to Immunotherapy by Regulating T Reg Recruitment via CCR4. *J. ImmunoTher. Cancer* **2020**, *8*, e000764. [[CrossRef](#)] [[PubMed](#)]
141. Ketcham, J.M.; Marshall, L.A.; Talay, O. CCR4 Antagonists Inhibit Treg Trafficking into the Tumor Microenvironment. *ACS Med. Chem. Lett.* **2018**, *9*, 953–955. [[CrossRef](#)] [[PubMed](#)]
142. Watanabe, M.; Kanao, K.; Suzuki, S.; Muramatsu, H.; Morinaga, S.; Kajikawa, K.; Kobayashi, I.; Nishikawa, G.; Kato, Y.; Zannami, K.; et al. Increased Infiltration of CCR4-Positive Regulatory T Cells in Prostate Cancer Tissue Is Associated with a Poor Prognosis. *Prostate* **2019**, *79*, 1658–1665. [[CrossRef](#)] [[PubMed](#)]
143. Nicolay, J.P.; Albrecht, J.D.; Alberti-Violetti, S.; Berti, E. CCR4 in Cutaneous T-Cell Lymphoma: Therapeutic Targeting of a Pathogenic Driver. *Eur. J. Immunol.* **2021**, *51*, 1660–1671. [[CrossRef](#)]
144. Hu, M.; Kang, G.; Cheng, X.; Wang, J.; Li, R.; Bai, Z.; Yang, D.; Huang, H. In Vitro Affinity Maturation to Improve the Efficacy of a Hypoxia-Inducible Factor 1 $\alpha$  Single-Domain Intrabody. *Biochem. Biophys. Res. Commun.* **2020**, *529*, 936–942. [[CrossRef](#)]
145. Zhao, H.; Bo, Q.; Wang, W.; Wang, R.; Li, Y.; Chen, S.; Xia, Y.; Wang, W.; Wang, Y.; Zhu, K.; et al. CCL17-CCR4 Axis Promotes Metastasis via ERK/MMP13 Pathway in Bladder Cancer. *J. Cell. Biochem.* **2019**, *120*, 1979–1989. [[CrossRef](#)]
146. Ling, Z.; Li, W.; Hu, J.; Li, Y.; Deng, M.; Zhang, S.; Ren, X.; Wu, T.; Xia, J.; Cheng, B.; et al. Targeting CCL2-CCR4 Axis Suppress Cell Migration of Head and Neck Squamous Cell Carcinoma. *Cell Death Dis.* **2022**, *13*, 158. [[CrossRef](#)]
147. Kohli, K.; Pillarisetty, V.G.; Kim, T.S. Key Chemokines Direct Migration of Immune Cells in Solid Tumors. *Cancer Gene Ther.* **2022**, *29*, 10–21. [[CrossRef](#)]
148. Shimizu, Y.; Koyasu, S.; Suzukida, M.; Izumi, K.; Kidera, E.; Shindo, T.; Saga, T.; Ono, M.; Takaori-Kondo, A.; Nakamoto, Y. Development of a Novel Indium-111 Radiolabeled Mogamulizumab Targeting CCR4 for Imaging Adult T-Cell Leukemia/Lymphoma in Vivo. *Ann. Nucl. Med.* **2022**, *36*, 319–326. [[CrossRef](#)]
149. Nazarenko, I.; Hede, S.M.; He, X.; Hedrén, A.; Thompson, J.; Lindström, M.S.; Nistér, M. PDGF and PDGF Receptors in Glioma. *Upsala J. Med. Sci.* **2012**, *117*, 99–112. [[CrossRef](#)]
150. Fletcher, C.D.M.; Berman, J.J.; Corless, C.; Gorstein, F.; Lasota, J.; Longley, B.J.; Miettinen, M.; O’Leary, T.J.; Remotti, H.; Rubin, B.P.; et al. Diagnosis of Gastrointestinal Stromal Tumors: A Consensus Approach. *Hum. Pathol.* **2002**, *33*, 459–465. [[CrossRef](#)]
151. Lemmon, M.A.; Schlessinger, J. Cell Signaling by Receptor Tyrosine Kinases. *Cell* **2010**, *141*, 1117–1134. [[CrossRef](#)]
152. Miettinen, M.; Lasota, J. Gastrointestinal Stromal Tumors: Review on Morphology, Molecular Pathology, Prognosis, and Differential Diagnosis. *Arch. Pathol. Lab. Med.* **2006**, *130*, 1466–1478. [[CrossRef](#)]
153. Lewis, B.P.; Burge, C.B.; Bartel, D.P. Conserved Seed Pairing, Often Flanked by Adenosines, Indicates That Thousands of Human Genes Are MicroRNA Targets. *Cell* **2005**, *120*, 15–20. [[CrossRef](#)]
154. Andrae, J.; Gallini, R.; Betsholtz, C. Role of Platelet-Derived Growth Factors in Physiology and Medicine. *Genes Dev.* **2008**, *22*, 1276–1312. [[CrossRef](#)]
155. Mavroidis, L.; Metaxa-Mariatou, V.; Papoudou-Bai, A.; Lampraki, A.M.; Kostadima, L.; Tsinokou, I.; Zarkavelis, G.; Papadaki, A.; Petrakis, D.; Gkoura, S.; et al. Comprehensive Molecular Screening by next Generation Sequencing Reveals a Distinctive Mutational Profile of KIT/PDGFR $\alpha$  Genes and Novel Genomic Alterations: Results from a 20-Year Cohort of Patients with GIST from North-Western Greece. *ESMO Open* **2018**, *3*, e000335. [[CrossRef](#)]
156. Chang, K.K.; Yoon, C.; Yi, B.C.; Tap, W.D.; Simon, M.C.; Yoon, S.S. Platelet-Derived Growth Factor Receptor- $\alpha$  and - $\beta$  Promote Cancer Stem Cell Phenotypes in Sarcomas. *Oncogenesis* **2018**, *7*, 47. [[CrossRef](#)]

157. Pantaleo, M.A.; Tarantino, G.; Agostinelli, C.; Urbini, M.; Nannini, M.; Saponara, M.; Castelli, C.; Stacchiotti, S.; Fumagalli, E.; Gatto, L.; et al. Immune Microenvironment Profiling of Gastrointestinal Stromal Tumors (GIST) Shows Gene Expression Patterns Associated to Immune Checkpoint Inhibitors Response. *OncolImmunology* **2019**, *8*, e1617588. [[CrossRef](#)]
158. Wang, J.; Cui, R.; Clement, C.G.; Nawgiri, R.; Powell, D.W.; Pinchuk, I.V.; Watts, T.L. Activation PDGFR- $\alpha$ /AKT Mediated Signaling Pathways in Oral Squamous Cell Carcinoma by Mesenchymal Stem/Stromal Cells Promotes Anti-Apoptosis and Decreased Sensitivity to Cisplatin. *Front. Oncol.* **2020**, *10*, 552. [[CrossRef](#)]
159. Maleddu, A.; Pantaleo, M.A.; Nannini, M.; Biasco, G. The Role of Mutational Analysis of KIT and PDGFRA in Gastrointestinal Stromal Tumors in a Clinical Setting. *J. Transl. Med.* **2011**, *9*, 75. [[CrossRef](#)]
160. Poveda, A.; García del Muro, X.; López-Guerrero, J.A.; Cubedo, R.; Martínez, V.; Romero, I.; Serrano, C.; Valverde, C.; Martín-Broto, J. GEIS Guidelines for Gastrointestinal Sarcomas (GIST). *Cancer Treat. Rev.* **2017**, *55*, 107–119. [[CrossRef](#)] [[PubMed](#)]
161. Verhaak, R.G.W.; Hoadley, K.A.; Purdom, E.; Wang, V.; Qi, Y.; Wilkerson, M.D.; Miller, C.R.; Ding, L.; Golub, T.; Mesirov, J.P.; et al. Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell* **2010**, *17*, 98–110. [[CrossRef](#)] [[PubMed](#)]
162. Wozniak, A.; Rutkowski, P.; Piskorz, A.; Ciwoniuk, M.; Osuch, C.; Bylina, E.; Sygut, J.; Chosia, M.; Rys, J.; Urbanczyk, K.; et al. Prognostic Value of KIT/PDGFR Mutations in Gastrointestinal Stromal Tumours (GIST): Polish Clinical GIST Registry Experience. *Ann. Oncol.* **2012**, *23*, 353–360. [[CrossRef](#)]
163. Shi, L.; Chen, H.; Qin, Y.-Y.; Gan, T.-Q.; Wei, K.-L. Clinical and Biologic Roles of PDGFRA in Papillary Thyroid Cancer: A Study Based on Immunohistochemical and in Vitro Analyses. *Int. J. Clin. Exp. Pathol.* **2020**, *13*, 1094–1107. [[PubMed](#)]
164. Lin, C.-L.; Tsai, M.-L.; Chen, Y.-H.; Liu, W.-N.; Lin, C.-Y.; Hsu, K.-W.; Huang, C.-Y.; Chang, Y.-J.; Wei, P.-L.; Chen, S.-H.; et al. Platelet-Derived Growth Factor Receptor- $\alpha$  Subunit Targeting Suppresses Metastasis in Advanced Thyroid Cancer In Vitro and In Vivo. *Biomol. Ther.* **2021**, *29*, 551–561. [[CrossRef](#)]
165. Gonzáles, M.F.; Islas, A.E. Receptor SLAMF7 Asociado a Cáncer. *Alianzas Y Tend.-BUAP* **2019**, *4*, 15–21.
166. Detre, C.; Keszei, M.; Romero, X.; Tsokos, G.C.; Terhorst, C. SLAM Family Receptors and the SLAM-Associated Protein (SAP) Modulate T Cell Functions. *Semin. Immunopathol.* **2010**, *32*, 157–171. [[CrossRef](#)]
167. Cannons, J.L.; Tangye, S.G.; Schwartzberg, P.L. SLAM Family Receptors and SAP Adaptors in Immunity. *Annu. Rev. Immunol.* **2011**, *29*, 665–705. [[CrossRef](#)]
168. Pérez-Quintero, L.-A.; Roncagalli, R.; Guo, H.; Latour, S.; Davidson, D.; Veillette, A. EAT-2, a SAP-like Adaptor, Controls NK Cell Activation through Phospholipase C $\gamma$ , Ca<sup>++</sup>, and Erk, Leading to Granule Polarization. *J. Exp. Med.* **2014**, *211*, 727–742. [[CrossRef](#)]
169. Gutierrez-Guerrero, A.; Mancilla-Herrera, I.; Maravillas-Montero, J.L.; Martinez-Duncker, I.; Veillette, A.; Cruz-Munoz, M.E. SLAMF7 Selectively Favors Degranulation to Promote Cytotoxicity in Human NK Cells. *Eur. J. Immunol.* **2022**, *52*, 62–74. [[CrossRef](#)]
170. Cruz-Munoz, M.-E.; Dong, Z.; Shi, X.; Zhang, S.; Veillette, A. Influence of CRACC, a SLAM Family Receptor Coupled to the Adaptor EAT-2, on Natural Killer Cell Function. *Nat. Immunol.* **2009**, *10*, 297–305. [[CrossRef](#)]
171. O’Connell, P.; Hyslop, S.; Blake, M.K.; Godbehere, S.; Amalfitano, A.; Aldhamen, Y.A. SLAMF7 Signaling Reprograms T Cells toward Exhaustion in the Tumor Microenvironment. *J. Immunol.* **2021**, *206*, 193–205. [[CrossRef](#)]
172. Zamagni, E.; Tacchetti, P.; Pantani, L.; Cavo, M. Anti-CD38 and Anti-SLAMF7: The Future of Myeloma Immunotherapy. *Expert Rev. Hematol.* **2018**, *11*, 423–435. [[CrossRef](#)]
173. Araldi, R.P.; Prezoto, B.C.; Gonzaga, V.; Policiquio, B.; Mendes, T.B.; D’Amélio, F.; Vigerelli, H.; Viana, M.; Valverde, C.W.; Pagani, E.; et al. Advanced Cell Therapy with Low Tissue Factor Loaded Product NestaCell<sup>®</sup> Does Not Confer Thrombotic Risk for Critically Ill COVID-19 Heparin-Treated Patients. *Biomed. Pharmacother.* **2022**, *149*, 112920. [[CrossRef](#)]
174. Gao, Q.; Chen, Z.; He, Y.; Hou, Z.; Ye, R.; Xue, W.; Lin, J.; Tu, X. CD142 Plays an Important Role in the Mobility of Colorectal Cancer Cells. *Biosci. Biotechnol. Biochem.* **2020**, *84*, 1856–1860. [[CrossRef](#)]
175. Xu, W.; Chen, B.; Ke, D.; Chen, X. CD142 Plays a Key Role in the Carcinogenesis of Gastric Adenocarcinoma by Inhibiting BCL2-Dependent Autophagy. *Biochem. Cell Biol.* **2022**, *100*, 17–27. [[CrossRef](#)]
176. Arderiu, G.; Peña, E.; Aledo, R.; Juan-Babot, O.; Badimon, L. Tissue Factor Regulates Microvessel Formation and Stabilization by Induction of Chemokine (C-C Motif) Ligand 2 Expression. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 2607–2615. [[CrossRef](#)]
177. Queiroz, K.C.S.; van’t Veer, C.; van den Berg, Y.; Duitman, J.; Versteeg, H.H.; Abernethy, H.L.; Groot, A.P.; Verstege, M.I.; Roelofs, J.J.T.H.; te Velde, A.A.; et al. Tissue Factor-Dependent Chemokine Production Aggravates Experimental Colitis. *Mol. Med.* **2011**, *17*, 1119–1126. [[CrossRef](#)]
178. Chanakira, A.; Westmark, P.R.; Ong, I.M.; Sheehan, J.P. Tissue Factor-Factor VIIa Complex Triggers Protease Activated Receptor 2-Dependent Growth Factor Release and Migration in Ovarian Cancer. *Gynecol. Oncol.* **2017**, *145*, 167–175. [[CrossRef](#)]
179. Bhanvadia, R.R.; VanOpstall, C.; Brechka, H.; Barashi, N.S.; Gillard, M.; McAuley, E.M.; Vasquez, J.M.; Paner, G.; Chan, W.-C.; Andrade, J.; et al. MEIS1 and MEIS2 Expression and Prostate Cancer Progression: A Role For HOXB13 Binding Partners in Metastatic Disease. *Clin. Cancer Res.* **2018**, *24*, 3668–3680. [[CrossRef](#)]
180. Pasquier, J.; Thomas, B.; Hoarau-Véchet, J.; Odeh, T.; Robay, A.; Chidiac, O.; Dargham, S.R.; Turjoman, R.; Halama, A.; Fakhro, K.; et al. Circulating Microparticles in Acute Diabetic Charcot Foot Exhibit a High Content of Inflammatory Cytokines, and Support Monocyte-to-Osteoclast Cell Induction. *Sci. Rep.* **2017**, *7*, 16450. [[CrossRef](#)] [[PubMed](#)]

181. Stojkovic, S.; Kaun, C.; Basilio, J.; Rauscher, S.; Hell, L.; Krychtiuk, K.A.; Bonstingl, C.; de Martin, R.; Gröger, M.; Ay, C.; et al. Tissue Factor Is Induced by Interleukin-33 in Human Endothelial Cells: A New Link between Coagulation and Inflammation. *Sci. Rep.* **2016**, *6*, 25171. [[CrossRef](#)] [[PubMed](#)]
182. Holnthoner, W.; Bonstingl, C.; Hromada, C.; Muehleder, S.; Zipperle, J.; Stojkovic, S.; Redl, H.; Wojta, J.; Schöchl, H.; Grillari, J.; et al. Endothelial Cell-Derived Extracellular Vesicles Size-Dependently Exert Procoagulant Activity Detected by Thromboelastometry. *Sci. Rep.* **2017**, *7*, 3707. [[CrossRef](#)] [[PubMed](#)]
183. Markham, A. Tisotumab Vedotin: First Approval. *Drugs* **2021**, *81*, 2141–2147. [[CrossRef](#)]
184. Liu, J.-N.; Kong, X.-S.; Huang, T.; Wang, R.; Li, W.; Chen, Q.-F. Clinical Implications of Aberrant PD-1 and CTLA4 Expression for Cancer Immunity and Prognosis: A Pan-Cancer Study. *Front. Immunol.* **2020**, *11*, 2048. [[CrossRef](#)]
185. Xu, F.; Jin, T.; Zhu, Y.; Dai, C. Immune Checkpoint Therapy in Liver Cancer. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 110. [[CrossRef](#)]
186. Buchbinder, E.I.; Desai, A. CTLA-4 and PD-1 Pathways. *Am. J. Clin. Oncol.* **2016**, *39*, 98–106. [[CrossRef](#)]
187. Zhang, H.; Dai, Z.; Wu, W.; Wang, Z.; Zhang, N.; Zhang, L.; Zeng, W.-J.; Liu, Z.; Cheng, Q. Regulatory Mechanisms of Immune Checkpoints PD-L1 and CTLA-4 in Cancer. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 184. [[CrossRef](#)]
188. Rowshanravan, B.; Halliday, N.; Sansom, D.M. CTLA-4: A Moving Target in Immunotherapy. *Blood* **2018**, *131*, 58–67. [[CrossRef](#)]
189. Pai, C.-C.S.; Simons, D.M.; Lu, X.; Evans, M.; Wei, J.; Wang, Y.; Chen, M.; Huang, J.; Park, C.; Chang, A.; et al. Tumor-Conditional Anti-CTLA4 Uncouples Antitumor Efficacy from Immunotherapy-Related Toxicity. *J. Clin. Investig.* **2018**, *129*, 349–363. [[CrossRef](#)]
190. Rotte, A. Combination of CTLA-4 and PD-1 Blockers for Treatment of Cancer. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 255. [[CrossRef](#)]
191. Carreau, N.A.; Pavlick, A.C. Nivolumab and Ipilimumab: Immunotherapy for Treatment of Malignant Melanoma. *Future Oncol.* **2019**, *15*, 349–358. [[CrossRef](#)]
192. Shitara, K.; Ajani, J.A.; Moehler, M.; Garrido, M.; Gallardo, C.; Shen, L.; Yamaguchi, K.; Wyrwicz, L.; Skoczytas, T.; Bragagnoli, A.C.; et al. Nivolumab plus Chemotherapy or Ipilimumab in Gastro-Oesophageal Cancer. *Nature* **2022**, *603*, 942–948. [[CrossRef](#)]
193. Overman, M.J.; Lonardi, S.; Wong, K.Y.M.; Lenz, H.-J.; Gelsomino, F.; Aglietta, M.; Morse, M.A.; Van Cutsem, E.; McDermott, R.; Hill, A.; et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer. *J. Clin. Oncol.* **2018**, *36*, 773–779. [[CrossRef](#)]
194. Owonikoko, T.K.; Park, K.; Govindan, R.; Ready, N.; Reck, M.; Peters, S.; Dakhil, S.R.; Navarro, A.; Rodríguez-Cid, J.; Schenker, M.; et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: Check-Mate 451. *J. Clin. Oncol.* **2021**, *39*, 1349–1359. [[CrossRef](#)]
195. Tremelimumab. *Drugs RD* **2010**, *10*, 123–132. [[CrossRef](#)]
196. Ricard-Blum, S. The Collagen Family. *Cold Spring Harb. Perspect. Biol.* **2011**, *3*, a004978. [[CrossRef](#)]
197. Nallanthighal, S.; Heiserman, J.P.; Cheon, D.-J. Collagen Type XI Alpha 1 (COL11A1): A Novel Biomarker and a Key Player in Cancer. *Cancers* **2021**, *13*, 935. [[CrossRef](#)]
198. Kadler, K.E.; Hill, A.; Canty-Laird, E.G. Collagen Fibrillogenesis: Fibronectin, Integrins, and Minor Collagens as Organizers and Nucleators. *Curr. Opin. Cell Biol.* **2008**, *20*, 495–501. [[CrossRef](#)]
199. Morris, N.P.; Bächinger, H.P. Type XI Collagen Is a Heterotrimer with the Composition (1 Alpha, 2 Alpha, 3 Alpha) Retaining Non-Triple-Helical Domains. *J. Biol. Chem.* **1987**, *262*, 11345–11350. [[CrossRef](#)]
200. Yoshioka, H.; Inoguchi, K.; Khaleduzzaman, M.; Ninomiya, Y.; Andrikopoulos, K.; Ramirez, F. Coding Sequence and Alternative Splicing of the Mouse A1(XI) Collagen Gene (Col11a1). *Genomics* **1995**, *28*, 337–340. [[CrossRef](#)] [[PubMed](#)]
201. Luo, Y.Y.; Karsdal, M.A. Type XI Collagen. In *Biochemistry of Collagens, Laminins and Elastin*; Elsevier: Amsterdam, The Netherlands, 2016; pp. 77–80.
202. Vázquez-Villa, F.; García-Ocaña, M.; Galván, J.A.; García-Martínez, J.; García-Pravia, C.; Menéndez-Rodríguez, P.; Rey, C.G.; Barneo-Serra, L.; de los Toyos, J.R. COL11A1/(pro)Collagen 11A1 Expression Is a Remarkable Biomarker of Human Invasive Carcinoma-Associated Stromal Cells and Carcinoma Progression. *Tumor Biol.* **2015**, *36*, 2213–2222. [[CrossRef](#)] [[PubMed](#)]
203. Tu, H.; Li, J.; Lin, L.; Wang, L. COL11A1 Was Involved in Cell Proliferation, Apoptosis and Migration in Non-Small Cell Lung Cancer Cells. *J. Investig. Surg.* **2021**, *34*, 664–669. [[CrossRef](#)] [[PubMed](#)]
204. Liu, Z.; Lai, J.; Jiang, H.; Ma, C.; Huang, H. Collagen XI Alpha 1 Chain, a Potential Therapeutic Target for Cancer. *FASEB J.* **2021**, *35*, e21603. [[CrossRef](#)]
205. Wu, Y.-H.; Chang, T.-H.; Huang, Y.-F.; Huang, H.-D.; Chou, C.-Y. COL11A1 Promotes Tumor Progression and Predicts Poor Clinical Outcome in Ovarian Cancer. *Oncogene* **2014**, *33*, 3432–3440. [[CrossRef](#)]
206. Giussani, M.; Landoni, E.; Merlino, G.; Turdo, F.; Veneroni, S.; Paolini, B.; Cappelletti, V.; Miceli, R.; Orlandi, R.; Triulzi, T.; et al. Extracellular Matrix Proteins as Diagnostic Markers of Breast Carcinoma. *J. Cell. Physiol.* **2018**, *233*, 6280–6290. [[CrossRef](#)]
207. Zhang, J.; Dong, R.; Shen, L. Evaluation and Reflection on Claudin 18.2 Targeting Therapy in Advanced Gastric Cancer. *Chin. J. Cancer Res.* **2020**, *32*, 263–270. [[CrossRef](#)]
208. Sweerus, K.; Lachowicz-Scroggins, M.; Gordon, E.; LaFemina, M.; Huang, X.; Parikh, M.; Kanegai, C.; Fahy, J.V.; Frank, J.A. Claudin-18 Deficiency Is Associated with Airway Epithelial Barrier Dysfunction and Asthma. *J. Allergy Clin. Immunol.* **2017**, *139*, 72–81.e1. [[CrossRef](#)]
209. Kojima, T.; Kyuno, D.; Sawada, N. Targeting Claudin-4 in Human Pancreatic Cancer. *Expert Opin. Ther. Targets* **2012**, *16*, 881–887. [[CrossRef](#)]

210. Kotton, D.N. Claudin-18: Unexpected Regulator of Lung Alveolar Epithelial Cell Proliferation. *J. Clin. Investig.* **2018**, *128*, 903–905. [[CrossRef](#)]
211. Athauda, A.; Chau, I. Claudin 18.2—A FAST-Moving Target in Gastric Cancer? *Ann. Oncol.* **2021**, *32*, 584–586. [[CrossRef](#)]
212. Hollande, F.; Blanc, E.M.; Bali, J.P.; Whitehead, R.H.; Pelegrin, A.; Baldwin, G.S.; Choquet, A. HGF Regulates Tight Junctions in New Nontumorigenic Gastric Epithelial Cell Line. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2001**, *280*, G910–G921. [[CrossRef](#)]
213. Hong, J.Y.; An, J.Y.; Lee, J.; Park, S.H.; Park, J.O.; Park, Y.S.; Lim, H.Y.; Kim, K.-M.; Kang, W.K.; Kim, S.T. Claudin 18.2 Expression in Various Tumor Types and Its Role as a Potential Target in Advanced Gastric Cancer. *Transl. Cancer Res.* **2020**, *9*, 3367–3374. [[CrossRef](#)]
214. Yang, J.; Liu, Z.; Zeng, B.; Hu, G.; Gan, R. Epstein–Barr Virus-Associated Gastric Cancer: A Distinct Subtype. *Cancer Lett.* **2020**, *495*, 191–199. [[CrossRef](#)]
215. Dottermusch, M.; Krüger, S.; Behrens, H.-M.; Halske, C.; Röcken, C. Expression of the Potential Therapeutic Target Claudin-18.2 Is Frequently Decreased in Gastric Cancer: Results from a Large Caucasian Cohort Study. *Virchows Arch.* **2019**, *475*, 563–571. [[CrossRef](#)]
216. Oue, N.; Sentani, K.; Sakamoto, N.; Yasui, W. Clinicopathologic and Molecular Characteristics of Gastric Cancer Showing Gastric and Intestinal Mucin Phenotype. *Cancer Sci.* **2015**, *106*, 951–958. [[CrossRef](#)]
217. Bednarz-Misa, I.; Fortuna, P.; Diakowska, D.; Jamrozik, N.; Krzystek-Korpacka, M. Distinct Local and Systemic Molecular Signatures in the Esophageal and Gastric Cancers: Possible Therapy Targets and Biomarkers for Gastric Cancer. *Int. J. Mol. Sci.* **2020**, *21*, 4509. [[CrossRef](#)]
218. Sahin, U.; Schuler, M.; Richly, H.; Bauer, S.; Krilova, A.; Dechow, T.; Jerling, M.; Utsch, M.; Rohde, C.; Dhaene, K.; et al. A Phase I Dose-Escalation Study of IMAB362 (Zolbetuximab) in Patients with Advanced Gastric and Gastro-Oesophageal Junction Cancer. *Eur. J. Cancer* **2018**, *100*, 17–26. [[CrossRef](#)]
219. Türeci, O.; Sahin, U.; Schulze-Bergkamen, H.; Zvirbulė, Z.; Lordick, F.; Koeberle, D.; Thuss-Patience, P.; Ettrich, T.; Arnold, D.; Bassermann, F.; et al. A Multicentre, Phase IIa Study of Zolbetuximab as a Single Agent in Patients with Recurrent or Refractory Advanced Adenocarcinoma of the Stomach or Lower Oesophagus: The MONO Study. *Ann. Oncol.* **2019**, *30*, 1487–1495. [[CrossRef](#)]
220. Sahin, U.; Türeci, Ö.; Manikhas, G.; Lordick, F.; Rusyn, A.; Vynnychenko, I.; Dudov, A.; Bazin, I.; Bondarenko, I.; Melichar, B.; et al. FAST: A Randomised Phase II Study of Zolbetuximab (IMAB362) plus EOX versus EOX Alone for First-Line Treatment of Advanced CLDN18.2-Positive Gastric and Gastro-Oesophageal Adenocarcinoma. *Ann. Oncol.* **2021**, *32*, 609–619. [[CrossRef](#)]
221. Horta, E.; Bongiorno, C.; Ezzeddine, M.; Neil, E.C. Neurotoxicity of Antibodies in Cancer Therapy: A Review. *Clin. Neurol. Neurosurg.* **2020**, *188*, 105566. [[CrossRef](#)] [[PubMed](#)]
222. Minor, M.; Alcedo, K.P.; Battaglia, R.A.; Snider, N.T. Cell Type- and Tissue-Specific Functions of Ecto-5'-Nucleotidase (CD73). *Am. J. Physiol.-Cell Physiol.* **2019**, *317*, C1079–C1092. [[CrossRef](#)] [[PubMed](#)]
223. Chen, Q.; Pu, N.; Yin, H.; Zhang, J.; Zhao, G.; Lou, W.; Wu, W. CD73 Acts as a Prognostic Biomarker and Promotes Progression and Immune Escape in Pancreatic Cancer. *J. Cell. Mol. Med.* **2020**, *24*, 8674–8686. [[CrossRef](#)] [[PubMed](#)]
224. Ghalamfarsa, G.; Kazemi, M.H.; Raoofi Mohseni, S.; Masjedi, A.; Hojjat-Farsangi, M.; Azizi, G.; Yousefi, M.; Jadidi-Niaragh, F. CD73 as a Potential Opportunity for Cancer Immunotherapy. *Expert Opin. Ther. Targets* **2019**, *23*, 127–142. [[CrossRef](#)] [[PubMed](#)]
225. Roh, M.; Wainwright, D.A.; Wu, J.D.; Wan, Y.; Zhang, B. Targeting CD73 to Augment Cancer Immunotherapy. *Curr. Opin. Pharmacol.* **2020**, *53*, 66–76. [[CrossRef](#)]
226. Borea, P.A.; Gessi, S.; Merighi, S.; Vincenzi, F.; Varani, K. Pharmacology of Adenosine Receptors: The State of the Art. *Physiol. Rev.* **2018**, *98*, 1591–1625. [[CrossRef](#)]
227. Hay, C.M.; Sult, E.; Huang, Q.; Mulgrew, K.; Fuhrmann, S.R.; McGlinchey, K.A.; Hammond, S.A.; Rothstein, R.; Rios-Doria, J.; Poon, E.; et al. Targeting CD73 in the Tumor Microenvironment with MEDI9447. *OncImmunology* **2016**, *5*, e1208875. [[CrossRef](#)]
228. Perrot, I.; Michaud, H.-A.; Giraudon-Paoli, M.; Augier, S.; Docquier, A.; Gros, L.; Courtois, R.; Déjou, C.; Jecko, D.; Becquart, O.; et al. Blocking Antibodies Targeting the CD39/CD73 Immunosuppressive Pathway Unleash Immune Responses in Combination Cancer Therapies. *Cell Rep.* **2019**, *27*, 2411–2425.e9. [[CrossRef](#)]
229. Samanta, D.; Park, Y.; Ni, X.; Li, H.; Zahnow, C.A.; Gabrielson, E.; Pan, F.; Semenza, G.L. Chemotherapy Induces Enrichment of CD47<sup>+</sup>/CD73<sup>+</sup>/PDL1<sup>+</sup> Immune Evasive Triple-Negative Breast Cancer Cells. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E1239–E1248. [[CrossRef](#)]
230. Chapoval, A.I.; Ni, J.; Lau, J.S.; Wilcox, R.A.; Flies, D.B.; Liu, D.; Dong, H.; Sica, G.L.; Zhu, G.; Tamada, K.; et al. B7-H3: A Costimulatory Molecule for T Cell Activation and IFN- $\gamma$  Production. *Nat. Immunol.* **2001**, *2*, 269–274. [[CrossRef](#)]
231. Liu, J.; Yang, S.; Cao, B.; Zhou, G.; Zhang, F.; Wang, Y.; Wang, R.; Zhu, L.; Meng, Y.; Hu, C.; et al. Targeting B7-H3 via Chimeric Antigen Receptor T Cells and Bispecific Killer Cell Engagers Augments Antitumor Response of Cytotoxic Lymphocytes. *J. Hematol. Oncol.* **2021**, *14*, 21. [[CrossRef](#)]
232. Feng, R.; Chen, Y.; Liu, Y.; Zhou, Q.; Zhang, W. The Role of B7-H3 in Tumors and Its Potential in Clinical Application. *Int. Immunopharmacol.* **2021**, *101*, 108153. [[CrossRef](#)]
233. Picarda, E.; Galbo, P.M.; Zong, H.; Rajan, M.R.; Wallenius, V.; Zheng, D.; Börgeson, E.; Singh, R.; Pessin, J.; Zang, X. The Immune Checkpoint B7-H3 (CD276) Regulates Adipocyte Progenitor Metabolism and Obesity Development. *Sci. Adv.* **2022**, *8*, eabm7012. [[CrossRef](#)]

234. MacGregor, H.L.; Sayad, A.; Elia, A.; Wang, B.X.; Katz, S.R.; Shaw, P.A.; Clarke, B.A.; Crome, S.Q.; Robert-Tissot, C.; Bernardini, M.Q.; et al. High Expression of B7-H3 on Stromal Cells Defines Tumor and Stromal Compartments in Epithelial Ovarian Cancer and Is Associated with Limited Immune Activation. *J. ImmunoTher. Cancer* **2019**, *7*, 357. [CrossRef]
235. Han, S.; Wang, Y.; Shi, X.; Zong, L.; Liu, L.; Zhang, J.; Qian, Q.; Jin, J.; Ma, Y.; Cui, B.; et al. Negative Roles of B7-H3 and B7-H4 in the Microenvironment of Cervical Cancer. *Exp. Cell Res.* **2018**, *371*, 222–230. [CrossRef]
236. Hu, X.; Xu, M.; Hu, Y.; Li, N.; Zhou, L. B7-H3, Negatively Regulated by MiR-128, Promotes Colorectal Cancer Cell Proliferation and Migration. *Cell Biochem. Biophys.* **2021**, *79*, 397–405. [CrossRef]
237. Zhou, W.T.; Jin, W.L. B7-H3/CD276: An Emerging Cancer Immunotherapy. *Front. Immunol.* **2021**, *12*, 701006. [CrossRef]
238. Zhang, H.; Zhang, J.; Li, C.; Xu, H.; Dong, R.; Chen, C.C.; Hua, W. Survival Association and Cell Cycle Effects of B7H3 in Neuroblastoma. *J. Korean Neurosurg. Soc.* **2020**, *63*, 707–716. [CrossRef]
239. Flem-Karlsen, K.; Fodstad, Ø.; Tan, M.; Nunes-Xavier, C.E. B7-H3 in Cancer—Beyond Immune Regulation. *Trends Cancer* **2018**, *4*, 401–404. [CrossRef]
240. Yang, S.; Wei, W.; Zhao, Q. B7-H3, a Checkpoint Molecule, as a Target for Cancer Immunotherapy. *Int. J. Biol. Sci.* **2020**, *16*, 1767–1773. [CrossRef]
241. Li, G.; Quan, Y.; Che, F.; Wang, L. B7-H3 in Tumors: Friend or Foe for Tumor Immunity? *Cancer Chemother. Pharmacol.* **2018**, *81*, 245–253. [CrossRef] [PubMed]
242. Memorial Sloan Kettering Cancer Center. MSK Kids–Neuroblastoma Treatments. Available online: <https://www.mskcc.org/pediatrics/cancer-care/types/neuroblastoma/treatment> (accessed on 13 July 2023).
243. McCormick, S.M.; Heller, N.M. Commentary: IL-4 and IL-13 Receptors and Signaling. *Cytokine* **2015**, *75*, 38–50. [CrossRef] [PubMed]
244. Junttila, I.S. Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes. *Front. Immunol.* **2018**, *9*, 888. [CrossRef] [PubMed]
245. Gandhi, N.A.; Pirozzi, G.; Graham, N.M.H. Commonality of the IL-4/IL-13 Pathway in Atopic Diseases. *Expert Rev. Clin. Immunol.* **2017**, *13*, 425–437. [CrossRef]
246. Zhang, Y.; Li, C.; Zhang, M.; Li, Z. IL-13 and IL-13R $\alpha$ 1 Are Overexpressed in Extranodal Natural Killer/T Cell Lymphoma and Mediate Tumor Cell Proliferation. *Biochem. Biophys. Res. Commun.* **2018**, *503*, 2715–2720. [CrossRef]
247. Suzuki, A.; Leland, P.; Joshi, B.H.; Puri, R.K. Targeting of IL-4 and IL-13 Receptors for Cancer Therapy. *Cytokine* **2015**, *75*, 79–88. [CrossRef]
248. Song, X.; Traub, B.; Shi, J.; Kornmann, M. Possible Roles of Interleukin-4 and -13 and Their Receptors in Gastric and Colon Cancer. *Int. J. Mol. Sci.* **2021**, *22*, 727. [CrossRef]
249. Jaén, M.; Martín-Regalado, Á.; Bartolomé, R.A.; Robles, J.; Casal, J.I. Interleukin 13 Receptor Alpha 2 (IL13R $\alpha$ 2): Expression, Signaling Pathways and Therapeutic Applications in Cancer. *Biochim. Biophys. Acta BBA- Rev. Cancer* **2022**, *1877*, 188802. [CrossRef]
250. Kornmann, M.; Kleeff, J.; Debinski, W.; Korc, M. Pancreatic Cancer Cells Express Interleukin-13 and -4 Receptors, and Their Growth Is Inhibited by Pseudomonas Exotoxin Coupled to Interleukin-13 and -4. *Anticancer. Res.* **1999**, *19*, 125–131.
251. Geng, B.; Pan, J.; Zhao, T.; Ji, J.; Zhang, C.; Che, Y.; Yang, J.; Shi, H.; Li, J.; Zhou, H.; et al. Chitinase 3-like 1-CD44 Interaction Promotes Metastasis and Epithelial-to-Mesenchymal Transition through  $\beta$ -Catenin/Erk/Akt Signaling in Gastric Cancer. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 208. [CrossRef]
252. Chen, Y.; Zhang, S.; Wang, Q.; Zhang, X. Tumor-Recruited M2 Macrophages Promote Gastric and Breast Cancer Metastasis via M2 Macrophage-Secreted CHI3L1 Protein. *J. Hematol. Oncol.* **2017**, *10*, 36. [CrossRef]
253. Lin, C.; Liu, H.; Zhang, H.; He, H.; Li, H.; Shen, Z.; Qin, J.; Qin, X.; Xu, J.; Sun, Y. Interleukin-13 Receptor A2 Is Associated with Poor Prognosis in Patients with Gastric Cancer after Gastrectomy. *Oncotarget* **2016**, *7*, 49281–49288. [CrossRef]
254. Manso, T.; Kushwaha, A.; Abdollahi, N.; Duroux, P.; Giudicelli, V.; Kossida, S. Mechanisms of Action of Monoclonal Antibodies in Oncology Integrated in IMGT/MAB-DB. *Front. Immunol.* **2023**, *14*, 1129323. [CrossRef]
255. O'Mahony, D.; Bishop, M. Monoclonal Antibody Therapy. *Front. Biosci.* **2006**, *11*, 1620–1635. [CrossRef]
256. Saldarriaga-Valiente, T. Monoclonal Antibodies: Mechanisms of Actions. *Diagnostico* **2021**, *60*, 213–217. [CrossRef]
257. Baltazar, E.; Christen, G. Conjugados Anticuerpo-Farmaco: El Estado de Arte. *Rev. Mex. De Cienc. Farm.* **2011**, *42*, 7–16.
258. Fu, Z.; Li, S.; Han, S.; Shi, C.; Zhang, Y. Antibody Drug Conjugate: The “Biological Missile” for Targeted Cancer Therapy. *Signal Transduct. Target. Ther.* **2022**, *7*, 93. [CrossRef]
259. Tsao, L.; Force, J.; Hartman, Z. Mechanisms of Therapeutic Antitumor Monoclonal Antibodies. *Cancer Res.* **2021**, *81*, 4641–4651. [CrossRef]
260. Rodríguez-Nava, C.; Ortuño-Pineda, C.; Illades-Aguilar, B.; Flores-Alfaro, E.; Leyva-Vázquez, M.; Parra-Rojas, I.; Moral-Hernández, O.; Vences-Velázquez, A.; Cortés-Sarabia, K.; Alarcón-Romero, O. Mechanisms of Action and Limitations of Monoclonal Antibodies and Single Chain Fragment Variable (ScFv) in the Treatment of Cancer. *Biomedicines* **2023**, *11*, 1610. [CrossRef]
261. Jin, S.; Sun, Y.; Liang, X.; Gu, X.; Ning, J.; Xu, Y.; Chen, S.; Pan, L. Emerging New Therapeutic Antibody Derivatives for Cancer Treatment. *Nature* **2022**, *7*, 39. [CrossRef]
262. Bayer, V. An Overview of Monoclonal Antibodies. *Semin. Oncol. Nurs.* **2019**, *35*, 15092. [CrossRef] [PubMed]

263. Redman, J.; Hill, E.; AlDeghaither, D.; Weiner, L. Mechanisms of Action of Therapeutic Antibodies for Cancer. *Mol. Immunol.* **2015**, *67*, 28–45. [[CrossRef](#)] [[PubMed](#)]
264. Zhou, Y.; Marks, J. Mechanism of Action for Therapeutic Antibodies. In *Biosimilars of Monoclonal Antibodies: A Practical Guide to Manufacturing, Preclinical, and Clinical Development*; Wiley: New York, NY, USA, 2016.
265. Weiner, G. Monoclonal Antibody Mechanisms of Action in Cancer. *Immunol. Res.* **2007**, *39*, 271–278. [[CrossRef](#)] [[PubMed](#)]
266. Yip, H.; Papa, A. Signaling Pathways in Cancer: Therapeutic Targets, Combinatorial Treatments, and New Developments. *Cells* **2021**, *10*, 659. [[CrossRef](#)]
267. Mezynski, M.; Farrelly, A.; Cremona, M.; Carr, A.; Morgan, C.; Workman, J.; Armstrong, P.; McAuley, J.; Madden, S.; Fay, J.; et al. Targeting the PI3K and MAPK Pathways to Improve Response to HER2-Targeted Therapies in HER2-Positive Gastric Cancer. *J. Transl. Med.* **2021**, *19*, 184. [[CrossRef](#)]
268. Costa, R.; Czerniecki, B. Clinical Development of Immunotherapies for HER2<sup>+</sup> Breast Cancer: A Review of HER2-Directed Monoclonal Antibodies and Beyond. *NPJ Breast Cancer* **2020**, *6*, 10. [[CrossRef](#)]
269. Min, H.; Lee, H. Molecular Targeted Therapy for Anticancer Treatment. *Exp. Mol. Med.* **2022**, *54*, 1670–1694. [[CrossRef](#)]
270. Li, X.; Shao, C.; Shi, Y.; Han, W. Lessons Learned from the Blockade of Immune Checkpoints in Cancer Immunotherapy. *J. Hematol. Oncol.* **2018**, *11*, 31. [[CrossRef](#)]
271. Forthal, D.; Finzi, A. Antibody-Dependent Cellular Cytotoxicity (ADCC) in HIV Infection. *AIDS* **2018**, *32*, 2439–2451. [[CrossRef](#)]
272. Tay, M.; Wuihe, K.; Pollara, J. Antibody-Dependent Cellular Phagocytosis in Antiviral Immune Responses. *Front. Immunol.* **2019**, *10*, 332. [[CrossRef](#)]
273. Mortensen, S.A.; Sander, B.; Jensen, R.K.; Pedersen, J.S.; Golas, M.M.; Jensenius, J.C. Structure and Activation of C1, the Complex Initiating the Classical Pathway of the Complement Cascade. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 986–991. [[CrossRef](#)]
274. Fishelson, Z.; Kirschfink, M. Complement C5b-9 and Cancer: Mechanisms of Cell Damage, Cancer Counteractions, and Approaches for Intervention. *Front. Immunol.* **2019**, *10*, 752. [[CrossRef](#)]
275. Natsume, A.; Niwa, R.; Satoh, M. Improving Effector Functions of Antibodies for Cancer Treatment: Enhancing ADCC and CDC. *Drug Des. Dev. Ther.* **2009**, *3*, 7–16. [[CrossRef](#)]
276. Zhang, J.; Woods, C.; He, F.; Han, H.; Treuheit, M.; Volkin, D. Structural Changes and Aggregation Mechanisms of Two Different Dimers of an IgG2 Monoclonal Antibody. *Biochemistry* **2018**, *57*, 5466–5479. [[CrossRef](#)]
277. Stapleton, N.; Andersen, J.; Stemerding, A.; Bjarnarson, S.; Verheul, R.; Gerritsen, J.; Zhao, Y.; Kleijer, M.; Sandlie, I.; Jonsdottir, M.; et al. Competition for FcRn-Mediated Transport Gives Rise to Short Half-Life of Human IgG3 and Offers Therapeutic Potential. *Nat. Commun.* **2011**, *2*, 599. [[CrossRef](#)]
278. Spiess, C.; Bevers, J.; Jackman, J.; Chiang, N.; Nakamura, G.; Dillon, M.; Liu, H.; Molina, P.; Elliott, J.; Shatz, W.; et al. Development of a Human IgG4 Bispecific Antibody for Dual Targeting of Interleukin-4 (IL-4) and Interleukin-13 (IL-13) Cytokines. *J. Biol. Chem.* **2013**, *288*, 26583–26593. [[CrossRef](#)]
279. Markham, A. Dostarlimab: First Approval. *Drugs* **2021**, *81*, 1213–1219. [[CrossRef](#)]
280. Markham, A.; Duggan, S. Cemiplimab: First Global Approval. *Drugs* **2018**, *78*, 1841–1846. [[CrossRef](#)]
281. Antonia, S.J.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Yokoi, T.; Chiappori, A.; Lee, K.H.; de Wit, M.; et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *377*, 1919–1929. [[CrossRef](#)]
282. Powles, T.; Park, S.H.; Voog, E.; Caserta, C.; Valderrama, B.P.; Gurney, H.; Kalofonos, H.; Radulović, S.; Demey, W.; Ullén, A.; et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *N. Engl. J. Med.* **2020**, *383*, 1218–1230. [[CrossRef](#)]
283. Collins, J.; Gulley, J. Product Review: Avelumab, an Anti-PD-L1 Antibody. *Hum. Vaccines Immunother.* **2019**, *15*, 891–908. [[CrossRef](#)] [[PubMed](#)]
284. Markham, A. Atezolizumab: First Global Approval. *Drugs* **2016**, *76*, 1227–1232. [[CrossRef](#)]
285. Hosseini, I.; Gadkar, K.; Stefanich, E.; Li, C.; Sun, L.; Chu, Y.; Ramanujan, S. Mitigating the Risk of Cytokine Release Syndrome in a Phase I Trial of CD20/CD3 Bispecific Antibody Mosunetuzumab in NHL: Impact of Translational System Modeling. *NPJ Syst. Biol. Appl.* **2020**, *6*, 28. [[CrossRef](#)] [[PubMed](#)]
286. Sehn, L.; Duell, J.; Avivi, I.; Brody, J.; Yoon, D.; Elliot, B.; Siddani, S.; Bai, Y.; Parikh, A.; Seliem, M.; et al. Subcutaneous Epcoritamab in Novel Combinations with Antineoplastic Agents Among Patients with B-Cell Non-Hodgkin Lymphoma in a Phase 1b/2, Multicenter, Open-Label Study: Assessing Safety, Tolerability, and Preliminary Efficacy (EPCORE NHL-5). *Blood* **2022**, *140* (Suppl. 1), 12108–12109. [[CrossRef](#)]
287. Markham, A. Margetuximab: First Approval. *Drugs* **2021**, *81*, 599–604. [[CrossRef](#)]
288. Keam, S. Trastuzumab Deruxtecan: First Approval. *Drugs* **2020**, *80*, 501–508. [[CrossRef](#)]
289. Lee, A. Loncastuximab Tesirine: First Approval. *Drugs* **2021**, *81*, 1229–1233. [[CrossRef](#)]
290. Hartley, J.A.; Flynn, M.J.; Bingham, J.P.; Corbett, S.; Reinert, H.; Tiberghien, A.; Masterson, L.A.; Antonow, D.; Adams, L.; Chowdhury, S.; et al. Pre-Clinical Pharmacology and Mechanism of Action of SG3199, the Pyrrolobenzodiazepine (PBD) Dimer Warhead Component of Antibody-Drug Conjugate (ADC) Payload Tesirine. *Sci. Rep.* **2018**, *8*, 10479. [[CrossRef](#)]
291. Hoy, S.M. Tafasitamab: First Approval. *Drugs* **2020**, *80*, 1731–1737. [[CrossRef](#)]
292. Salles, G.; Długosz-Danecka, M.; Ghesquières, H.; Jurczak, W. Tafasitamab for the Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Expert Opin. Biol. Ther.* **2021**, *21*, 455–463. [[CrossRef](#)]
293. Markham, A. Naxitamab: First Approval. *Drugs* **2021**, *81*, 291–296. [[CrossRef](#)]

294. Kang, C. Teclistamab: First Approval. *Drugs* **2022**, *82*, 1613–1619. [CrossRef]
295. Markham, A. Belantamab Mafodotin: First Approval. *Drugs* **2020**, *80*, 1607–1613. [CrossRef]
296. Syed, Y.Y. Sacituzumab Govitecan: First Approval. *Drugs* **2020**, *80*, 1019–1025. [CrossRef]
297. Bardia, A.; Hurvitz, S.A.; Tolaney, S.M.; Loirat, D.; Punie, K.; Oliveira, M.; Brufsky, A.; Sardesai, S.D.; Kalinsky, K.; Zelnak, A.B.; et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N. Engl. J. Med.* **2021**, *384*, 1529–1541. [CrossRef]
298. Dhillon, S. Isatuximab: First Approval. *Drugs* **2020**, *80*, 905–912. [CrossRef]
299. Feng, X.; Zhang, L.; Acharya, C.; An, G.; Wen, K.; Qiu, L.; Munshi, N.; Tai, Y.; Anderson, K. Targeting CD38 Suppresses Induction and Function of T Regulatory Cells to Mitigate Immunosuppression in Multiple Myeloma. *Clin. Cancer Res.* **2017**, *23*, 4290–4300. [CrossRef]
300. Shen, F.; Shen, W. Isatuximab in the Treatment of Multiple Myeloma: A Review and Comparison With Daratumumab. *Technol. Cancer Res. Treat.* **2022**, *21*, 15330338221106563. [CrossRef]
301. Alt, M.; Stecca, C.; Tobin, S.; Jiang, D.M.; Sridhar, S.S. Enfortumab Vedotin in Urothelial Cancer. *Ther. Adv. Urol.* **2020**, *12*, 175628722098019. [CrossRef]
302. Internet. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*; Internet, 2019.
303. Lamb, Y.N. Inotuzumab Ozogamicin: First Global Approval. *Drugs* **2017**, *77*, 1603–1610. [CrossRef]
304. Subramaniam, J.M.; Whiteside, G.; McKeage, K.; Croxtall, J.C. Mogamulizumab. *Drugs* **2012**, *72*, 1293–1298. [CrossRef]
305. Duvic, M.; Evans, M.; Wang, C. Mogamulizumab for the Treatment of Cutaneous T-Cell Lymphoma: Recent Advances and Clinical Potential. *Ther. Adv. Hematol.* **2016**, *7*, 171–174. [CrossRef] [PubMed]
306. Shirley, M. Olaratumab: First Global Approval. *Drugs* **2017**, *77*, 107–112. [CrossRef] [PubMed]
307. Markham, A. Elotuzumab: First Global Approval. *Drugs* **2016**, *76*, 397–403. [CrossRef] [PubMed]
308. Llovet, J.M.; Castet, F.; Heikenwalder, M.; Maini, M.K.; Mazzaferro, V.; Pinato, D.J.; Pikarsky, E.; Zhu, A.X.; Finn, R.S. Immunotherapies for Hepatocellular Carcinoma. *Nat. Rev. Clin. Oncol.* **2022**, *19*, 151–172. [CrossRef] [PubMed]
309. Keam, S. Tremelimumab: First Approval. *Drugs* **2023**, *83*, 93–102. Available online: <https://link.springer.com/article/10.1007/s40265-022-01827-8> (accessed on 13 July 2023). [CrossRef]
310. Farkona, S.; Diamandis, E.P.; Blasutig, I.M. Cancer Immunotherapy: The Beginning of the End of Cancer? *BMC Med.* **2016**, *14*, 73. [CrossRef]
311. Cercek, A.; Lumish, M.; Sinopoli, J.; Weiss, J.; Shia, J.; Lamendola-Essel, M.; El Dika, I.H.; Segal, N.; Shcherba, M.; Sugarman, R.; et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N. Engl. J. Med.* **2022**, *386*, 2363–2376. [CrossRef]
312. Pasello, M.; Mallano, A.; Flego, M.; Zamboni, S.; Giudice, A.; Scotlandi, K. Construction of Human Naive Antibody Gene Libraries. In *Antibody Engineering*; Nevoltris, D., Patrick, C., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; pp. 73–91. ISBN 978-1-4939-8648-4.
313. Caucheteur, D.; Robin, G.; Perez, V.; Martineau, P. Construction of Synthetic Antibody Libraries. In *Antibody Engineering*; Nevoltris, D., Chames, P., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; pp. 93–108.
314. Kugler, J.; Tomszak, F.; Frenzel, A.; Hust, M. Construction of Human Immune and Naive ScFv Libraries. In *Phage Display Methods and Protocols*; Hust, M., Lim, T.S., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; Volume 1701, pp. 3–24. ISBN 978-1-4939-7446-7.
315. Scholler, N. Selection of Antibody Fragments by Yeast Display. In *Antibody Engineering Methods and Protocols*; Nevoltris, D., Chames, P., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; pp. 211–233.
316. Dreier, B.; Pluckthun, A. Rapid Selection of High-Affinity Antibody ScFv Fragments Using Ribosome Display. In *Antibody Engineering*; Nevoltris, D., Chames, P., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; pp. 235–268.
317. Nemoto, N.; Kumachi, S.; Arai, H. In Vitro Selection of Single-Domain Antibody (VHH) Using CDNA Display. In *Antibody Engineering Methods and Protocols*; Nevoltris, D., Chames, P., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; pp. 269–285.
318. Smith, G.P. Phage Display: Simple Evolution in a Petri Dish (Nobel Lecture). *Angew. Chem.-Int. Ed.* **2019**, *58*, 14428–14437. [CrossRef]

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.