Review Article

The global landscape of approved antibody therapies

Xiaochen Lyu1,†, Qichao Zhao2,†, Julia Hui3, Tiffany Wang4, Mengyi Lin1, Keying Wang1, Jialing Zhang1, Jiaqian Shentu1, Paul A. Dalby5, Hongyu Zhang1,2,* and Bo Liu3,*

1Big Data and Bioinformatics, Zhanyuan Therapeutics Ltd, Hangzhou, Zhejiang 310000, China, 2Research and Development, Zhanyuan Therapeutics Ltd, Hangzhou, Zhejiang 310000, China, 3Big Data and Discovery, Umabs Therapeutics Inc., Salem, NH 03079, USA, 4Department of Applied Mathematics, Harvard College, Cambridge, MA 02138, USA, and 5Department of Biochemical Engineering, University College London, London WC1E 6BT, UK

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ABSTRACT

Antibody therapies have become an important class of therapeutics in recent years as they have exhibited outstanding efficacy and safety in the treatment of several major diseases including cancers, immune-related diseases, infectious disease and hematological disease. There has been significant progress in the global research and development landscape of antibody therapies in the past decade. In this review, we have collected available data from the Umabs Antibody Therapies Database (Umabs-DB, https://umabs.com) as of 30 June 2022. The Umabs-DB shows that 162 antibody therapies have been approved by at least one regulatory agency in the world, including 122 approvals in the US, followed by 114 in Europe, 82 in Japan and 73 in China, whereas biosimilar, diagnostic and veterinary antibodies are not included in our statistics. Although the US and Europe have been at the leading position for decades, rapid advancement has been witnessed in Japan and China in the past decade. The approved antibody therapies include 115 canonical antibodies, 14 antibody-drug conjugates, 7 bispecific antibodies, 8 antibody fragments, 3 radiolabeled antibodies, 1 antibody-conjugate immunotoxin, 2 immunoconjugates and 12 Fc-Fusion proteins. They have been developed against 91 drug targets, of which PD-1 is the most popular, with 14 approved antibody-based blockades for cancer treatment in the world. This review outlined the global landscape of the approved antibody therapies with respect to the regulation agencies, therapeutic targets and indications, aiming to provide an insight into the trends of the global development of antibody therapies.

Statement of Significance: This article gives a comprehensive review of the global approved antibody therapies on their approval statistics in each country/region, types of engineering formats, targets and therapeutic indications, aiming to provide an insight into the trends of the global development of antibody therapies.

KEYWORDS: antibody format; antibody targets; global regulatory agency; approved antibody; antibody therapies

INTRODUCTION

Antibody therapy is a form of targeted treatment that uses antibody-based molecules to treat human diseases [1]. Monoclonal antibodies (mAbs) are immunoglobulins produced by plasma B cells as stimulated by a specific antigen. Antibodies can perform several roles in the human immune system, such as facilitating humoral and cellular immune responses to a wide range of antigens with high specificity and long-term efficacy. Thus, it has emerged as a major class of therapeutics since the approval of the first mAb, anti-CD3 OKT3 (also known as muromonab-CD3), by the United States Food and Drug Administration (US FDA) in

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1To whom correspondence should be addressed. Hongyu Zhang. E-Mail: hongyu.zhang@umabstx.com; Bo Liu. E-Mail: bo.liu@umabstx.com
†These authors contributed equally to this work.
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The number of approved and marketed antibody therapies has reached 162 as of 30 June 2022, targeting a wide range of diseases including cancers, immune-related disease, infectious disease and hematological disease. The benefits of using antibody therapies stem from their high selectivity and optimal binding affinity. In addition, the safety and efficacy of antibody therapies are closely related to the characteristics of their therapeutic targets, such as expression patterns and the role they perform in the progression of disease [3]. Targets in cancers and immune-related diseases are well characterized, such as PD-1/PD-L1, CD20, tumor necrosis factor (TNF)-alpha, HER2 and CD3. As a result, the approved antibody therapies are mostly developed for the treatment of these indications, although a broader range of diseases have also been investigated [4]. Moreover, SARS-CoV-2 spike protein in COVID-19 infectious disease and calcitonin gene-related peptide (CGRP) in the central nervous system (CNS) disorders, have aroused broad interest in recent years [5, 6].

The global antibody therapies market was merely 0.3 billion USD in 1997 and rapidly increased to 186 billion USD in 2021. However, there are thousands of ongoing clinical trials and preclinical studies, and so the market is estimated to reach 445 billion USD by 2028, with a compound annual growth rate (CAGR) of 13.2% from 2022 to 2028 [7]. The market of antibody therapies has been growing fast and shows great market potential in the overall healthcare industry in the US, Europe, Japan and China. Companies with the largest number of approved antibodies and greatest share of the market are mostly located in the US due to their long-term investment into R&D. The market position of the US is followed by Europe, whereas there has been a rapid growth in the number of companies and approved antibodies in China and Japan over the past 5 years [8].

In this review, we collected data from the Umabs Antibody Therapies Database (Umabs-DB) [9], to make a statistical analysis of the antibodies approved by at least one drug regulatory agency of the world, excluding biosimilar, diagnostic and veterinary antibodies. We firstly inspected the number of antibody therapies approved by drug regulatory agencies for each year, which shows the trend of the approval of antibody therapies in different regions. Then, the format of antibody therapies on the year of their first approval is presented, showing the historical map to the development of new antibody formats. Targets and indications of antibody therapies in each historical period are presented to show the progress of global R&D. Lastly, approvals from companies in different countries and regions are analyzed to predict the future trend in the development of antibody therapies.

GLOBAL LANDSCAPE OF ANTIBODY THERAPIES APPROVAL

As of 30 June 2022, we reviewed a total of 162 antibody therapies approved by at least one drug regulatory agency in the world, including nine that were later withdrawn. Biosimilar, diagnostic and veterinary antibodies were not included for the analysis. An overview on the number of antibody therapies approved in each year and in different regions is presented in Fig. 1 and Table 1.
| Antibody name  | Brand name                               | Target                        | Antibody type               | Approved indication                                                                 | Approval               |
|---------------|------------------------------------------|-------------------------------|-----------------------------|-------------------------------------------------------------------------------------|------------------------|
| Muromonab     | Orthoclone OKT3                          | CD3                           | Canonical antibody; Rodent   | 1. Heart transplant rejection                                                       | EMA Europe: 1986*      |
| IOR-T3        | IOR-T3, aioushan                         | CD3                           | Canonical antibody; Rodent   | 1. Organ transplant rejection                                                       | CECMED Cuba: 1989      |
| Nebacumab     | Centoxin                                 | Lipid A region of endotoxin   | Canonical antibody; Human    | 1. Sepsis                                                                            | EMA Europe: 1991*      |
| Abciximab     | ReoPro, Clotinab                         | Integrin alpha IIb beta 3     | Fab fragment; Chimeric       | 1. Unstable angina                                                                   | FDA US: 1994           |
| Edrecolomab   | Panorex                                  | Epithelial cell adhesion      | Canonical antibody; Rodent   | 1. Colorectal cancer                                                                  | EMA Europe: 1995       |
| Daclizumab    | Zenapax, Zinbryta                        | CD25                          | Canonical antibody; Humanized| 1. Organ transplant rejection                                                       | EMA Europe: 1997*      |
| Rituximab     | Rituxan, MabThera                        | CD20                          | Canonical antibody; Chimeric | 1. Multiple sclerosis                                                                | EMA Europe: 1999*      |
| Infliximab    | Remicade                                 | Tumor necrosis factor-alpha   | Canonical antibody; Chimeric | 1. Ankylosing spondylitis                                                            | FDA US: 1998           |
| Trastuzumab   | Herceptin                                | Human epidermal growth factor | Canonical antibody; Humanized| 1. Breast cancer                                                                     | FDA US: 1998           |
| Palivizumab   | Synagis                                  | Respiratory syncytial virus   | Canonical antibody; Humanized| 1. Respiratory syncytial virus prophylaxis                                             | EMA Europe: 1999       |
| Antibody name            | Brand name       | Target                  | Antibody type                  | Approved indication                                                                 | Approval                   |
|-------------------------|------------------|-------------------------|--------------------------------|-------------------------------------------------------------------------------------|----------------------------|
| Basiliximab             | Simulect         | CD25                    | Canonical antibody; Chimeric    | 1. Organ transplant rejection 1. Renal transplant rejection                          | FDA US:1998                |
|                         |                  |                         |                                | 2. Ankylosing spondylitis 2. Psoriatic arthritis                                    | EMA Europe:1998            |
|                         |                  |                         |                                | 3. Rheumatoid arthritis 4. Plaque psoriasis                                        | PMDA Japan:2002            |
|                         |                  |                         |                                | 5. Juvenile rheumatoid arthritis                                                    | NMPA China:2004            |
| Etanercept              | Enbrel           | Tumor necrosis factor-alpha (TNF-α) | Fe-Fusion protein              | 1. Ankylosing spondylitis 2. Psoriatic arthritis 3. Rheumatoid arthritis 4. Plaque psoriasis |
|                         |                  |                         |                                | 5. Juvenile rheumatoid arthritis                                                    | FDA US:1998                |
|                         |                  |                         |                                | 6. Juvenile rheumatoid arthritis                                                    | EMA Europe:2000            |
|                         |                  |                         |                                | 7. Juvenile rheumatoid arthritis                                                    | PMDA Japan:2005            |
| Gemtuzumab ozogamicin   | Mylotarg         | CD33                    | Antibody-drug conjugate; Humanized | 1. Acute myelogenous leukemia                                                       | FDA US:2000                |
|                         |                  |                         |                                | 2. Chronic lymphocytic leukemia                                                      | PMDA Japan:2005            |
|                         |                  |                         |                                | 3. Multiple sclerosis                                                              | EMA Europe:2018            |
| Alemtuzumab             | Lemtrada, Campath| CD52                    | Canonical antibody; Humanized   | 1. Graft versus host disease                                                       | FDA US:2001                |
|                         |                  |                         |                                | 2. Ankylosing spondylitis                                                          | EMA Europe:2001            |
|                         |                  |                         |                                | 3. Psoriatic arthritis                                                             | PMDA Japan:2008            |
|                         |                  |                         |                                | 4. Rheumatoid arthritis                                                             | NMPA China:2010            |
| Wut3                    | Shudankang       | CD3                     | Canonical antibody; Rodent      | 1. Ankylosing spondylitis                                                          | FDA US:2010                |
|                         |                  |                         |                                | 2. Psoriatic arthritis                                                             | EMA Europe:2010            |
| Adalimumab              | Humira           | Tumor necrosis factor-alpha (TNF-α) | Canonical antibody; Human      | 1. Non-Hodgkin’s lymphoma                                                         | FDA US:2002                |
|                         |                  |                         |                                | 2. Plaque psoriasis                                                               | EMA Europe:2003            |
|                         |                  |                         |                                | 3. Generalized pustular psoriasis                                                   | PMDA Japan:2008            |
|                         |                  |                         |                                | 4. Pyoderma gangrenosum                                                           | NMPA China:2010            |
|                         |                  |                         |                                | 5. Uveitis                                                                       |                            |
| Ibritumomab tiuxetan    | Zevalin, Zevaman | CD20                    | Canonical antibody; Rodent      | 1. Allergic asthma                                                                | FDA US:2002                |
|                         |                  |                         |                                | 2. Urticaria                                                                      | EMA Europe:2004            |
|                         |                  |                         |                                | 3. Psoriasis                                                                      | FDA USA:2003               |
|                         |                  |                         |                                | 4. Psoriasis                                                                      | NMPA China:2017            |
|                         |                  |                         |                                | 5. Atopic dermatitis                                                              | FDA US:2003*               |
|                         |                  |                         |                                | 6. Generalized pustular psoriasis                                                  | EMA Europe:2004*           |
|                         |                  |                         |                                | 7. Atopic dermatitis                                                              | NMPA China:2003            |
| Anti human interleukin-8 monoclonal antibody | Enboke | Interleukin 8 (IL-8) | Canonical antibody; Rodent     | 1. Atopic dermatitis                                                              |                            |
|                         |                  |                         |                                | 2. Generalized pustular psoriasis                                                  |                            |

(continue)
| Antibody name          | Brand name          | Target                        | Antibody type                  | Approved indication                          | Approval                      |
|------------------------|---------------------|-------------------------------|--------------------------------|----------------------------------------------|-------------------------------|
| Alefacept              | Amevive             | CD2                           | Fe-Fusion protein              | 1. Psoriasis                                 | FDA US:2003*                  |
| Iodine 131 tositumomab | Biexxar             | CD20                          | Radiolabeled antibody; Rodent   | 1. Non-Hodgkin’s lymphoma                    | FDA US:2003*                  |
| Cetuximab              | Erbitux             | Epidermal growth factor receptor (EGFR) | Canonical antibody; Chimeric     | 1. Colorectal cancer                         | FDA US:2004                  |
|                        |                     |                               |                                | 2. Head and Neck cancer                      | EMA Europe:2003*              |
|                        |                     |                               |                                |                                              | EMU Europe:2003*              |
|                        |                     |                               |                                |                                              | PMDA Japan:2008               |
|                        |                     |                               |                                |                                              | NMPA China:2005               |
|                        |                     |                               |                                |                                              |                               |
| Bevacizumab            | Avastin             | Vascular endothelial growth factor A (VEGF-A) | Canonical antibody; Humanized     | 1. Breast cancer                             | FDA US:2004                  |
|                        |                     |                               |                                | 2. Cervical cancer                           | EMA Europe:2005               |
|                        |                     |                               |                                | 3. Colorectal cancer                         | PMDA Japan:2007               |
|                        |                     |                               |                                | 4. Glioblastoma                              | NMPA China:2010               |
|                        |                     |                               |                                | 5. Liver cancer                              |                               |
|                        |                     |                               |                                | 6. Non-small cell lung cancer                 |                               |
|                        |                     |                               |                                | 7. Ovarian cancer                            |                               |
|                        |                     |                               |                                | 8. Glioma                                    |                               |
|                        |                     |                               |                                | 9. Renal cell carcinoma                      |                               |
|                        |                     |                               |                                |                                               |                               |
| Natalizumab            | Tysabri, Antegren   | Integrin subunit alpha 4 (ITGA4) | Canonical antibody; Humanized     | 1. Crohn’s disease                           | FDA US:2004                  |
|                        |                     |                               |                                | 2. Multiple sclerosis                        | EMA Europe:2006               |
|                        |                     |                               |                                |                                               | PMDA Japan:2014               |
| Tocilizumab            | Actemra, RoActemra  | Interleukin 6 receptor (IL-6R) | Canonical antibody; Humanized     | 1. Juvenile rheumatoid arthritis             | FDA US:2010                  |
|                        |                     |                               |                                | 2. Rheumatoid arthritis                      | EMA Europe:2009               |
|                        |                     |                               |                                | 3. Castleman’s disease                        | PMDA Japan:2005               |
|                        |                     |                               |                                | 4. Drug hypersensitivity                     | NMPA China:2013               |
|                        |                     |                               |                                | 5. Giant cell arteritis                       |                               |
|                        |                     |                               |                                | 6. Severe acute respiratory syndrome coronavirus 2 |                               |
|                        |                     |                               |                                | 7. Systemic scleroderma                       |                               |
|                        |                     |                               |                                | 8. Adult-onset Still’s disease                |                               |
|                        |                     |                               |                                | 9. Vasculitis                                 |                               |
| Abatacept              | Orenica             | CD80, CD86                    | Fc-Fusion protein               | 1. Psoriatic arthritis                       | FDA US:2005                  |
|                        |                     |                               |                                | 2. Graft versus host disease                 | EMA Europe:2007               |
|                        |                     |                               |                                | 3. Rheumatoid arthritis                      | PMDA Japan:2010               |
|                        |                     |                               |                                | 4. Juvenile rheumatoid arthritis             | NMPA China:2020               |
| Panitumumab            | Vectibix            | Epidermal growth factor receptor (EGFR) | Canonical antibody; Humanized     | 1. Colorectal cancer                         | FDA US:2006                  |
|                        |                     |                               |                                |                                               | EMA Europe:2007               |
|                        |                     |                               |                                |                                               | PMDA Japan:2010               |
|                        |                     |                               |                                |                                               | NMPA China:2006               |
| Iodine 131 derlotuximab biotin | Cotara, Vivatuxin   | DNA/Histone H1                | Radiolabeled antibody; Chimeric | 1. Lung cancer                              | NMPA China:2006               |
| Iodine 131 metuximab   | Licartin            | CD147                         | Radiolabeled antibody; Chimeric | 1. Liver cancer                              | NMPA China:2006               |

(continue)
| Antibody name | Brand name | Target | Antibody type | Approved indication | Approval |
|---------------|------------|--------|---------------|---------------------|---------|
| Nimotuzumab   | Taixinsheng, TheraCIM, Theraloc, CIMAb, BIOMAb EGFR | Epidermal growth factor receptor (EGFR) | Canonical antibody; Humanized | 1. Anaplastic astrocytoma, 2. Brain cancer, 3. Esophageal cancer, 4. Glioblastoma, 5. Head and neck cancer, 6. Nasopharyngeal cancer, 7. Glioma | CECMED Cuba: 2006, NMPA China: 2012 |
| Ranibizumab   | Lucentis | Vascular endothelial growth factor A (VEGF-A) | Fab fragment; Humanized | 1. Choroidal neovascularization, 2. Degenerative myopia, 3. Diabetic macular edema, 4. Diabetic retinopathy, 5. Retinal edema, 6. Wet age-related macular degeneration, 7. Retinopathy of prematurity | FDA US: 2006, EMA Europe: 2007, PMDA Japan: 2009, NMPA China: 2011 |
| Eculizumab    | Soliris | Complement C5 (C5) | Canonical antibody; Humanized | 1. Hemolytic uremic syndrome, 2. Myasthenia gravis, 3. Neuromyelitis optica, 4. Paroxysmal nocturnal hemoglobinuria | FDA US: 2007, EMA Europe: 2007, PMDA Japan: 2010, NMPA China: 2018 |
| Racotumomab   | Vaxira | Ganglioside GM3 (GM3), Interleukin 1 alpha, Interleukin 1 beta (IL-1α, IL-1β) | Canonical antibody; RodentFc-Fusion protein | 1. Non-small cell lung cancer, 2. Cryopyrin-associated periodic syndrome, 3. Inborn genetic diseases, 4. Pericarditis | CECMED Cuba: 2008, FDA US: 2008 |
| Rilonacept    | Arcalyst | Tumor necrosis factor-alpha (TNF-α) | Fab fragment; Humanized | 1. Ankylosing spondylitis, 2. Psoriatic arthritis, 3. Rheumatoid arthritis, 4. Crohn’s disease, 5. Psoriasis, 6. Axial spondyloarthritis | FDA US: 2008, EMA Europe: 2009, PMDA Japan: 2012, NMPA China: 2019 |
| Certolizumab pegol | Cimzia | Thrombopoietin receptor (TPOR) | Fc-Fusion protein | 1. Idiopathic thrombocytopenic purpura, 2. Acute radiation syndrome, 3. Aplastic anemia | FDA US: 2008, EMA Europe: 2009, PMDA Japan: 2011, NMPA China: 2022 |
| Canakinumab   | Ilaris | Interleukin 1 beta (IL-1β) | Canonical antibody; Humanized | 1. Adult-onset Still’s disease, 2. Gouty arthritis, 3. Juvenile rheumatoid arthritis, 4. Rheumatoid arthritis, 5. Chronic obstructive pulmonary disease, 6. Cryopyrin-associated periodic syndrome, 7. Familial Mediterranean fever, 8. Familial periodic fever, 9. Peroxisomal disorder | FDA US: 2009, EMA Europe: 2009, PMDA Japan: 2011 |
| Antibody name          | Brand name   | Target                                             | Antibody type                              | Approved indication                                   | Approval          |
|------------------------|--------------|----------------------------------------------------|---------------------------------------------|-------------------------------------------------------|-------------------|
| Catumaxomab            | Removab      | CD3, Epithelial cell adhesion molecule (CD3, EpCAM) | Bispecific antibody; Rodent                | 1. Gastric cancer                                      | EMA Europe:2009*  |
| Ustekinumab            | Stelara      | Interleukin 12, Interleukin 23 (IL-12, IL-23)      | Canonical antibody; Human                  | 1. Psoriatic arthritis                                | EMA Europe:2009   |
|                        |              |                                                    |                                             | 2. Ulcerative colitis                                 | FDA US:2009       |
|                        |              |                                                    |                                             | 3. Crohn’s disease                                    | PMDA Japan:2011   |
|                        |              |                                                    |                                             | 4. Plaque psoriasis                                   | NMPA China:2017   |
| Ofatumumab             | Arzerra, Kesimpta | CD20                           | Canonical antibody; Human                  | 1. Chronic lymphocytic leukemia                        | FDA US:2009       |
|                        |              |                                                    |                                             | 2. Multiple sclerosis                                 | EMA Europe:2010    |
|                        |              |                                                    |                                             |                                                       | PMDA Japan:2013   |
|                        |              |                                                    |                                             |                                                       | NMPA China:2021   |
| Golimumab              | Simponi      | Tumor necrosis factor-alpha (TNF-α)               | Canonical antibody; Human                  | 1. Ankylosing spondylitis                             | EMA Europe:2009   |
|                        |              |                                                    |                                             | 2. Juvenile rheumatoid arthritis                      | FDA US:2009       |
|                        |              |                                                    |                                             | 3. Psoriatic arthritis                                | PMDA Japan:2011   |
|                        |              |                                                    |                                             | 4. Rheumatoid arthritis                               | NMPA China:2017   |
|                        |              |                                                    |                                             | 5. Ulcerative colitis                                 |                   |
|                        |              |                                                    |                                             | 6. Axial spondyloarthritis                            |                   |
| Denosumab              | Prolia, Ranmark, Xgeva | Receptor activator of nuclear factor kappaB ligand (RANKL) | Canonical antibody; Human                  | 1. Corticosteroid-induced osteoporosis                 | FDA US:2010       |
|                        |              |                                                    |                                             | 2. Rheumatoid arthritis                              | EMA Europe:2020    |
|                        |              |                                                    |                                             | 3. Bone Metastases                                    | PMDA Japan:2012   |
|                        |              |                                                    |                                             | 4. Bone cancer                                        | NMPA China:2019   |
|                        |              |                                                    |                                             | 5. Bone disorder                                      |                   |
|                        |              |                                                    |                                             | 6. Male osteoporosis                                  |                   |
|                        |              |                                                    |                                             | 7. Malignant hypercalcaemia                           |                   |
|                        |              |                                                    |                                             | 8. Osteopetrosis                                      |                   |
|                        |              |                                                    |                                             | 9. Postmenopausal Osteoporosis                        |                   |
| Brentuximab vedotin    | Adcetris     | CD30                                              | Antibody-drug conjugate; Chimeric           | 1. Hodgkin’s lymphoma                                 | FDA US:2011       |
|                        |              |                                                    |                                             | 2. T-cell lymphoma                                    | EMA Europe:2012    |
|                        |              |                                                    |                                             | 3. Peripheral T-cell lymphoma                         | NMPA China:2020   |
|                        |              |                                                    |                                             | 4. Anaplastic large cell lymphoma                     | PMDA Japan:2014    |
|                        |              |                                                    |                                             | 5. Sezary syndrome                                    |                   |
|                        |              |                                                    |                                             | 6. Mycosis fungoides                                  |                   |
|                        |              |                                                    |                                             | 7. Primary cutaneous anaplastic large cell lymphoma  |                   |
| Belatacept             | Nulojix      | CD80, CD86                                        | Fc-Fusion protein                           | 1. Renal transplant rejection                         | FDA US:2011       |
|                        |              |                                                    |                                             |                                                       | EMA Europe:2011    |
| Aflibercept            | Zaltrap, Eylea | Vascular endothelial growth factor (VEGF)       | Fc-Fusion protein                           | 1. Branch retinal vein occlusion                      | FDA US:2011       |
|                        |              |                                                    |                                             | 2. Colorectal cancer                                  | EMA Europe:2012    |
|                        |              |                                                    |                                             | 3. Central retinal vein occlusion                     | PMDA Japan:2012    |
|                        |              |                                                    |                                             | 4. Choroidal neovascularization                       | NMPA China:2018    |
|                        |              |                                                    |                                             | 5. Diabetic macular edema                             |                   |
|                        |              |                                                    |                                             | 6. Diabetic retinopathy                               |                   |
|                        |              |                                                    |                                             | 7. Glaucoma                                          |                   |
|                        |              |                                                    |                                             | 8. Wet age-related macular degeneration               |                   |
|                        |              |                                                    |                                             | 9. Macular edema                                      |                   |
| Antibody name       | Brand name        | Target                             | Antibody type                      | Approved indication                                         | Approval                  |
|---------------------|-------------------|------------------------------------|------------------------------------|-------------------------------------------------------------|---------------------------|
| Belimumab           | Benlysta, LymphoStat-B | B cell activating factor (BAFF)    | Canonical antibody; Human          | 1. Lupus nephritis                                          | FDA US:2011               |
|                     |                   |                                    |                                    | 2. Systemic lupus erythematosus                             | EMA Europe:2011           |
|                     |                   |                                    |                                    |                                                             | PMDA Japan:2017           |
|                     |                   |                                    |                                    |                                                             | NMPA China:2022           |
|                     |                   |                                    |                                    | 3. Renal cell carcinoma                                     |                          |
| Ipilimumab          | Yervoy            | Cytotoxic T-lymphocyte antigen 4 (CTLA4) | Canonical antibody; Human          | 1. Liver cancer                                             | FDA US:2011               |
|                     |                   |                                    |                                    | 2. Non-small cell lung cancer                               | EMA Europe:2011           |
|                     |                   |                                    |                                    | 3. Mesothelioma                                             | PMDA Japan:2015           |
|                     |                   |                                    |                                    | 4. Malignant melanoma                                       | NMPA China:2021           |
|                     |                   |                                    |                                    | 5. Renal cell carcinoma                                     |                          |
| Pertuzumab          | Perjeta           | Human epidermal growth factor receptor 2 (HER2) | Canonical antibody; Humanized     | 1. Breast cancer                                            | FDA US:2012               |
|                     |                   |                                    |                                    |                                                             | EMA Europe:2013           |
|                     |                   |                                    |                                    |                                                             | PMDA Japan:2013           |
|                     |                   |                                    |                                    |                                                             | NMPA China:2018           |
| Raxibacumab         | Abthrax           | Bacillus anthracis protective antigen (B. anthracis PA) | Canonical antibody; Human          | 1. Anthrax infection                                        | FDA US:2012               |
|                     |                   |                                    |                                    |                                                             |                           |
| Mogamulizumab       | Poteligeo         | C-C chemokine receptor type 4 (CCR4) | Canonical antibody; Humanized      | 1. Adult T-cell leukemia/lymphoma                           | PMDA Japan:2012           |
|                     |                   |                                    |                                    | 2. Cutaneous T-cell lymphoma                                | FDA US:2018               |
|                     |                   |                                    |                                    | 3. Periheral T-cell lymphoma                                | EMA Europe:2018           |
|                     |                   |                                    |                                    | 4. Mycosis fungoides                                        |                           |
|                     |                   |                                    |                                    | 5. Sezary syndrome                                          |                           |
| Trastuzumab emtansine | Kadcyla           | Human epidermal growth factor receptor 2 (HER2) | Antibody-drug conjugate; Humanized | 1. Breast cancer                                            | FDA US:2013               |
|                     |                   |                                    |                                    |                                                             | EMA Europe:2013           |
|                     |                   |                                    |                                    |                                                             | PMDA Japan:2013           |
|                     |                   |                                    |                                    |                                                             | NMPA China:2020           |
| Obinutuzumab        | Gazyvaro, Gazyva  | CD20                               | Canonical antibody; Humanized      | 1. Chronic lymphocytic leukemia                              | FDA US:2013               |
|                     |                   |                                    |                                    | 2. Follicular lymphoma                                      | EMA Europe:2014           |
|                     |                   |                                    |                                    | 3. Non-Hodgkin's lymphoma                                   | PMDA Japan:2018           |
|                     |                   |                                    |                                    |                                                             | NMPA China:2021           |
| Conbercept          | Langmu, Lumitin   | Vascular endothelial growth factor (VEGF) | Fe-Fusion protein                  | 1. Wet age-related macular degeneration                     |                           |
|                     |                   |                                    |                                    |                                                             |                           |
| Itolizumab          | Alzumab           | CD6                                | Canonical antibody; Humanized      | 1. Cytokine release syndrome                                |                           |
|                     |                   |                                    |                                    | 2. Plaque psoriasis                                         |                           |
|                     |                   |                                    |                                    | 3. Severe acute respiratory syndrome coronavirus 2         |                           |
| Blinatumomab        | Blincyto          | CD19, CD3                          | Bispecific antibody; Rodent        | 1. B-cell acute lymphoblastic leukemia                      | FDA US:2014               |
|                     |                   |                                    |                                    |                                                             | EMA Europe:2015           |
|                     |                   |                                    |                                    |                                                             | PMDA Japan:2018           |
|                     |                   |                                    |                                    |                                                             | NMPA China:2020           |
| Antibody name        | Brand name       | Target                          | Antibody type         | Approved indication                                                                 | Approval          |
|----------------------|------------------|---------------------------------|-----------------------|--------------------------------------------------------------------------------------|-------------------|
| **Pembrolizumab**    | Keytruda         | Programmed cell death 1         | Canonical antibody; Humanized | 1. Breast cancer                                                                      | FDA US:2014       |
|                      |                  | (PD-1)                          |                       | 2. Cervical cancer                                                                    | EMA Europe:2015   |
|                      |                  |                                 |                       | 3. Colorectal cancer                                                                  | PMDA Japan:2016   |
|                      |                  |                                 |                       | 4. Esophageal cancer                                                                  | NMPA China:2018   |
|                      |                  |                                 |                       | 5. Gastric cancer                                                                     |                   |
|                      |                  |                                 |                       | 6. Head and neck cancer                                                               |                   |
|                      |                  |                                 |                       | 7. Liver cancer                                                                       |                   |
|                      |                  |                                 |                       | 8. Non-small cell lung cancer                                                         |                   |
|                      |                  |                                 |                       | 9. Diffuse large B-cell lymphoma                                                       |                   |
|                      |                  |                                 |                       | 10. Hodgkin’s lymphoma                                                                |                   |
|                      |                  |                                 |                       | 11. Pancreatic cancer                                                                 |                   |
|                      |                  |                                 |                       | 12. Squamous cell carcinoma                                                            |                   |
|                      |                  |                                 |                       | 13. Urogenital cancer                                                                  |                   |
|                      |                  |                                 |                       | 14. Malignant melanoma                                                                |                   |
| **Eftrenonacog alfa**| Alprolix         | Factor VIII                     | Fc-Fusion protein      | 1. Hemophilia B                                                                      | FDA US:2014       |
|                      |                  |                                 |                       | 2. Hemophilia A                                                                      | PMDA Japan:2014   |
|                      |                  |                                 |                       | 3. Hemophilia A                                                                      | EMA Europe:2016   |
|                      |                  |                                 |                       | 4. Hemophilia A                                                                      | NMPA China:2021   |
| **Vedolizumab**      | Entyvio, Kynteles| Integrin alpha4 beta7           | Canonical antibody; Humanized | 1. Ulcerative colitis                                                                 | FDA US:2014       |
|                      |                  | (Integrin α4β7)                 |                       | 2. Crohn’s disease                                                                    | EMA Europe:2014   |
|                      |                  |                                 |                       | 3. Non-radiographic axial spondyloarthropathy                                         | PMDA Japan:2018   |
| **Secukinumab**      | Cosentyx, Scapho | Interleukin 17A (IL-17A)        | Canonical antibody; Human| 1. Ankylosing spondylitis                                                            | FDA US:2015       |
|                      |                  |                                 |                       | 2. Psoriatic arthritis                                                                | EMA Europe:2015   |
|                      |                  |                                 |                       | 3. Non-radiographic axial spondyloarthropathy                                         | NMPA China:2019   |
|                      |                  |                                 |                       | 4. Plaque psoriasis                                                                  |                   |
|                      |                  |                                 |                       | 5. Generalized pustular psoriasis                                                     |                   |
| **Ramucirumab**      | Cyramza          | Vascular endothelial growth factor receptor 2 (VEGFR-2) | Canonical antibody; Human | 1. Colorectal cancer                                                                  | FDA US:2014       |
|                      |                  |                                 |                       | 2. Gastric cancer                                                                     | EMA Europe:2014   |
|                      |                  |                                 |                       | 3. Liver cancer                                                                       | PMDA Japan:2015   |
|                      |                  |                                 |                       | 4. Non-small cell lung cancer                                                         | NMPA China:2022   |
| **Efmorectocog alfa**| Elocta, Eloctate | Factor IX                       | Fc-Fusion protein      | 1. Hemophilia A                                                                      | FDA US:2014       |
|                      |                  |                                 |                       | 2. Hemophilia A                                                                      | PMDA Japan:2014   |
|                      |                  |                                 |                       | 3. Hemophilia A                                                                      | EMA Europe:2015   |
| **Siltuximab**       | Sylvant          | Interleukin 6 (IL-6)            | Canonical antibody; Chimeric | 1. Castleman’s disease                                                                | FDA US:2014       |
|                      |                  |                                 |                       | 2. Gastric cancer                                                                     | EMA Europe:2014   |
|                      |                  |                                 |                       | 3. Liver cancer                                                                       | PMDA Japan:2021   |
|                      |                  |                                 |                       | 4. Non-small cell lung cancer                                                         | NMPA China:2021   |
| **Nivolumab**        | Opdive           | Programmed cell death 1         | Canonical antibody; Human | 1. Colorectal cancer                                                                  | FDA US:2014       |
|                      |                  | (PD-1)                          |                       | 2. Esophageal cancer                                                                  | EMA Europe:2015   |
|                      |                  |                                 |                       | 3. Gastric cancer                                                                     | PMDA Japan:2014   |
|                      |                  |                                 |                       | 4. Head and neck cancer                                                               | NMPA China:2019   |
|                      |                  |                                 |                       | 5. Non-small cell lung cancer                                                         |                   |
|                      |                  |                                 |                       | 6. Hodgkin’s lymphoma                                                                 |                   |
|                      |                  |                                 |                       | 7. Mesothelioma                                                                       |                   |
|                      |                  |                                 |                       | 8. Squamous cell carcinoma                                                            |                   |
|                      |                  |                                 |                       | 9. Urogenital cancer                                                                  |                   |
|                      |                  |                                 |                       | 10. Malignant melanoma                                                                |                   |
|                      |                  |                                 |                       | 11. Renal cell carcinoma                                                               |                   |
| (continue)
| Antibody name   | Brand name       | Target                                      | Antibody type                  | Approved indication                                      | Approval                |
|-----------------|------------------|---------------------------------------------|--------------------------------|----------------------------------------------------------|-------------------------|
| Elotuzumab      | Empliciti        | SLAM family member 7 (SLAMF7)               | Canonical antibody; Humanized  | 1. Multiple myeloma                                      | FDA US:2015, EMA Europe:2016, PMDA Japan:2016 |
| Alirocumab      | Praluent         | Proprotein convertase subtilisin/kexin Type 9 (PCSK9) | Canonical antibody; Humanized  | 1. Hypercholesterolemia 2. Hyperlipoproteinemia Type IIa | FDA US:2015, EMA Europe:2015 |
| Mepolizumab     | Nucala           | Interleukin 5 (IL-5)                        | Canonical antibody; Humanized  | 1. Asthma                                                | PMDA Japan:2016, FDA US:2015, EMA Europe:2015, PMDA Japan:2016, NMPA China:2021 |
| Necitumumab     | Portrazza        | Epidermal growth factor receptor (EGFR)     | Canonical antibody; Human      | 1. Non-small cell lung cancer                            | FDA US:2015, EMA Europe:2016, PMDA Japan:2019 |
| Idarucizumab    | Praxbind         | Dabigatran                                  | Fab fragment; Humanized        | 1. Blood coagulation disorders                           | FDA US:2015, EMA Europe:2015, PMDA Japan:2016, NMPA China:2018 |
| Dinutuximab     | Unituxin, Qarziba| GD2 ganglioside (GD2)                       | Canonical antibody; Chimeric   | 1. Nephroblastoma                                        | FDA US:2015, EMA Europe:2015, PMDA Japan:2021, NMPA China:2021 |
| Daratumumab     | Darzalex         | CD38                                        | Canonical antibody; Human      | 1. Multiple myeloma                                      | FDA US:2015, EMA Europe:2016, PMDA Japan:2017, NMPA China:2019 |
| Evolocumab      | Repatha          | Proprotein convertase subtilisin/kexin Type 9 (PCSK9) | Canonical antibody; Humanized  | 1. Coronary artery disease 2. Hypercholesterolemia 3. Hyperlipoproteinemia Type IIa 4. Myocardial infarction 5. Stroke | FDA US:2015, EMA Europe:2015, PMDA Japan:2016, NMPA China:2018 |
| Atezolizumab    | Tecentriq        | Programmed cell death 1 ligand 1 (PD-L1)    | Canonical antibody; Humanized  | 1. Breast cancer 2. Liver cancer 3. Non-small cell lung cancer 4. Small cell lung cancer 5. Urogenital cancer 6. Malignant melanoma | FDA US:2016, EMA Europe:2017, PMDA Japan:2018, NMPA China:2020 |
| Olaratumab      | Lartruvo         | Platelet-derived growth factor receptor alpha (PDGFRA) | Canonical antibody; Human      | 1. Soft tissue sarcoma                                    | FDA US:2016*, EMA Europe:2016* |
| Bezlotoxumab    | Zinplava          | *Clostridium difficile Toxin B*              | Canonical antibody; Human      | 1. *C. difficile* infection                              | FDA US:2016, EMA Europe:2017, PMDA Japan:2017 |

(continue)
| Antibody name | Brand name               | Target                                      | Antibody type                            | Approved indication                                                                 | Approval        |
|--------------|--------------------------|---------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------|-----------------|
| Brodalumab   | Siliq, Kyntheum, Lumicef | Interleukin 17 receptor alpha (IL-17 RA)    | Canonical antibody; Human                 | 1. Ankylosing spondylitis                                                            | PMDA Japan:2016 |
|              |                          |                                             |                                           | 2. Psoriatic arthritis                                                               | FDA US:2017     |
|              |                          |                                             |                                           | 3. Erythrodermic psoriasis                                                           | EMA Europe:2017 |
|              |                          |                                             |                                           | 4. Plaque psoriasis                                                                 | NMPA China:2020 |
|              |                          |                                             |                                           | 5. Psoriasis                                                                        |                 |
|              |                          |                                             |                                           | 6. Axial spondyloarthritis                                                          |                 |
|              |                          |                                             |                                           | 7. Generalized pustular psoriasis                                                    |                 |
|              |                          |                                             |                                           | 8. Generalized pustular psoriasis                                                    |                 |
|              |                          |                                             |                                           | 9. Generalized pustular psoriasis                                                    |                 |
|              |                          |                                             |                                           | 10. Generalized pustular psoriasis                                                   |                 |
| Ixekizumab   | Taltz                    | Interleukin 17A (IL-17A)                    | Canonical antibody; Humanized             | 1. Ankylosing spondylitis                                                            | FDA US:2016     |
|              |                          |                                             |                                           | 2. Psoriatic arthritis                                                               | EMA Europe:2016 |
|              |                          |                                             |                                           | 3. Erythrodermic psoriasis                                                           | PMDA Japan:2016 |
|              |                          |                                             |                                           | 4. Plaque psoriasis                                                                 | NMPA China:2019 |
|              |                          |                                             |                                           | 5. Generalized pustular psoriasis                                                    |                 |
|              |                          |                                             |                                           | 6. Generalized pustular psoriasis                                                    |                 |
| SII rmb      | Rabishield               | Rabies virus glycoprotein (Rabies virus GP) | Canonical antibody; Human                 | 1. Rabies virus infection                                                            | CDSCO India:2016|
| Reslizumab   | Cinqair, Cinqaero        | Interleukin 5 (IL-5)                        | Canonical antibody; Humanized             | 1. Asthma                                                                            | FDA US:2016     |
| Obiltoximab  | Anthim                  | B. anthracis Protective antigen (B. anthracis PA) | Canonical antibody; Chimeric             | 1. Anthrax infection                                                                 | FDA US:2016     |
| Inotuzumab   | Besponsa                | CD22                                        | Antibody-drug conjugate; Humanized        | 1. B-cell acute lymphoblastic leukemia                                                | FDA US:2017     |
|              |                         |                                             |                                           | 2. B-cell acute lymphoblastic leukemia                                                | EMA Europe:2017 |
| Sarilumab    | Kevzara                 | Interleukin 6 receptor (IL-6R)              | Canonical antibody; Human                 | 1. Rheumatoid arthritis                                                              | FDA US:2017     |
|              |                         |                                             |                                           | 2. Rheumatoid arthritis                                                              | EMA Europe:2017 |
| Dupilumab    | Dupixent                | Interleukin 4 receptor alpha (IL-4RA)       | Canonical antibody; Human                 | 1. Asthma                                                                            | FDA US:2017     |
|              |                         |                                             |                                           | 2. Atopic dermatitis                                                                | EMA Europe:2017 |
|              |                         |                                             |                                           | 3. Nasal polyps                                                                     | NMPA China:2018 |
|              |                         |                                             |                                           | 4. Eosinophilic esophagitis                                                          |                 |
| Durvalumab   | Imfinzi                 | Programmed cell death 1 ligand 1 (PD-L1)    | Canonical antibody; Human                 | 1. Non-small cell lung cancer                                                       | FDA US:2017     |
|              |                         |                                             |                                           | 2. Small cell lung cancer                                                            | EMA Europe:2018 |
|              |                         |                                             |                                           | 3. Small cell lung cancer                                                            | NMPA China:2019 |
| Avelumab     | Bavencio                | Programmed cell death 1 ligand 1 (PD-L1)    | Canonical antibody; Human                 | 1. Merkel cell carcinoma                                                             | FDA US:2017     |
|              |                         |                                             |                                           | 2. Urogenital cancer                                                                | EMA Europe:2017 |
|              |                         |                                             |                                           | 3. Renal cell carcinoma                                                              | PMDA Japan:2017 |
| Emicizumab   | Hemlibra                | Coagulation factor IX, Coagulation factor X (Factor IX, Factor X) | Bispecific antibody; Humanized | 1. Hemophilia A                                                                      | FDA US:2017     |
|              |                         |                                             |                                           | 2. Hemophilia A                                                                     | EMA Europe:2018 |
|              |                         |                                             |                                           | 3. Hemophilia A                                                                     | PMDA Japan:2018 |
|              |                         |                                             |                                           | 4. Hemophilia A                                                                     | NMPA China:2018 |
| Antibody name     | Brand name   | Target                                      | Antibody type                         | Approved indication                                      | Approval                     |
|-------------------|--------------|---------------------------------------------|---------------------------------------|----------------------------------------------------------|-----------------------------|
| Benralizumab      | Fasenra      | Interleukin 5 receptor subunit alpha (IL-5RA) | Canonical antibody; Humanized         | 1. Asthma                                                 | FDA US:2017, EMA Europe:2018, PMDA Japan:2018 |
| Ocrelizumab       | Ocrevus      | CD20                                        | Canonical antibody; Humanized          | 1. Multiple sclerosis                                    | FDA US:2017, EMA Europe:2018 |
| Guselkumab        | Tremfya      | Interleukin 23 p19 (IL-23p19)               | Canonical antibody; Human              | 1. Psoriatic arthritis                                   | FDA US:2017, EMA Europe:2018, PMDA Japan:2018 |
|                   |              |                                             |                                       | 2. Erythodermic psoriasis                                |                             |
|                   |              |                                             |                                       | 3. Plaque psoriasis                                      |                             |
|                   |              |                                             |                                       | 4. Palmoplantar pustulosis                                |                             |
|                   |              |                                             |                                       | 5. Generalized pustular psoriasis                         |                             |
| Erenumab          | Aimovig      | Calcitonin gene-related peptide receptor (CGRP-R) | Canonical antibody; Human              | 1. Migraine                                              | FDA US:2018, EMA Europe:2018, PMDA Japan:2021 |
| Moxetumomab pasudotox | Lumoxiti | CD22                                         | Immunotoxin; Rodent                    | 1. Hairy cell leukemia                                    | FDA US:2018, EMA Europe:2021 |
| Ravulizumab       | Ultomiris    | Complement C5 (C5)                          | Canonical antibody; Humanized          | 1. Haemolytic uraemic syndrome                            | FDA US:2018, EMA Europe:2019, PMDA Japan:2019, EMA Europe:2019 |
|                   |              |                                             |                                       | 2. Myasthenia gravis                                     |                             |
|                   |              |                                             |                                       | 3. Paroxysmal nocturnal hemoglobinuria                    |                             |
| Fremanezumab      | Ajovy        | Calcitonin gene-related peptide (CGRP)      | Canonical antibody; Human              | 1. Migraine                                              | FDA US:2018, EMA Europe:2019, PMDA Japan:2021 |
| Sintilimab        | Tyvyt, Daboshu | Programmed cell death 1 (PD-1)               | Canonical antibody; Human              | 1. Gastric cancer                                         | NMPA China:2018             |
|                   |              |                                             |                                       | 2. Esophageal cancer                                      |                             |
|                   |              |                                             |                                       | 3. Liver cancer                                           |                             |
|                   |              |                                             |                                       | 4. Non-small cell lung cancer                             |                             |
|                   |              |                                             |                                       | 5. Hodgkin’s lymphoma                                     |                             |
| Ibalizumab        | Trogarzo     | CD4                                         | Canonical antibody; Humanized          | 1. HIV infection                                          | FDA US:2018, EMA Europe:2019 |
| Galcanezumab      | Emgality     | Calcitonin gene-related peptide (CGRP)      | Canonical antibody; Humanized          | 1. Cluster headache                                       | FDA US:2018, EMA Europe:2019, PMDA Japan:2021 |
|                   |              |                                             |                                       | 2. Migraine                                               |                             |
| Tildrakizumab     | Ilumetri, Ilumya | Interleukin 23 p19 (IL-23p19)               | Canonical antibody; Human              | 1. Plaque psoriasis                                       | FDA US:2018, EMA Europe:2018, PMDA Japan:2020 |
| Emapalumab        | Gamifant     | Interferon gamma (IFN-γ)                     | Canonical antibody; Human              | 1. Hemophagocytic Lymphohistiocytosis                     | FDA US:2018, EMA Europe:2021, NMPA China:2022 |
| Cemiplimab        | Libtayo      | Programmed cell death 1 (PD-1)               | Canonical antibody; Human              | 1. Basal cell carcinoma                                   | FDA US:2018, EMA Europe:2019 |
|                   |              |                                             |                                       | 2. Non-small cell lung cancer                             |                             |
|                   |              |                                             |                                       | 3. Squamous cell carcinoma                                |                             |

(continue)
| Antibody name   | Brand name | Target                                      | Antibody type                        | Approved indication                  | Approval                  |
|-----------------|------------|---------------------------------------------|--------------------------------------|--------------------------------------|--------------------------|
| Toripalimab     | Tuoyi      | Programmed cell death 1 (PD-1)              | Canonical antibody; Humanized        | 1. Nasopharyngeal cancer             | NMPA China: 2018         |
|                 |            |                                             |                                      | 2. Urogenital cancer                 |                          |
|                 |            |                                             |                                      | 3. Malignant melanoma                |                          |
| Caplacizumab    | Cablivi    | von Willebrand Factor (vWF)                 | VHH-VHH, Humanized                   | 1. Thrombotic thrombocytopenic purpura | EMA Europe: 2018         |
|                 |            |                                             |                                      |                                      | FDA US: 2019              |
| Lanadelumab     | Takhzyro   | Kallikrein                                   | Canonical antibody; Human             | 1. Hereditary angioedema             |                          |
| Burosumab       | Crysvita   | Fibroblast growth factor 23 (FGF23)         | Canonical antibody; Human             | 1. Osteomalacia                      | EMA Europe: 2018         |
|                 |            |                                             |                                      | 2. X-linked hypophosphatemia         | FDA US: 2018              |
| Tislelizumab    | Baizean    | Programmed cell death 1 (PD-1)              | Canonical antibody; Humanized        | 1. Liver cancer                      |                          |
|                 |            |                                             |                                      | 2. Non-small cell lung cancer        |                          |
|                 |            |                                             |                                      | 3. Hodgkin’s lymphoma                |                          |
|                 |            |                                             |                                      | 4. Nasopharyngeal cancer             |                          |
|                 |            |                                             |                                      | 5. Squamous cell carcinoma           |                          |
|                 |            |                                             |                                      | 6. Urogenital cancer                 |                          |
| Risankizumab    | Skyrizi    | Interleukin 23 p19 (IL-23p19)               | Canonical antibody; Humanized        | 1. Psoriatic arthritis               | PMDA Japan: 2019         |
|                 |            |                                             |                                      | 2. Plaque psoriasis                  | FDA US: 2019              |
|                 |            |                                             |                                      | 3. Psoriasis                        | EMA Europe: 2019         |
| Trastuzumab deruxtecan | Enhertu | Human epidermal growth factor receptor 2 (HER2) | Antibody-drug conjugate; Humanized | 1. Breast cancer                     | FDA US: 2019              |
| Brolucizumab    | Beovu      | Vascular endothelial growth factor A (VEGF-A) | ScFv fragment; Humanized             | 1. Wet age-related macular degeneration | FDA US: 2019              |
| Crizanlizumab   | Adakveo    | P-selectin                                   | Canonical antibody; Humanized        | 1. Vaso-occlusive crisis             | EMA Europe: 2019         |
| Enfortumab vedotin | Padcev | Nectin Cell Adhesion Molecule 4 (Nectin 4) | Antibody-drug conjugate; Human       | 1. Urogenital cancer                 | FDA US: 2019              |
| Romosozumab     | Evenity    | Sclerostin                                   | Canonical antibody; Humanized        | 1. Male osteoporosis                 | EMA Europe: 2019         |
|                 |            |                                             |                                      | 2. Postmenopausal osteoporosis       | FDA US: 2019              |
| Fgartigimod alfa | Vyvgart | Neonatal Fc Receptor (FcRn)                 | Fc fragment; Human                   | 1. Myasthenia gravis                 | EMA Europe: 2019         |
|                 |            |                                             |                                      |                                      | FDA US: 2019              |
| Camrelizumab    | Airuika    | Programmed cell death 1 (PD-1)              | Canonical antibody; Humanized        | 1. Esophageal cancer                 | NMPA China: 2019         |
## Table 1. Continued.

| Antibody name | Brand name | Target | Antibody type | Approved indication | Approval |
|---------------|------------|--------|---------------|---------------------|---------|
| Polatuzumab vedotin | Polivy | CD79b | Antibody-drug conjugate; Humanized | 1. Diffuse large B-cell lymphoma | FDA US:2019, EMA Europe:2020, PMDA Japan:2021, FDA US:2019, EMA Europe:2020, PMDA Japan:2022, NMPA China:2022, CDSCO India:2019 |
| Luspatercept | Reblozyl | Transforming growth factor-beta (TGF-β) | Fc-Fusion protein | 1. Beta-thalassemia | FDA US:2019 |
| Rabimab | Tivarat | Rabies virus glycoprotein (Rabies virusGP) | Canonical antibody; Rodent | 1. Rabies virus infection | FDA US:2019 | 1. Plasma porcineis | EMA Europe:2020 | 1. Plasma porcineis | PMDA Japan:2021 | EMA Europe:2022 | NMPA China:2020 |
| Netakimab | Efleira | Interleukin 17A (IL-17A) | Canonical antibody; Humanized | 1. Plaque psoriasis | FDA US:2019 |
| Inebilizumab | Uplizna | 1. Interleukin 6 receptor (IL-6R) | Canonical antibody; Humanized | 1. Neovascular disease of the retina | FDA US:2020 |
| Teprotumumab | Tepezza | Insulin-like growth factor 1 receptor (IGF-1R) | Canonical antibody; Humanized | 1. Graves’ ophthalmopathy | FDA US:2020 |
| Sacituzumab govitecan | Trodelvy | Tumor-associated calcium signal transducer 2 (TACSTD2) | Antibody-drug conjugate; Humanized | 1. Breast cancer | FDA US:2020 |
| Cetuximab | Aklix | Human epidermal growth factor receptor 2 (HER2) | Antibody-drug conjugate; Chimeric | 1. Breast cancer | FDA US:2020 |
| Belantamab mafodotin | Beltepha | B cell maturation antigen (BCMA) | Antibody-drug conjugate; Humanized | 1. Diffuse large B-cell lymphoma | FDA US:2020 |
| Levilimab | Ilsira | Interleukin 6 receptor (IL-6R) | Canonical antibody; Humanized | 1. Neuromyelitis optica | FDA US:2020 | 1. Multiple myeloma | PMDA Japan:2020 | EMA Europe:2022 | NMPA China:2020 | EMA Europe:2020 | PMDA Japan:2021 | FDA US:2020 |
| Margetuximab | Margenza | Human epidermal growth factor receptor 2 (HER2) | Antibody-drug conjugate; Humanized | 1. Breast cancer | FDA US:2020 | 1. Multiple myeloma | EMA Europe:2022 | NMPA China:2021 | EMA Europe:2020 | PMDA Japan:2021 | FDA US:2020 |
| Satralizumab | Enspryng | Interleukin 6 receptor (IL-6R) | Canonical antibody; Humanized | 1. Diffuse large B-cell lymphoma | FDA US:2020 |
| Tafasitamab | Monjuvi | CD19 | Antibody-drug conjugate; Humanized | 1. Multiple myeloma | FDA US:2020 | 1. Diffuse large B-cell lymphoma | EMA Europe:2022 | NMPA China:2022 | EMA Europe:2020 | PMDA Japan:2021 | FDA US:2020 |
| Naxitamab | Danyelza | GD2 ganglioside (GD2) | Antibody-drug conjugate; Humanized | 1. Neuroblastoma | FDA US:2020 | 1. Diffuse large B-cell lymphoma | EMA Europe:2022 | NMPA China:2022 | EMA Europe:2020 | PMDA Japan:2021 | FDA US:2020 |
Table 1. Continued.

| Antibody name     | Brand name | Target                                | Antibody type                        | Approved indication                                                                 | Approval                  |
|-------------------|------------|---------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------|---------------------------|
| Ansuvimab         | Ebanga     | Ebola virus glycoprotein              | Canonical antibody; Human             | 1. Ebola virus infection                                                              | FDA US:2020               |
|                    |            | Calcitonin gene-related peptide (CGRP)| Canonical antibody; Humanized         | 1. Migraine                                                                          | FDA US:2020               |
| Prolgolimab       | Forteca    | Programmed cell death 1 (PD-1)        | Antibody-drug conjugate; Humanized    | 1. Melanoma                                                                          | Minzdrav Russia:2020      |
| Olokizumab        | Artlegia   | Interleukin 6 (IL-6)                  | Canonical antibody; Humanized         | 1. Rheumatoid arthritis 2. Severe acute respiratory syndrome coronavirus 2           | Minzdrav Russia:2020      |
| Penpulimab        | Annike     | Programmed cell death 1 (PD-1)        | Canonical antibody; Humanized         | 1. Non-small cell lung cancer 2. Hodgkin’s lymphoma 3. Nasopharyngeal cancer         | NMPA China:2021           |
| Dostarlimab       | Jemperli   | Programmed cell death 1 (PD-1)        | Canonical antibody; Humanized         | 1. Endometrial cancer 2. Solid cancer                                               | EMA Europe:2021           |
| Evinacumab        | Evkeeza    | Angiopoietin-like protein 3 (ANGPTL3) | Canonical antibody; Human             | 1. Hyperlipoproteinemia Type II                                                     | FDA US:2021               |
| Sugemalimab       | Cejemly    | Programmed cell death 1 ligand 1 (PD-L1) | Canonical antibody; Human             | 1. Non-small cell lung cancer                                                       | EMA Europe:2021           |
| Envafolimab       | enweida    | Programmed cell death 1 ligand 1 (PD-L1) | Fc-Fusion VH; Humanized              | 1. Solid cancer                                                                    | NMPA China:2021           |
| Telitacicept      | Taiai      | B cell activating factor (BAFF), A proliferation-inducing ligand (APRIL) | Fc-Fusion protein                     | 1. Systemic lupus erythematosus                                                   | NMPA China:2021           |
| Regdanvimab       | Regkirona  | SARS-CoV-2 spike protein (SARS-CoV-2 S protein) | Canonical antibody; Human             | 1. Severe acute respiratory syndrome coronavirus 2                                  | ANVISA Brazil:2021        |
| Amubarvimab +     |            |                                       |                                       |                                                                                        |                           |
| Romlusevimab      |            |                                       |                                       |                                                                                        |                           |
| Amivantamab       | Rybrevant  | Epidermal growth factor receptor, C-Met (EGFR, cMet) | Bispecific antibody; Human            | 1. Non-small cell lung cancer                                                        | FDA US:2021               |
| Zimberelimab      | Yutuo      | Programmed cell death 1 (PD-1)        | Canonical antibody; Human             | 1. Hodgkin’s lymphoma                                                               | NMPA China:2021           |
| Bimekizumab       | Bimzelx    | Interleukin 17A, Interleukin 17F (IL-17A, IL-17F) | Canonical antibody; Humanized         | 1. Erythrodermic psoriasis 2. Plaque psoriasis 3. Generalized pustular psoriasis 2  | EMA Europe:2021  PMDA Japan:2022 |
| Loncastuximab     | Lonca, Zynlonta | CD19                          | Antibody-drug conjugate; Chimeric     | 1. Diffuse large B-cell lymphoma                                                    | FDA US:2021               |
| Tisotumab vedotin  | Tivdak     | Tissue factor (TF)                   | Antibody-drug conjugate; Human        | 1. Cervical cancer                                                                  | FDA US:2021               |
| Tralokinumab      | Adtralza, Adbry | Interleukin 13 (IL-13)              | Canonical antibody; Human             | 1. Atopic dermatitis                                                               | EMA Europe:2021  FDA US:2021 |

(continue)
| Antibody name | Brand name | Target | Antibody type | Approved indication | Approval |
|--------------|------------|--------|----------------|--------------------|----------|
| Tezepelumab | Tezspire | Thymic stromal lymphopoietin (TSLP) | Canonical antibody; Human | 1. Asthma | FDA US:2021 |
| Aducanumab | Aduhelm | Amyloid beta | Canonical antibody; Human | 1. Alzheimer’s disease | FDA US:2021 |
| Disitamab vedotin | Aidixi | Human epidermal growth factor receptor 2 (HER2) | Antibody-drug conjugate; Humanized | 1. Gastric cancer, 2. Urothelial carcinoma, 3. Severe acute respiratory syndrome coronavirus 2, 4. Microsporidia diarrhea II | FDA US:2021, PMDA Japan:2021, EMA Europe:2022 |
| Sotrovimab | Xevudy | SARS-Cov-2 spike protein (SARS-Cov-2 S protein) | Canonical antibody; Human | 1. Severe acute respiratory syndrome coronavirus 2 prophylaxis | FDA US:2021, PMDA Japan:2021, EMA Europe:2022 |
| Faricimab | Vabysmo | Vascular endothelial growth factor A, Angiopoietin 2 | Bispecific antibody; Humanized | 1. Wet age-related macular degeneration, 2. Cold agglutinin disease, 3. Follicular lymphoma | FDA US:2022, EMA Europe:2022 |
| Sutimlimab | Enjaymo | Complement C1s (C1s) | Canonical antibody; Humanized | 1. Autoimmune hemolytic anemia | FDA US:2022, PMDA Japan:2021 |
| Mosunetuzumab | Lunsumio | CD3, CD20 | Bispecific antibody; Humanized | 1. Severe acute respiratory syndrome coronavirus 2, 2. Non-small cell lung cancer, 3. Small cell lung cancer, 4. Lymphocyte activation gene 3, 5. Programmed cell death 1 (PD-L1) | FDA US:2022, PMDA Japan:2021, EMA Europe:2022 |
| Tebentafusp | Kimmtrak | CD3, Glycoprotein 100 (GP100) | Immunoconjugate; Humanized | 1. Melanoma, 2. Small cell lung cancer, 3. Solid tumors | FDA US:2022, EMA Europe:2022 |

∗ indicates the antibody therapy was withdrawn.
of antibody therapies approved in China was <5 for each year. But since 2018, the annual approvals have increased to > 10, and even reached 18 in 2021. Although a total of 73 antibody therapies were approved by the NMPA in China for a wide range of indications, only 18 antibodies were developed by local companies. However, very recently, there was a first-in-class anti-PD-1/CTLA-4 bispecific antibody, Cadonilimab, approved by the NMPA for the treatment of metastatic cervical cancer [18]. Cadonilimab, the first bispecific antibody with dual immune checkpoint inhibition approved in the world, could signal a future increase in innovative antibody therapy development in China.

ANTIBODY DISCOVERY AND ENGINEERING IN APPROVED ANTIBODIES

In 1975, Georges Köhler and César Milstein established the hybridoma platform based on the fusion of murine B cell and myeloma cells, which enables the in vitro production of a large amount of pure mAbs [19]. Subsequently, chimeric antibodies formed by domain recombination, and then humanized antibodies, obtained primarily by complementary-determining region (CDR) grafting, have been enabled for mAb production [20]. Furthermore, fully human antibodies have been developed from phage display [21, 22], yeast display [23], mammalian cell display [24], transgenic animals [25, 26] and human blood samples [27, 28]. It is noted that the phage display developed antibodies are not naturally occurring human antibodies as their heavy chain and light chain sequences were not from the same B cells. More recently, glycoengineering has become a powerful tool to optimize the pharmacodynamic and pharmacokinetic properties of an antibody [29, 30]. For example, Fc core fucosylation has been shown to enhance FcγRIIa binding and antibody-dependent cellular cytotoxicity (ADCC) activity of antibodies [31]. Meanwhile, an antibody lacking core fucosylation (afucosylated) increased ADCC activity through highly increased IgG-Fc receptor IIIa (FcγRIIa) affinity [32]. There are currently four approved afucosylated antibodies: Obinutuzumab, Mogamulizumab Benralizumab and Inebilizumab.

The total number of rodent antibody therapies is only 11, out of which four have been withdrawn. In 1986, the first antibody therapy based on this technique, OKT3, was a murine mAb against CD3 expressed on the T cell surface, acting as an immunosuppressor in organ transplant rejection [2, 33]. No more murine antibody therapies have been approved since Rabimabs, which was approved in India for the treatment of rabies in 2019 [34]. For those approved non-humanized antibodies, anti-CD3/EpCAM Catumaxomab is a mouse-rat hybrid bispecific antibody, first approved by the EMA for the treatment of gastric cancer in 2009. This was also the first bispecific antibody to gain regulatory approval despite being withdrawn due to commercial failure [35, 36]. Moxetumomab pasudotox is the only murine antibody-conjugate immunotoxin and was approved by the FDA in 2018 for the treatment of hairy cell leukemia (HCL) [37].

There are risks and disadvantages of murine mAbs or mAbs from other animals for human administration. For example, patients would produce a rapid immune response through generation of human anti-mouse antibody (HAMA) against the murine antibodies, which greatly shortens the serum half-life of the therapy [38]. In addition, the ability of the murine Fc region to elicit ADCC in patients is limited [39]. To overcome these problems of murine mAbs, several engineering techniques have been developed to make their sequence more similar to the
human antibody while maintaining binding affinity and specificity. The first technique developed was to create a chimeric antibody, which recombined the murine variable domains with a human constant region (Fig. 2A) [11, 40]. There are a total of 16 approved chimeric antibody therapies which are in multiple formats, including naked whole IgGs, fragments, and antibody drug conjugates (ADCs). The first murine antibody therapy, Abciximab [10, 11], was first approved in Cuba. A chimeric fragment antibody radiolabeled with Iodine 131, denoted as Iodine 131 Metuximab, was also approved by the NMPA in 2006 for the treatment of liver cancer [41]. In addition, in 2021, there was a chimeric ADC, loncastuximab tesirine, approved by the FDA for the treatment of large B-cell lymphoma. This indicates that the chimeric antibody is still popular for some applications [42].

Later, researchers set out to humanize an antibody mainly by grafting the CDR regions from mice into a human framework sequence [20]. After humanization, antibody therapies show much less immunogenicity but are often associated with loss of affinity. Therefore, a variety of methods have been innovated to restore and increase antibody affinity and specificity [43, 44]. As an important method of antibody engineering, 66 humanized antibodies from a diverse range of animals with multiple formats have been approved. The first humanized antibody therapy, anti CD25 Daclizumab, was approved by the FDA in 1997 for the treatment of transplant rejection [45, 46]. Since then, humanized antibody therapies accounted for a high proportion of the approved antibody therapies each year (Fig. 2C).

In 1990, Gregory P. Winter introduced phage display of antibody fragments, in which exogenous human antibody genetic sequences can be incorporated into the filamentous bacteriophage genome and expressed on the phage surface for further specificity and affinity screening [21, 22]. Transgenic animals provided another powerful technique for the development of fully human antibodies, and was developed in 1994 by creating two transgenic mouse models that were genetically engineered to have human immunoglobulin genes, thus allowing the mice to express fully human antibodies after immunization [25]. In addition, the single B cell technique was developed to directly isolate antigen-specific B cells from human blood for the generation of human natural antibodies [47–49]. A total of 55 fully human antibody therapies have been approved so far. The first fully human antibody therapy, the IgM antibody Nebacumab, was approved in 1991 [13]. The first human whole IgG antibody therapy Adalimumab was approved by the FDA in 2002, which was developed by phage display to target against TNF-alpha for the treatment of rheumatic diseases [50]. The technique to isolate antigen-specific B cells directly from human blood has been successfully applied to discover antiviral antibodies [51, 52] such as REGN-EB3 targeting Ebola viral surface glycoprotein approved by the FDA in 2020 [53], and Evusheld targeting SARS-CoV-2 spike protein and first approved by the EMA in 2022 [54].

In addition, the recent advances in Next Generation Sequencing (NGS) make it a useful tool in rapid antibody discovery [55–57]. With the ever-progressing antibody discovery technologies, we believe there will likely be another wave of clinical trials and approvals for antibody therapies discovered from such innovative platforms.

Engineering of antibodies has evolved through a few stages whereby at first naked whole animal IgG antibodies were used directly as therapeutics, followed by recombination, humanization and affinity maturation. However, today we see more engineered antibody formats in a variety of shapes and sizes (Fig. 2B). We have categorized all approved antibody therapies into five classes: canonical antibody, fragment of antibody, ADC, bispecific antibody and other formats (Fig. 2C). Canonical antibodies have the whole antibody structure, consisting of two full-length heavy chains and two light chains. Of all approved antibodies, there are 115 canonical antibodies, 114 of which are IgGs and the other one is IgM (Nebacumab) [13]. Antibody fragments are composed of a few domains of the whole antibody structure but can act as therapies themselves. This format includes Fab fragments, single-chain variable fragments (scFvs), Fc fragments, and the variable regions of the camelid heavy chain of heavy-chain-only antibodies (VHH), which was fused with a human Fc fragment or with another VHH. There has been a total of eight fragment antibody therapies approved so far. The only scFv is the anti-vascular endothelial growth factor (VEGF)-A Brolucizumab for the treatment of wet age-related macular degeneration, approved by the FDA in 2019 [58]. Four Fab fragments have been approved so far, of which the first approved Fab fragment antibody therapy was Abciximab [10, 11]. There has also been one PEGylated Fab fragment, Certolizumab Pegol, approved in 2008 for the treatment of autoimmune-related diseases [59, 60]. ScFv is a small-sized antibody, which fuses only the variable regions of the heavy and light chain of the whole antibody, making it easier to penetrate the tissues [61–63]. The only Fc fragment antibody therapy, Efgartigimod alfa, was first approved by the FDA in 2021, targeting neonatal Fc Receptor (FcRn) for the treatment of myasthenia gravis [64]. There are two antibody therapies composed of VHH, Caplacizumab and Enfamilomab, which were first approved by the EMA in 2018 and the NMPA in 2021, respectively. Caplacizumab is a bivalent single domain antibody with VHH–VHH format, whereas Enfamilomab is a VHH-Fc fusion.

ADCs are composed of a monoclonal antibody chemically linked to a small molecule drug as a payload. There have been 14 ADCs approved so far. Meanwhile, bispecifics are engineered antibodies or antibody fragments designed to combine two or more different antigen-binding domains in an integrated structure. There have been seven bispecific antibodies approved to date. The structures of bispecific antibodies include the heterodimeric bispecific antibody (Catumaxomab, Emicizumab, Amivantamab, Faricimab, Mosunetuzumab), scFv-based bispecific antibody such as bispecific T-cell engager (BiTE) (Blinatumomab), and IgG-scFv-based tetravalent (Cadonilimab). As for other special formats of antibody therapies, we have classified them into the “others” group, which includes antibody-conjugate immunotoxin (with a bacterial toxin, moxetumomab pasudotox), radiolabeled antibodies (Iodine 131 derlotuximab biotin, Iodine 131 Tositumomab), radiolabeled Fab fragments (Iodine 131 Metuximab), Fc-fusion proteins, an scFv fused with a TCR (Tebentafusp), and an antibody fused with an enzyme (Pabinafusp alfa).
Figure 2. Antibody discovery and engineering for approved antibodies. A: Antibody therapies of different degree of humanization: a: the non-human antibody; b: the chimeric antibody, where the variable region (green region) is from a non-human animal, and the other domains (blue region) are from human; c: humanized antibody, where only the hypervariable region fragment is non-human; d: full human antibody. B: Different engineering formats of approved antibody therapies: a. canonical antibodies; b. fragments: including Fab fragment, single-chain variable fragment (scFv), Fc fragment, the variable regions of camelid heavy-chain-only antibodies (VHH) fused with human Fc fragment or with another VHH; c. antibody drug conjugates (ADCs): monoclonal antibody conjugate with cytotoxic small molecule drug payloads; d. bispecifics: including heterodimeric bispecific antibody, scFv-scFv bispecific antibody such as bispecific T-cell engager (BiTE) and IgG-scFv-based tetravalent; e. others: including antibody-conjugate immunotoxin, radiolabeled canonical antibody, radiolabeled Fab fragment, Fc-fusion protein, a scFv fused with a soluble T-cell receptor (TCR), and an IgG fused with an enzyme. C: The number of different formats of antibody therapies for the year that they were first approved (Fc-fusion proteins are not included).
LANDSCAPES OF TARGETS AND INDICATIONS OF APPROVED ANTIBODY THERAPIES

There are several effects when an antibody binds to its targets, including blocking of a ligand, blocking receptor dimerization, mediating receptor internalization, antibody-dependent cellular phagocytosis, ADCC, and complement-dependent cytotoxicity [65]. Validation of a therapeutic target takes considerable research input, rendering the number of targets for clinical development very limited. There are 91 targets involved in the 162 approved antibody therapies. Some targets have been extensively studied, such as PD-1, CD3, CD20, EGFR, VEGF, and HER2, such that a large proportion of approved antibody therapies have been based on these targets, which are all cancer and immune-related disease targets [66–70]. It is notable that CD3 is used as a target for T cell-dependent bispecific antibodies, rather than as a direct tumor target for cancer treatment. Furthermore, other targets emerged recently such as the SARS-CoV-2 spike protein for SARS-CoV-2 infections since the Covid-19 pandemic (antibody therapy Regdanvimab, Amubarvimab + Romlusevimab cocktail, Sotrovimab, and Evusheld) and the CGRP for CNS diseases (antibody Fremanezumab, Galcanezumab, and Eptinezumab) (Fig. 3A).

For approved antibody therapies, 112 have been developed against 30 targets, and the remaining 61 targets are associated with the 63 antibody therapies. Of those antibody therapies against the 30 targets, seven are bispecific antibodies, one is a combination therapy (Relatlimab + Nivolumab), two are canonical antibodies (Ustekinumab and Bimekizumab), two are Fc-Fusion proteins (Abatacept and Belatacept) and one is an immunoconjugate (TebEntasusp) developed against two targets (thus counted twice), resulting in significant research and market competition on these popular targets. The most popular 20 targets are mainly applied to the treatment of cancers (PD-1/PD-L1, CD20 [71, 72], VEGF [69], EGFR [67, 73], HER2 [70], CD3 [74], CD19 [75], CD22 [76], GD2 [77]), immune-related diseases (TNF-alpha [59], IL-6R [78], IL-23 [79], IL-17A [80], IL-1 [81]), infectious diseases (SARS-CoV-2 spike protein [82], Rabies virus GP [83]), CNS diseases (CGRP [5]), and hematological disease (C5 [84], Factor IX [85]). Approval agencies of these antibodies and their targets are also presented showing different healthcare demands in these countries or regions (Fig. 3B).

Choices of therapeutic targets have progressed over time. Among the top 20 targets, there are some “new” targets (PD-1/PD-L1, CD19, SARS-CoV-2 spike protein, CGPR, Rabies virus GP, and IL-6R) with antibodies approved only after 2011. In contrast, the target TNF-alpha has no antibodies approved after 2010, showing that it has been thoroughly developed and left no market space. In 2018, the Nobel Prize for Physiology or Medicine was awarded to the discovery of the immune checkpoint PD-1, which acts as a “brake” for activated T cells in the tumor microenvironment and is considered to be a key target for the treatment of many cancers [86]. With the global pandemics of COVID-19, there came an emerging focus on the discovery of neutralizing antibodies for the prevention or treatment of respiratory syndromes from COVID-19, for which a total of four antibody therapies have been approved so far.

With respect to the indications of the approved antibodies, we have categorized seven classes based on their pathology. It can be easily interpreted that nearly half (42.6%) of the antibody therapies are for cancers, 37% for immune-related diseases, 11% for infectious diseases, and 7.4% for hematological diseases, whereas antibodies for other indications only account for < 3% (Fig. 3C). Likewise, interests on indications have changed over time. Cancers have always been the largest indication for antibody therapies, enabled by the extensive characterization of several key therapeutic targets, as discussed before. The first antibody therapy for the treatment of cancer, Rituximab, was a chimeric IgG1 mAb targeting CD20 and was approved for non-Hodgkin’s lymphoma in 1997 by the FDA [87, 88]. Rituximab worked well in the clinic as a chimeric antibody, as it caused prompt and nearly complete depletion of peripheral B cells, which alleviated the immunogenic concern introduced by the administration of a chimeric antibody. Antibody therapies have revolutionized the treatment of immune-related diseases due to their efficacy, specificity, speed of onset, and tolerability. It should be noted that CNS diseases have been an emerging therapeutic area for antibody therapies since 2016, in which antibodies could lead to some breakthrough treatments (Fig. 3D).

COMPANIES/ORGANIZATIONS

Scrutinizing the companies with at least one approved antibody, there are a total of 82 companies. The number of companies that have had their antibody therapies first approved by the FDA is 33. For the EMA, it is 15 companies, for the NMPA it is 17, for the PDMA it is 7, and for other agencies it is 10 (Fig. 4A and Table 1). The number of companies suggests that the US is in a leading position in antibody therapy as it also dominates the research and clinical development in the field. For the companies in the FDA group, most approvals occurred between 2016 and 2020, which is similar to the first approvals by the EMA, PMDA, and agencies in the other group. However, the year 2021 saw a peak (8 companies) in the number of companies that had first approvals by the NMPA (Fig. 4A). This suggests an enormous scale of research funding and capital was put into the field over the past decade in China.

For the top 10 companies with the greatest number of approved antibodies, their product portfolio shows different R&D focuses of therapeutic areas (Fig. 4B and Supplementary Table 1) such as cancer, immune-related disease, infectious disease, hematological disease, and CNS disease. GSK, BMS, Amgen, and Eli Lily show a stronger historical interest in cancer antibody therapies as they possess 5, 4, 3, and 3 approvals, respectively. In comparison, they possess 2, 2, 2, and 1 approvals in immune-related diseases, which are their second largest therapeutic field. Johnson & Johnson, AstraZeneca and Novartis show higher achievement in immune-related disease antibody therapies, as they possess 6, 3 and 3 approvals, which outnumber their approvals in cancer. Roche, Sanofi and
Figure 3. The landscape of targets and indications of approved antibody therapies based on the Umabs-DB data are available as of 30 June 2022. A: Statistics of the top 20 approved antibody targets by their first approval year; B: Top 20 targets and their related indications approved by different agencies; C: The proportion of different therapeutic areas of approved antibody therapies; D: Approval antibodies over indications and year of approval.

Figure 4. A. Companies with their first approval by different regulatory agencies (the MHRA from the UK is included in the Others group). B. Top 10 companies ranking by the number of approved antibody therapies.

Regeneron show a balanced output in antibody therapy for cancer (8, 2, and 2 approvals) and immune-related disease (8, 2 and 2 approvals). Hematological disorder has been more explored by AstraZeneca and Sanofi (2 and 2 approvals). Similarly, antibody therapy of infectious disease is characteristic to GSK and AstraZeneca (2 and 2 approvals).
CONCLUSION AND PERSPECTIVE

Antibody therapies have become the leading treatment for a range of human diseases. More than 160 antibody therapies have been approved in the world, but this is just a start. The emerging discovery technologies play an important role in speeding up R&D that will make more antibody candidates available for clinical development. Several antibody discovery technologies are widely applicable today, including hybridoma, in vitro display (phage display, yeast display and mammalian cell display, etc.) and single B cell technology. During the COVID-19 pandemic, several neutralizing antibodies that were discovered by characterizing single B cells in patients’ blood have been approved. Bamlanivimab (LY-CoV555) was the first antibody receiving FDA emergency use authorization to treat COVID-19 infection [89]. It only took a few months to complete the early discovery of neutralizing antibodies by the combination of single B cells characterization, NGS, and a machine learning algorithm. Furthermore, NGS, bioinformatics, and artificial intelligence are advancing antibody discovery to find and generate new antibody molecules that have better pharmacological properties. We believe further advancements in the fields of NGS, bioinformatics, and data-driven technology will continue to accelerate antibody discovery. Antibody discovery advancement and the discovery of new antibody targets will also combine to benefit the development of new antibody therapies.

The past decade has witnessed that the immunotherapeutic PD-1/PD-L1 blockade revolutionized the treatment of many types of cancer. The success of anti-PD-1/PD-L1 antibodies catalyzed the development of cancer immunotherapy. So far, the global regulatory authority has approved 12 antibodies targeting PD-1 (Pembrolizumab, Nivolumab, Sintilimab, Cemiplimab, Toripalimab, Tislelizumab, Camrelizumab, Proqolimab, Pembrolizumab, Dostarlimab, Zimberelimab, and Serplulimab) and five antibodies targeting PD-L1 (Atezolizumab, Durvalumab, Avelumab, Sugemalimab, and Envafolimab). In addition, a bispecific antibody targeting CTLA-4 and PD-1 (Cadonilimab) and a two-antibody cocktail targeting LAG-3 and PD-1 (Relatlimab + Nivolumab) were approved this year. However, among the immune checkpoint antibodies, only anti-CTLA-4 and anti-LAG-3 antibodies have shown promising efficacy in combination with anti-PD-1/PD-L1 antibodies; it may help overcome the limitations seen in prior treatments. Apart from PD-1/PD-L1 antibodies, the limited efficacy of the immune checkpoint antibodies encouraged the discovery of novel targets for cancer immunotherapy.

Over the past four decades, there has been a significant change in the spectrum of antibody modalities. Traditional modalities of antibody therapies are protein-based molecules including canonical antibodies, ADCs, bispecific antibodies, and antibody fragments. Recently, the Chinese Antibody Society (CAS) introduced a new concept of AntibodyPlus™ for future antibody therapies. The AntibodyPlus™ therapies contain an antibody component and/or other modalities in medicine such as cell and mRNA expressing antibody therapies. There is no doubt that CAR-T cell therapy is getting more attention in such AntibodyPlus™ therapies. The FDA has already approved five CAR-T cell therapies (Abecma [90], Breyanzi [91], Kymriah [92], Tecartus [93], and Yescarta [94]) to treat hematological malignancies. With the novel strategies introduced to enhance the efficacy of CAR-T cell therapies, we will see a breakthrough for the treatment of solid tumors soon. In addition, one more interesting modality of antibody therapies is mRNA-encoded antibodies. The mRNA-encoded antibody circumvents the problems of complex production and purification processes, aberrant post-translational modifications inherent in protein-based antibodies. In addition, a mixture of mRNA sequences can simplify the manufacturing of antibody cocktails [95, 96]. The potential of mRNA-based antibody therapies is one of the most attractive aspects of next-generation antibody therapies.

In spite of these advancements, antibody therapies are still one of the fastest growing therapeutic forms in the world. This is achieved by consistent investment in R&D and the maturation of emerging markets. The global antibody therapy industry and its market will be substantially larger in the future.

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None.

CONFLICT OF INTEREST STATEMENT

Xiaochen Lyu, Qichao Zhao and Hongyu Zhang are current employees of Zhanyuan Therapeutics Ltd., and Bo Liu is a current employee of Umabs Therapeutics Inc. Hongyu Zhang holds the position of Assistant Editor for Antibody Therapeutics and is blinded from reviewing or making decisions for the manuscript.

ETHICS AND CONSENT STATEMENT

The consent is not required.

ANIMAL ETHICS STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

All relevant data are available in Umabs Antibody Therapies Database (Umabs-DB, https://umabs.com).

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