Trend In Approval of Targeted Biologics in The Last Two Decades

By

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Declaration

It is hereby declared that,

1. The thesis submitted is my own original work while completing the degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through complete and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted for any other degree or diploma at a university or other institution.
4. I have acknowledged all primary sources of help.

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Approval

The thesis titled “Trends in Approval of Targeted Biologics in the Past Two Decades,” submitted by Khadiza Siddika (19346027) of Summer, 2019, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on April 2024.

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Ethics Statement

The project does not involve any use of animal models. Hence, no animals were harmed in the process. Additionally, there was no involvement of human participants as well, and thus, informed consent is not applicable.

Abstract

Over the past two decades, the approval of targeted biologics has significantly transformed therapeutic landscapes, particularly for chronic diseases like cancer. These therapies, specifically target diseases' molecular pathways, offer enhanced efficacy and fewer side effects than traditional chemotherapy. This review assesses the trends in regulatory approval by the FDA, noting a surge in approvals for targeted biologics over the last two decades. The shift towards targeted biologics promises more precise management of the complexities of cancer. This review compiles the FDA's trends in approving targeted biologics for cancer from January 2000 to December 2022 based on product class, rate of approvals, biological target, and disease site. Despite the advancements in targeted cancer therapies, there is a need to comprehensively understand the evolving trends in FDA approvals during the twenty-first century. This study investigates the approval patterns, identifies influencing factors, and provides insights that can contribute to optimizing the development and processes of targeted biologics. This may serve as a good insight for researchers in academia and industry to identify fields in which cancer research and funding may be mostly directed.

Keywords: Cancer, Targeted biologics, Molecular pathway, Biological target, Approval patterns.

Dedication

It is dedicated to my family and friends.

Acknowledgment

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List of Acronyms

FDA	Food and Drug Administration
WHO	World Health Organization
HER2	Human Epidermal growth factor Receptor 2
CDER	Center for Drug Evaluation and Research
CBER	Center for Biologics Evaluation and Research
NCI	National Cancer Institute
Anti-TAA	Anti-Tumor Associate Antigen
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
ICI	Immune Checkpoint Inhibitor
GU	Genitourinary
NSCLC	Non-Squamous Cell Lung Cancer

Chapter 1

Introduction

1.1 Cancer

Cancer is a disease in which cells grow uncontrollably and spread to other body parts. The hallmarks of cancer consist of six biological competencies required during the multistep development of human tumors such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan & Weinberg, 2011). According to the World Health Organization (WHO), cancer is one of the leading causes of death after cardiovascular disease. It takes an estimated 9.6 million lives each year; approximately, around 1 in 5 men and 1 in 6 women developed cancer in 2018 (Mattiuzzi & Lippi, 2019). Cancer cells lose their ability to control their growth and divide rapidly and uncontrollably, unlike normal cells. This uncontrolled growth leads to a mass of abnormal cells called a tumor. And this abnormal growth can spread to other body parts through metastasis. The exact cause of cancer is still not fully understood, but it is believed to be caused by a combination of genetic and environmental factors. Genetic mutations can disrupt cells' normal functioning and lead to cancer development. Environmental factors such as exposure to harmful substances, smoking, unhealthy eating habits, lack of exercise, and certain infections can also increase the risk of cancer (Anand et al., 2023). Cancer can significantly impact the body, interfering with the normal functioning of organs and tissues.

1.2 Evolution of cancer treatment

The hallmark of cancer treatment has been conventional chemotherapy. Chemotherapeutic drugs are designed to target rapidly dividing cells, such as cancer cells, and specific normal

cells, such as intestinal epithelium. During World War II, nitrogen mustard, a type of chemotherapy drug, was developed as a chemical weapon. Interestingly, American pharmacologists Louis Goodman and Alfred Gilman discovered in the 1940s that it had an unintended side effect, significantly reducing white blood cell counts (Falzone et al., 2018). This led them to test the drug on patients with lymphoma, resulting in promising outcomes. This discovery marked the first successful use of chemotherapy in treating cancer. Nitrogen mustard and other chemotherapy drugs remain crucial in cancer treatment (Falzone et al., 2018). As it cannot distinguish between cancer cells and normal cells, it has significant toxicity and side effects. Over the past several years, there are many cancer treatments have come to the forefront, like surgery, radiation, and targeted cancer therapies. Different treatments may be used alone or in combination, depending on the situation. For example, surgery is a standard treatment for solid cancer, especially for localized or early-stage cancer. The procedure involves removing the tumor and surrounding tissue to prevent cancer from spreading. Radiation is another treatment procedure for cancerous cells by killing or shrinking tumors. It can be external or internal, depending on the type and stage of cancer. Surgery and radiotherapy dominated the field of cancer therapy into the 1960s until it became clear that cure rates after ever more radical local treatments had plateaued at about 33% due to the presence of micrometastases, and new data showed that combination chemotherapy could cure patients with various advanced cancers (Arruebo et al., 2011). The latter observation opened up the opportunity to apply drugs in conjunction with surgery and radiation treatments to deal with the issue of micrometastases, initially in breast cancer patients, and the field of adjuvant chemotherapy was born (Chew, 2001). Nowadays, researchers want to target specific genes or proteins responsible for the cancerous growth. This process is known as targeted therapy or precision medicine. Some hormone-sensitive cancers like breast or prostate cancer need to block the production or the action of the hormones. Sometimes, they leverage the body's

immune system to fight cancer by helping the immune system recognize and attack cancer cells. Treatment choice depends on various factors, such as the type and stage of cancer, the patient's overall health, and the potential side effects of treatment (Iqubal et al., 2022). Like conventional chemotherapy, targeted cancer therapies use pharmacological agents that inhibit growth, increase cell death, and restrict the spread of cancer. As the name suggests, targeted therapies interfere with specific proteins involved in tumorigenesis. Rather than using broad-based cancer treatments, focusing on specific molecular changes that are unique to a particular cancer, targeted cancer therapies may be more therapeutically beneficial for many cancer types, including lung, colorectal, breast, lymphoma, and leukemia. Moreover, recent advances have made it possible to analyze and tailor treatments to a patient’s tumor (Baudino, 2015).

1.3 Differences between Targeted therapy and Chemotherapy

Presently, targeted therapies are the popular choice for advanced cancer patients. Not only does it specify its target, but it also has less toxicity. Though chemotherapy and targeted therapy are two distinct methods used to treat cancer, they are differentiated in many ways.

Chemotherapy is a systemic treatment that uses medication to destroy cancer cells throughout the body (Anand et al., 2023). These drugs can be administered orally or intravenously and are designed to attack fast-growing cells, including cancer cells. However, chemotherapy drugs also harm healthy cells, which can result in side effects such as hair loss, fatigue, and nausea. In contrast, targeted therapy is a treatment that specifically targets molecules or proteins responsible for the growth and spread of cancer cells. These therapies are often more precise and cause fewer side effects than chemotherapy. Targeted therapies can be administered through a pill, injection, or infusion. Overall, chemotherapy is a more general treatment that can be effective against many types of cancer. At the same time, targeted therapy is more specific and can be tailored to a patient's cancer (Anand et al., 2023).

1.4 Approval process by the US FDA

Having high efficiency and low toxicity, there has been a significant increase in the number of FDA-approved targeted drugs for cancer treatment in the past two decades (Baldo, 2016). Hence, targeted drugs have rapidly developed and entered a golden development period. To date, there are 100 monoclonal antibodies, 89 small molecules of compounds, and 64 targeted biologics approved by the FDA (Baldo, 2016). The landscape of cancer treatment changed drastically in the late 1990s and early 2000s with the emergence of targeted therapies designed to take advantage of genetic susceptibilities in cancer cells, leading to selective killing of these cells. The approvals of trastuzumab (an anti-HER2 antibody) for breast cancer in 1998 and imatinib (a small-molecule BCR–ABL inhibitor) for chronic myeloid leukemia in 2001 is credited with ushering in the era of targeted therapy (Suttorp et al., 2018).

FDA approval plays a pivotal role in safeguarding patients by validating the safety and efficacy of targeted cancer therapies. The FDA employs a comprehensive evaluation process for targeted cancer therapies, emphasizing rigorous scientific scrutiny. This involves thorough preclinical studies assessing the therapy's mechanism of action, toxicity profiles, and potential efficacy. Clinical trials then follow, with phases designed to progressively gather data on safety and effectiveness. FDA evaluation trends often focus on biomarkers to identify patient subgroups likely to benefit. Additionally, the agency emphasizes real-world evidence, considering broader patient populations and long-term outcomes (Li & Bergan, 2020). Using innovative trial designs, adaptive pathways, and collaboration with industry and academia reflects a commitment to staying abreast of scientific advancements. Continuous monitoring of post-market data further ensures ongoing safety assessment, allowing the FDA to adopt regulations as needed (Khurana et al., 2018). This dynamic approach aligns with the evolving landscape of cancer research and treatment.

Chapter 2

Methodology

2.1 Data collection

The data for the analysis was collected from the FDA website (including but not limited to the FDA Purple Book database) and relevant literature searches. The literature search used reputable and well-known sources like PubMed, Google Scholar, ScienceDirect, the National Cancer Institute, and the Food and Drug Administration. Use pertinent keywords like "Targeted Biologics," "Approved cancer drug," and "Targeted pathways" to find relevant papers. The analysis dataset collected included all oncology therapeutic products granted regular and accelerated approvals by the FDA Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) from 1 January 2000 to 31 December 2022.

2.2 Data Analysis

The analysis dataset excluded the following: approvals that did not include new or modified indications; non-oncology indications (such as non-neoplastic haematology, palliative treatment, cancer prevention, and supportive care); approvals for haematopoietic stem cell transplantation and its complications; supplemental approvals that converted an indication from accelerated to regular approval without any modifications to the indication; supplemental approvals that only included or modified 'Limitation of Use' statements; supplemental approvals that were only related to companion diagnostics; and co-packaged combinations where the same indication was already approved for at least one of the distinct product applications. The authors of this study have developed a novel hierarchical classification system by thoroughly analyzing the entire dataset and creating three hierarchical levels: therapeutic product groups, classes, and subclasses. These levels are used to categorize

products based on their primary mechanism of action, resulting in more specific categories. The evaluation of class names, classification system organization, and different product attributes was conducted using several sources, such as product labels (Kinch et al., 2022), the WHO Anatomical Therapeutic Chemical (WHO-ATC) classification system (Mullard, 2021), and the NCI thesaurus (Flaherty et al., 2020). Distinct products were distinguished based on their respective product names, with each different product potentially encompassing several formulas and dosages. The FDA classification of items as novel molecular entities for FDA assessment is determined by active components rather than product names (Al-Madhagi, 2023). This classification is not related to the topic at hand. The primary molecular target for each medicine was determined by analyzing the prescribing instructions section. The molecular target prioritized or highlighted as the mechanism of action is the primary molecular target. In the case of bispecific medicines, the main focus was on the target located on the tumor cell. Alternatively, for a product that targets two proteins on the tumor cell, the target was listed as the first in the pharmacologic class created by the FDA (for the sake of simplicity). The primary target for targeted cytotoxic drugs is the specific target of the antibody or protein associated with a cytotoxic chemical. The collected dataset was subjected to analysis using Excel Software.

Mendeley software (version 2.111.0) was used for accurate and ethical referencing to show respect for the writer's original works.

Chapter 3

Result

Since 2000, the FDA has approved many oncology therapeutic products. Though it is more advantageous, one prominent reason for the accelerated approval rate is that the FDA implemented expedited review processes for promising cancer therapies to allow quicker access to needy patients. Moreover, they ensure accelerated clinical trial infrastructure and international collaborations to speed up the approval process. The list of targeted biologics for oncology treatment approved by the FDA is given in Table 1.

Table 1: List of targeted biologics approved by the US FDA between the year 2000 and 2022.

Sl.	Product	Approval Year	Class	Pathway/ Subclass	Disease Site	Specific Disease
1.	Gemtuzumab ozogamicin	2000	Targeted cytotoxic agent	Anti-CD33 antibody-drug conjugate	Leukemia	Acute Myeloid Leukemia
2.	Alemtuzumab	2001	Anti-TAA Antibody	Anti-CD52 antibody	Leukemia	B cell chronic lymphocytic leukemia
3.	Ibritumomab tiuxetan	2002	Radiotherapy Antibody	Anti-CD20 targeted radioactive agent	Lymphoma	Non-hodgkin's lymphoma
4.	Tositumomab iodine I-131 tositumomab	2003	Radiotherapy Antibody	Anti-CD20 targeted radioactive agent	Lymphoma	Non-hodgkin's lymphoma
5.	Cetuximab	2004	Anti-TAA Antibody	Anti-EGFR antibody	Colorectal	Metastatic Colorectal Cancer
6.	Bevacizumab	2004	Anti-VEGF construct	Anti-VEGF fusion protein	Colorectal	Metastatic Colorectal Cancer
7.	Trastuzumab	2006	Anti-TAA Antibody	Anti-HER2 antibody	Breast	Breast cancer
8.	Panitumumab	2006	Anti-TAA Antibody	Anti-EGFR antibody	Colorectal	Refractory Colorectal cancer
9.	Pegaspargase	2006	Aspargine deplete	L-asparaginase	Leukemia	Acute Lymphoblastic leukemia

10.	Rituximab	2006	Anti-TAA Antibody	Anti-CD20 antibody	Lymphoma	Non-hodgkin's lymphoma
11.	Ranibizumab-nuna	2006	Anti-VEGF construct	Anti-VEGF antibody	Opthalmic	Neovascular Macular Edema
12.	Ofatumumab	2009	Anti-TAA Antibody	Anti-CD20 antibody	Leukemia	Chronic lymphocytic leukemia
13.	Sipuleucel-T	2010	Autologous cell therapy	Anti-PAP autologous cellular immunotherapy	GU	Prostate cancer
14.	Brentuximab vedotin	2011	Targeted cytotoxic agent	Anti-CD30 antibody	Lymphoma	Relapsed or refractory Hodgkin lymphoma
15.	Ipilimumab	2011	ICI	Anti-CTLA4 antibody	Myeloma	Malignant Melanoma
16.	Peginterferon alfa-2b	2011	Immunostimulant	Interferon	Skin	Melanoma
17.	Pertuzumab	2012	Anti-TAA Antibody	Anti-HER2 antibody	Breast	Metastatic Breast cancer
18.	Denosumab	2013	Anti-TAA Antibody	Anti-RANKL antibody	Bone	Bone metastases from Breast, Prostate
19.	Ado-trastuzumab emtansine	2013	Targeted cytotoxic agent	Anti-HER2 antibody-drug conjugate	Breast	Metastatic Breast Cancer
20.	Obinutuzumab	2013	Anti-TAA Antibody	Anti-CD20 antibody	Lymphoma	Follicular Lymphoma
21.	Blinatumomab	2014	Bispecific Antibody	Anti-CD3 anti-CD19 bispecific construct	Leukemia	B cell Acute lymphoblastic leukemia
22.	Nivolumab	2014	ICI	Anti-PD1 antibody	Lung	Squamous NSCLC
23.	Pembrolizumab	2014	ICI	Anti-PD1 antibody	Lung	Squamous or non-squamous NSCLC
24.	Ramucirumab	2014	Anti-VEGF construct	Anti-VEGFR2 antibody	Site-agnostic	Solid cancer
25.	Dinutuximab	2015	Anti-TAA Antibody	Anti-GD2 glycolipid antibody	Brain	Neuroblastoma
26.	Necitumumab	2015	Anti-TAA Antibody	Anti-EGFR antibody	Lung	NSCLC
27.	Daratumumab	2015	Anti-TAA Antibody	Anti CD38 antibody	Myeloma	Multiple Myeloma
28.	Elotuzumab	2015	Anti-TAA Antibody	Anti-SLAMF7 antibody	Myeloma	Multiple Myeloma

29.	Talimogene laherparepvec	2015	Oncolytic viral therapy	Anti GM-CSF	Skin	Advance Melanoma
30.	Atezolizumab	2016	ICI	Anti-PD-L1 antibody	Lung	NSCLC
31.	Olaratumab	2016	Anti-TAA Antibody	Anti-PDGFRA antibody	Sarcoma	Soft tissue sarcoma
32.	Tisagenlecleucel	2017	Autologous cell therapy	Anti-CD19 CAR T cell therapy	Leukemia	B-cell lymphoblastic Leukemia
33.	Inotuzumab ozogamicin	2017	Targeted cytotoxic agent	Anti-CD22 antibody-drug conjugate	Leukemia	Relapsed/refractory acute lymphoblastic leukemia
34.	Durvalumab	2017	ICI	Anti-PD-L1 antibody	Lung	NSCLC
35.	Axicabtagene ciloleucel	2017	Autologous cell therapy	Anti-CD19 CAR T cell therapy	Lymphoma	Large B cell lymphoma
36.	Avelumab	2017	ICI	Anti-PD-L1 antibody	Skin	Merkel cell carcinoma
37.	Tagraxofusp-erzs	2018	Targeted cytotoxic agent	CD123-directed cytotoxin	Hematologic	Blastic plasmacytoid dendritic cell neoplasm
38.	Calaspargase pegol-mknl	2018	Aspargine deplete	L-asparaginase	Leukemia	Acute Lymphoblastic leukemia
39.	Moxetumomab pasudotox-tdfk	2018	Targeted cytotoxic agent	Anti-CD22 antibody-drug conjugate	Leukemia	Relapsed/refractory hairy cell leukemia
40.	Mogamulizumab-kpkc	2018	Anti-TAA Antibody	Anti-CCR4 antibody	Lymphoma	T-cell Lymphoma
41.	Cemiplimab-rwlc	2018	ICI	Anti-PD-1 antibody	Skin	Squamous cell carcinoma
42.	Fam-trastuzumab deruxtecan-nxki	2019	Targeted cytotoxic agent	Anti-HER2 antibody-drug conjugate	Breast	Breast cancer
43.	Enfortumab vedotin-ejfv	2019	Targeted cytotoxic agent	Anti-NECTIN4 antibody-drug conjugate	GU	Urothelial cancer
44.	Polatuzumab vedotin-piiq	2019	Targeted cytotoxic agent	Anti-CD79b antibody-drug conjugate	Lymphoma	Non-hodgkin's lymphoma
45.	Naxitamab-gqgk	2020	Anti-TAA Antibody	Anti-GD2 glycolipid antibody	Brain	Neuroblastoma
46.	Margetuximab-cmkb	2020	Anti-TAA Antibody	Anti-HER2 antibody	Breast	Metastatic Breast cancer

47.	Sacituzumab govitecan-hziy	2020	Targeted cytotoxic agent	Anti-TROP2 antibody-drug conjugate	Breast	Refractory Metastatic Breast cancer
48.	Tafasitamab-cxix	2020	Anti-TAA Antibody	Anti-CD19 antibody	Lymphoma	Relapsed/refractory large B-cell lymphoma
49.	Isatuximab-irfc	2020	Anti-TAA Antibody	Anti-CD38 antibody	Myeloma	Multiple Myeloma
50.	Belantamab mafodotin-blmf	2020	Targeted cytotoxic agent	Anti-BCMA antibody	Myeloma	Relapsed/refractory multiple Myeloma
51.	Dostarlimab-gxly	2021	ICI	Anti-PD1 antibody	Gynecologic	Endometrial cancer
52.	Tisotumab vedotin-tftv	2021	Targeted cytotoxic agent	Anti-tissue factor antibody-drug conjugate	Gynecologic	Metastatic Cervical cancer
53.	Ropeginterferon alfa-2b-njft	2021	Immunostimulant	Interferon	Hematologic	Polycythemia vera
54.	Amivantamab-vmjw	2021	Bispecific Antibody	Anti-EGFR and Anti-MET bispecific protein	Lung	NSCLC
55.	Brexucabtagene autoleucel	2021	Autologous cell therapy	Anti-CD19 CAR T cell therapy	Lymphoma	Mantle cell Lymphoma
56.	Lisocabtagene maraleucel	2021	Autologous cell therapy	Anti-CD19 CAR T cell therapy	Lymphoma	Relapsed/refractory large B-cell lymphoma
57.	Loncastuximab tesirine-lpyl	2021	Targeted cytotoxic agent	Anti-CD19 antibody-drug conjugate	Lymphoma	Relapsed/refractory large B-cell lymphoma
58.	Asparaginase erwinia chrysanthemi (recombinant)-rywn	2021	Aspargine deplete	L-asparaginase	Leukemia	Acute Lymphoblastic leukemia
59.	Daratumumab and hyaluronidase-fihj	2021	Anti-TAA Antibody	Anti-CD38 antibody	Myeloma	Multiple Myeloma
60.	Idecabtagene vicleucel	2021	Autologous cell therapy	Anti-BCMA CAR T cell therapy	Myeloma	Relapsed/refractory multiple Myeloma
61.	Ciltacabtagene autoleucel	2022	Autologous cell therapy	Anti-BCMA CAR T cell therapy	Myeloma	Relapsed/refractory multiple Myeloma
62.	Teclistamab-cqyv	2022	Bispecific Antibody	Anti-CD3 anti-BCMA	Myeloma	Relapsed/refractory Multiple Myeloma

increasing approval rate, peaking during 2015-2019. On the contrary, anti-VEGF and asparagine depleter approvals have appeared sporadically across the years. Autologous cell therapies have seen an increase in approvals, especially in the latest period (2020-2022). However, bispecific antibodies, immunostimulants, oncolytic, and radiotherapeutic agents have fewer approvals overall, with some periods having zero approvals. Though targeted cytotoxic agents had the highest approvals in the earliest period (2000-2004), they saw a significant increase again in 2015-2019. Lastly, ICI has been progressive from 2010 to 2014. The general trend suggests an overall increase in the diversity and rate of approvals for targeted biologic therapies over the last two decades, indicating progress and expansion in this oncology treatment area.

3.7 Approval based on Target/Pathways

Approval of targeted biologics often depends on demonstrating efficacy and safety in clinical trails which typically involved the molecular pathways against specific types of cancer. Here are the list of targeted biologics approved by FDA based on pathways.

Table 2: Approval of targeted biologics based on pathways.

Class	Targets	Products
Anti-TAA antibody	CCR4	1
	CD19	1
	CD20	3
	CD38	3
	CD52	1
	EGFR	3
	GD2 glycolipid	2
	HER2	3
	PDGFRA	1
	RANKL	1
	SLAMF7	1
Anti-VEGF construct	VEGF fusion protein	1
	VEGF	1
	VEGFR2	1
Asparagine depleter	L-Asparaginase	3
Autologous cell therapy	PAP	1
	CD19 CAR T cell	4
	BCMA CAR T cell	2
Bispecific construct	CD3 and CD19	1
	EGFR and MET	1
	CD3 and peptide-HLA	1
	CD3 and BCMA	1
Immune checkpoint inhibitor	CTLA4	2
	PD1	4
	PD-L1	3
Immunostimulant	Interferon	2
Oncolytic viral therapy	GM-CSF	1
Radiotherapeutic antibody	CD20 targeted radioactive	2
Targeted cytotoxic agent	CD33	1
	CD30	1
	HER2	2
	CD22	2

have made their impact on the oncology therapeutic product landscape in part through high numbers of approvals for a few target proteins.

Chapter 4

Discussion

Over the past two decades, the landscape of targeted biologics has seen significant advances, with a growing number of drugs gaining approval. These targeted biologics focus on specific molecular targets associated with cancer, offering more personalized and effective treatment options. The approval of these has notably shifted towards precision medicine, leveraging a detailed understanding of cancer biology and specific pathways involved in tumorigenesis. These targeted biologics have become increasingly significant in oncology.

Targeted biologics are many prominent classes of biologics. They are often targeted against antigens on cancer cells or involved in signaling pathways like epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). They also target aberrant kinase activities in cancer cells, such as mutations in EGFR and anaplastic lymphoma kinase (ALK), which are crucial in lung cancer. A newer class of targeted biologics, ICI, started gaining market approval around 2011 and has rapidly increased in number (Robert, 2020). These drugs target proteins such as PD-1 and CTLA-4 that cancer cells use to protect themselves from immune system attacks (Keir et al., 2008). Recently, bispecific antibodies and other novel biological formats have also been introduced that simultaneously target multiple cancer-related pathways. The approval trends indicate a growing interest in combination therapies, including targeted biologics and traditional treatments, to enhance efficacy and overcome resistance (Lin et al., 2023).

The use of biomarkers in the approval of targeted biologics has been expanding. This approach has been integral to the personalized medicine strategy that dominates current oncologic treatment paradigms, aiding in identifying the patient subgroups most likely to benefit from specific biologic therapies (Falconi et al., 2014). Moreover, there has been an increase in the

use of regulatory pathways such as accelerated approval for targeted biologics, especially those showing significant benefits over existing therapies or those treating severe conditions without satisfactory alternatives (Sharma et al., 2022).

More precisely, CAR T cell therapy is now a new hope for oncology treatment. The CAR T cell therapy improves and causes complete remission of acute lymphoblastic leukemia in 90% of cases. It is also effective 50 to 60 % in the case of large B cell lymphoma (Portell & Advani, 2014). The CD-19 CAR T cell has more approval than other CAR T cells. However, it is not that effective for solid tumors like glioblastoma, breast cancer, or lung cancer. CAR T cell causes T cell exhaustion that makes tumors suppress these T cells. But, if the genes named Regnase-1 and Roquin-1 terminated from the T cells, they will be ten times more active T cells and destroy even solid tumors (Czarnywojtek et al., 2023).

Targeted biologics is directed toward specific markers present in different cells and gives a target for specifically directing treatment to those cells. The HER2-positive breast cancer has a third receptor called ERBB2 or HER2-positive receptor on the cancer cell. These receptors are present in everyone's cells, but in HER2-positive breast cancer, they are over-amplified. And it is used as the target for treatment. Targeted antibodies lock on to the over-amplification of those receptors, causing cell death when that receptor can't function appropriately. Some newer targeted therapies, like antibody-drug conjugates, have an antibody again that locks onto the receptor and then delivers a payload to those cancer cells. Hence, the maximum breast cancer is an anti-TAA antibody (Parks et al., 2023).

Presently, lung cancer is the most common cancer. Earlier, the treatment for lung cancer used to be surgery, radiation, and chemotherapy, but now, the favored treatment is targeted therapy. Lung cancer can be small cell lung cancer or non-small cell lung cancer. About 85% of the patients have non-small cell lung cancer (Molina et al., 2008). The treatment for lung cancer

depends on various factors like the types of cells (Squamous cells, Adenocarcinoma) and the stages (one, two, three, four). The stage is crucial in determining the treatments the patients will get and the prognosis in the long run. Researchers now find druggable targets for cancer cells by Next-Generation sequencing, which looks at many genes and finds a particular target (Cainap et al., 2021). Targets like EGFR, PD-L1, or MET can use a specific drug as a lock and key mechanism where the response rate increases from 30 with just chemotherapy to 80 with these targeted biologics (Mao et al., 2016).

The approval of targeted biologics has particularly accelerated in the past few years. For instance, drugs like patritumab deruxtecan, targeting specific pathways in cancer cells, have been developed and approved, expanding the arsenal of treatments available (Koyama et al., 2022). The FDA has continually approved new therapies for B-cell malignancies and colorectal cancer. Notably, targeted therapies have been combined with immune checkpoint inhibitors, providing a synergistic approach that enhances treatment efficacy in conditions like advanced melanoma (Webb et al., 2018).

Overall, the trend towards more targeted therapies reflects a broader shift in oncology towards precision medicine, which aims to tailor treatments to individual patient profiles and specific genetic markers of tumors. This has led to improved outcomes and reduced side effects compared to traditional therapies like chemotherapy.

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