Review

Immune- and Non-Immune-Mediated Adverse Effects of Monoclonal Antibody Therapy: A Survey of 110 Approved Antibodies

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Abstract: Identification of new disease-associated biomarkers; specific targeting of such markers by monoclonal antibodies (mAbs); and application of advances in recombinant technology, including the production of humanized and fully human antibodies, has enabled many improved treatment outcomes and successful new biological treatments of some diseases previously neglected or with poor prognoses. Of the 110 mAbs preparations currently approved by the FDA and/or EMA, 46 (including 13 antibody–drug conjugates) recognizing 29 different targets are indicated for the treatment of cancers, and 66, recognizing 48 different targets, are indicated for non-cancer disorders. Despite their specific targeting with the expected accompanying reduced collateral damage for normal healthy non-involved cells, mAbs, may cause types I (anaphylaxis, urticaria), II (e.g., hemolytic anemia, possibly early-onset neutropenia), III (serum sickness, pneumonitis), and IV (Stevens–Johnson syndrome, toxic epidermal necrolysis) hypersensitivities as well as other cutaneous, pulmonary, cardiac, and liver adverse events. MAbs can provoke severe infusion reactions that resemble anaphylaxis and induce a number of systemic, potentially life-threatening syndromes with low frequency. A common feature of most of these syndromes is the release of a cascade of cytokines associated with inflammatory and immunological processes. Epidermal growth factor receptor-targeted antibodies may provoke papulopustular and mucocutaneous eruptions that are not immune-mediated.

Keywords: approved monoclonal antibodies; monoclonal antibody adverse events; monoclonal antibody hypersensitivities; monoclonal antibody non-immune adverse events; monoclonal antibody immune adverse events; monoclonal antibody targets

1. Introduction

In the last decade, along with the continuing development of the disciplines of genomics, proteomics, and bioinformatics and the application of molecular biological approaches to elucidate the functions of single genes, advances have led to insights into the complexities and multifaceted nature of diseases such as cancer, immune and inflammatory-based diseases, metabolic disorders, neurological diseases, transplantation, and some poorly understood dermatologic toxicities [1–6]. Specific, targeted approaches now employed in many monoclonal antibody (mAb), fusion protein, and cytokine therapies have been enabled by advances in recombinant DNA technology, the preparation of human recombinant antibody libraries, today’s sequencing methods, parallel proteome analyses employing techniques such as mass spectroscopy, and single B cell technologies [5–7]. The U.S. Food and Drug Authority (FDA) Office of Orphan Products Development and its European equivalent have provided extra stimulus for the development of therapies for “orphan diseases”, that is, diseases with less than 200,000 patients [8]. This stimulus has led to the introduction of effective approved mAb therapies for some diseases with low
patient numbers previously neglected because of the lack of pathogenetic and pathophysi-
ological insights into rare disorders where the potentially small market often precluded
investigations [9].

Expanding understanding of ligand–receptor interactions; downstream signaling; and
the delineation of immunological and inflammatory interplay between cells, anti-bodies,
cytokines, and chemokines has contributed to the identification and selection of new disease
biomarker targets. This, in turn, has created the opportunity to specifically target implicated
cells, largely without inflicting collateral damage on normal healthy non-involved cells [10].
However, in addition to true hypersensitivities and infusion reactions, the expanding list of
disease indications has sometimes brought with it adverse effects on the lungs, heart, liver,
immune system, and skin in a variety of poorly, or partially understood, complex adverse
responses [3]. A number of systemic potentially life-threatening syndromes most associated
with inflammatory and immunological processes, often with cytokine involvement, also
occur with low frequency during or following mAb therapy [3].

Although there are many hundreds of mAbs intended for therapeutic use at various
stages of development, here we restrict examination to the 110 antibodies currently regis-
tered and approved by the U.S. Food and Drug Administration (FDA) and/or European
Medicines Agency (EMA). Note, however, that some of these mAbs were first approved by
other agencies while some others are already approved by other agencies but not the FDA
and EMA.

Here, focus is directed to the classification of the 110 mAbs, their antibody targets,
approved disease indications, and the adverse events associated with their use.

2. Evolution of Monoclonal Antibodies to Avoid Immunogenicity

Early realization that the murine composition of the first mAbs provoked a high
incidence of adverse events including anaphylaxis and cytokine release syndrome, to-
gether with their poor pharmacokinetics, led to an ongoing iterative program to reduce,
and ultimately eliminate, these undesirable features [3,11,12]. The mouse mAbs ibritu-
momab tiuxetan and tositumomab were soon followed by chimeric antibodies such as
abciximab, cetuximab, infliximab, and others in which variable (antigen binding) regions
were inserted into the constant regions of human immunoglobulins (Figure 1). Occasional
serious hypersensitivities occurring after chimeric antibody infusions led to production of
so-called humanized antibodies in which only approx. 5–10% of murine proteins remained
after substituting mouse complementarity-determining (hypervariable) regions in place
of human sequences (Figure 1). It became apparent, however, that even single amino acid
changes could result in changes in antibody binding and affinity, and posttranslational
glycosylation sometimes produced reductions in specificity, potency, and solubility with-
out a reduction in immunogenicity. Development of the powerful technologies of phage
display and transgenic mice finally enabled the production of fully human mAbs; however,
immunogenicity can still be an occasional problem [3] due to the presence of anti-idiotype
antibodies and antibodies to some mAbs (anti-glycan, anti-hinge, anti-allotype, rheumatoid
factors) occurring in normal sera and sera of pretreated patients.
Figure 1. Evolution of the development of therapeutic monoclonal antibodies from murine to fully human proteins to avoid unwanted immunogenicity. The iterative process proceeded stepwise through chimeric constructs incorporating mouse immunoglobulin variable regions into constant regions of human immunoglobulins and via humanized antibodies by substituting mouse complementarity determining regions (CDRs) in place of human sequences. Fully human antibodies have been developed with the application of phage display and transgenic mice technologies. Reproduced with permission from Baldo BA. Safety of biologics therapy. Monoclonal antibodies, cytokines, fusion proteins, hormones, enzymes, coagulation proteins, vaccines, botulinum toxins. Cham, Switzerland: Springer Nature; 2016 [3].

3. Monoclonal Antibody Targets and Indications

Of the 110 currently approved and registered mAbs (Tables 1 and 2), two, alemtuzumab and denosumab, are each marketed as two separately approved products with different indications for each. Alemtuzumab, under trade names of Lemtrada® and Campath®/MabCampath®, is indicated for multiple sclerosis and B cell chronic lymphocytic leukemia, respectively, while denosumab as Prolia® is indicated for bone loss and, as Xgeva®, for bone metastases from solid tumors and giant cell tumor of bone [15,16]. Therefore, while the total number of approved mAbs shown in Tables 1 and 2 is 112 (66 for non-cancer and 46 for cancer therapies), alemtuzumab and denosumab each appear in both lists under different trade names.

Table 1. Therapeutic monoclonal antibodies for non-cancer therapy currently marketed with regulatory approval from the U.S. FDA or EMA or both (as at December 2021).

| Monoclonal Antibody INN and Trade Names | Antibody Type | Target | Approved Indications |
|----------------------------------------|--------------|--------|----------------------|
| **Human–Mouse Chimeric (-ximab)**      |              |        |                      |
| Abciximab (ReoPro®)                    | Chimeric IgG Fab | Glycoprotein IIb/IIIa | Adjunct therapy for prevention of cardiac ischemic complications |
| Basiliximab (Simulect®)                | Chimeric IgG1 | α-chain IL-2 receptor (CD25) | Prevent organ transplant rejection |
| Infliximab (Remicade®)                 | Chimeric IgG1 | TNF | Crohn’s disease; ulcerative colitis; RA; ankylosing spondylitis; psoriatic arthritis; plaque psoriasis |
| Obiltoxaximab (Anthim®)                | Chimeric IgG1 | *Bacillus anthracis* PA | Inhalational anthrax *Bacillus anthracis* PA |
| Monoclonal Antibody INN and Trade Names | Antibody Type | Target | Approved Indications |
|----------------------------------------|---------------|--------|---------------------|
| **Humanized (-zumab)**                 |               |        |                     |
| Alemtuzumab (Lemtrada<sup>®</sup>)     | Humanized IgG1| CD52   | Lemtrada<sup>®</sup>: multiple sclerosis |
| Benralizumab (Fasenra<sup>®</sup>)     | Humanized IgG1 (afucosylated) | IL-5Rx | Asthma |
| Bimekizumab (Bimzelx<sup>®</sup>)      | Humanized IgG1| IL-17A, IL-17E, IL-17AF | Plaque psoriasis |
| Brolucizumab (Beovu<sup>®</sup>)       | Humanized single-chain (scFv) fragment | VEGF-A | Neovascular (wet) age-related macular degeneration |
| Caplacizumab-yhdp (Caplivi<sup>®</sup>) | Humanized bivalent single-domain nanobody | von Willebrand factor (vWF) | Acquired thrombotic thrombocytopenic purpura |
| Certolizumab pegol (Cimzia<sup>®</sup>)| Humanized IgG1 Fab, pegylated | TNF | Crohn’s disease; RA |
| Crizanlizumab-tmca (Adakveo<sup>®</sup>)| Humanized IgG2 | P-selectin | Sickle cell disease |
| Daclizumab (Zinbryta<sup>®</sup>)      | Humanized IgG2| α-chain IL-2 receptor (CD25) | Multiple sclerosis |
| Eculizumab (Soliris<sup>®</sup>)       | Humanized IgG2/4 | Complement C5 | Paroxysmal nocturnal hemoglobinuria; atypical hemolytic uremic syndrome; neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive |
| Emmicizumab-kxwh (Hemlibra<sup>®</sup>)| Humanized IgG4 bispecific | Factors IXa and X | Hemophilia A |
| Eptinezumab-jjmr (Vyepti<sup>®</sup>)  | Humanized IgG1 | CGRP | Migraine |
| Fremanezumab-vfrm (Ajovy<sup>®</sup>)  | Humanized IgG4 | CGRP | Migraine |
| Galcanezumab-gnlm (Emgality<sup>®</sup>)| Humanized IgG4 | CGRP | Migraine |
| Ilbuzumab-uiyk (Trogarzo<sup>®</sup>)  | Humanized IgG4 | CD4 | HIV-1 infection |
| Idarucizumab (Praxbind<sup>®</sup>)    | Humanized IgG1 antibody fragment Fab | Dabigatran | Reversal of anticoagulant effects of dabigatran; life-threatening or uncontrolled bleeding |
| Inebilizumab-cdon (Uplizna<sup>®</sup>)| Humanized afucosylated IgG1 | CD19 | Neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive |
| Ixekizumab (Taltz<sup>®</sup>)         | Humanized IgG4 | IL-17A | Plaque psoriasis; psoriatic arthritis |
| Mepolizumab (Nucala<sup>®</sup>)       | Humanized IgG1 | IL-5 | Asthma; eosinophilic granulomatosis with polyangiitis |
| Natalizumab (Tysabri<sup>®</sup>)      | Humanized IgG4 | α4 integrin (binds to α4β1 and α4β7 integrins) | Multiple sclerosis; Crohn’s disease |
| Monoclonal Antibody INN and Trade Names | Antibody Type | Target | Approved Indications |
|----------------------------------------|--------------|--------|---------------------|
| Ocrelizumab (Ocrevus®)                 | Humanized IgG1 | CD20   | Multiple sclerosis  |
| Omalizumab (Xolair®)                   | Humanized IgG1 | IgE    | Persistent asthma; chronic idiopathic urticaria |
| Palivizumab (Synagis®)                 | Humanized IgG1 | RSVF   | Prevention of lower respiratory tract disease RSV in children |
| Ranibizumab (Lucentis®)                | Humanized IgG1 Fab | VEGF-A | Neovascular (wet) age-related macular degeneration; macular edema following retinal vein occlusion; diabetic macular edema |
| Ravulizumab-cwvz (Ultomiris®)          | Humanized IgG2/4 | Complement C5 | Paroxysmal nocturnal hemoglobinuria |
| Reslizumab (Cinqair®)                  | Humanized IgG4 | IL-5   | Asthma              |
| Risankizumab-rraa (Skyrizi®)           | Humanized IgG1 | IL-23 p19 | Plaque psoriasis |
| Romosozumab-aqqg (Evenity®)            | Humanized IgG2 | Sclerostin | Osteoporosis |
| Satralizumab-mwge (Enspryng®)          | Humanized IgG2 | IL-6R  | Neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive |
| Tildrakizumab-asmn (Ilumetri®; Ilumya®) | Humanized IgG1 | IL-23 p19 | Plaque psoriasis |
| Tocilizumab (Actemra®; RoActemra®)     | Humanized IgG1 | IL-6R  | RA; polyarticular juvenile idiopathic arthritis; systemic juvenile idiopathic arthritis |
| Vedolizumab (Entyvio®)                 | Humanized IgG1 | α4β7 integrin | Adult ulcerative colitis; adult Crohn’s disease |
| **Fully human (-umab)**                |              |        |                     |
| Adalimumab (Humira®)                   | Human IgG1   | TNF    | RA; psoriatic arthritis; ankylosing spondylitis; plaque psoriasis; Crohn’s disease |
| Aducanumab-avwa (Aduhelm®)             | Human IgG1   | Amyloid beta | Alzheimer’s disease |
| Alirocumab (Praluent®)                 | Human IgG1   | PCSK9  | Heterozygous FH; atherosclerotic CV disease requiring additional ↓ of LDL-C |
| Anifrolumab-fnia (Saphnelo®)           | Human IgG1   | Subunit I type I interferon receptor (IFNAR) | Systemic lupus erythematosus |
| Ansuvimab-zykl (Ebanga®)               | Human IgG1   | Zaire ebolavirus (EBOV) glycoprotein 1 (GP1) | Zaire ebolavirus infection |
| Atoltivimab, Maftivimab and Odesivimab-ebgn (Inmazeb®) | Human IgG1 | Zaire ebolavirus (EBOV) glycoprotein 1 (GP1) | Zaire ebolavirus infection |
Table 1. Cont.

| Monoclonal Antibody INN and Trade Names | Antibody Type | Target | Approved Indications |
|----------------------------------------|---------------|--------|----------------------|
| Belimumab (Benlysta<sup>®</sup>)       | Human IgG1    | BlyS   | Systemic lupus erythematosus |
| Bezlotoxumab (Zinplava<sup>®</sup>)    | Human IgG1    | *Clostridium difficile* toxin B | Recurrence of *Clostridium difficile* toxin B infection |
| Brodalumab (Siliq<sup>®</sup>; Kyntheum<sup>®</sup>; Lumicef<sup>®</sup>) | Human IgG2    | IL-17RA | Plaque psoriasis |
| Burosumab-twza (Crysvita<sup>®</sup>)  | Human IgG1    | FGF23  | X-linked hypophosphatemia |
| Canakinumab (Ilaris<sup>®</sup>)       | Human IgG1    | IL-1β  | Cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory and Muckle–Wells syndromes; SJIA with body weight ≥7.5 kg; NOMID/CINCA; FCAS/FCU; gouty arthritis |
| Casirivimab + Imdevimab (REGEN-COV<sup>®</sup>; Ronapreve<sup>®</sup>) | Human IgG1 | The 2 mAbs bind to separate epitopes of the spike protein RBD of SARS-CoV-2, thus preventing its binding to the human ACE2 receptor and subsequent cell entry | COVID-19 disease |
| Canakinumab (Ilaris<sup>®</sup>)       | Human IgG1    | RANKL  | Bone loss—for osteoporosis and to increase bone mass in menopausal women at high risk of fracture |
| Dupilumab (Dupixent<sup>®</sup>)       | Human IgG4    | IL-4Rx subunit | Atopic dermatitis |
| Efgartigimod-alfa-fcab (Vyvgart<sup>®</sup>) | Human IgG1 Fc fragment | Neonatal Fc receptor FcRn | Generalized myasthenia gravis |
| Emapalumab-lzsg (Gamifant<sup>®</sup>) | Human IgG1    | IFNγ   | HLH |
| Erenumab-zooe (Aimovig<sup>®</sup>)    | Human IgG2    | CGRP receptor | Migraine |
| Evinacumab-dgnb (Evkeeza<sup>®</sup>)  | Human IgG4    | ANGIPTL3 (angiotopoietin-like 3) | Homozygous familial hypercholesterolemia (HoFH) |
| Evolocumab (Repatha<sup>®</sup>)       | Human IgG2    | PCSK9  | Primary hyperlipidemia and mixed dyslipidemia; homozygous FH to reduce LDL-C and other lipids |
| Golimumab (Simponi<sup>®</sup>)        | Human IgG1    | TNF    | RA; psoriatic arthritis (both in combination with methotrexate); ankylosing spondylitis |
| Guselkumab (Tremfya<sup>®</sup>)       | Human IgG1    | IL-23  | Plaque psoriasis |
| Lanadelumab-flyo (Takhzyro<sup>®</sup>) | Human IgG1    | Plasma kallikrein | HAE prevention |
| Raxibacumab (ABthrax<sup>®</sup>)      | Human IgG1    | *Bacillus anthracis* PA | Inhalational anthrax to *Bacillus anthracis* and prophylaxis in absence of alternative therapies |
Table 1. Cont.

| Monoclonal Antibody INN and Trade Names | Antibody Type | Target | Approved Indications |
|----------------------------------------|---------------|--------|----------------------|
| Regdanvirimab (Regkirona®)             | Human IgG1    | mAb binds to the spike protein RBD of SARS-CoV-2 preventing its binding to the human ACE2 receptor and subsequent cell entry | COVID-19 disease |
| Sarilumab (Kevzara®)                   | Human IgG1    | IL-6R  | RA                   |
| Secukinumab (Cosentyx®)                | Human IgG1    | IL-17A | Moderate to severe plaque psoriasis |
| Sotrovimab (Xevudy®)                   | Human IgG1    | Spike protein RBD of SARS-CoV-2 | COVID-19 disease |
| Teprotumab-trbw (Tepezza®)             | Human IgG1    | IGF-1R | Thyroid eye disease |
| Tezepelumab-ekko (Tezspire®)           | Human IgG2    | Thymic stromal lymphopoietin | Severe asthma |
| Tralokinumab (Adtralza®)               | Human IgG4    | IL-13  | Atopic dermatitis |
| Ustekinumab (Stelara®)                 | Human IgG1    | IL-12, IL-23 | Plaque psoriasis |

ACE2—angiotensin-converting enzyme 2; ADCC—antibody-dependent cell-mediated cytotoxicity; BlyS—B lymphocyte stimulator, also known as B cell-activating factor, BAFF; C5—complement component 5; CDC—complement-dependent cytotoxicity; CGRP—calcitonin gene-related peptide; CHO—Chinese hamster ovary cells; CINCA—chronic infantile neurological, cutaneous, articular syndrome; COVID—coronavirus disease; CV—cardiovascular; EMA—European Medicines Agency; FCAS—familial cold autoinflammatory syndrome; FCU—familial cold urticaria; FDA—U.S. Food and Drug Administration; FH—familial hypercholesterolemia; GFG23—fibroblast growth factor 23; GI—gastrointestinal; HAE—hereditary angioedema; HIV—human immunodeficiency virus; HLH—primary hemophagocytic lymphohistiocytosis; IGF-1R—insulin-like growth factor-1 receptor; IPP—International Nonproprietary Name; LDL—low-density lipoprotein; LDL-C—LDL-cholesterol; LDLR—LDL receptor; NOMID—neonatal-onset multisystem inflammatory disease; NSCLC—non-small cell lung cancer; NSO—non-Ig-secreting, non-L chain-synthesizing, 8-azaguanine-resistant and HAT-sensitive mouse myeloma cell line; PA—protective antigen of B. anthracis toxin; PCSK9—proprotein convertase subtilisin/kexin type 9; RA—rheumatoid arthritis; RANKL—receptor activator of nuclear factor kappa-B ligand (CD254), a member of the TNF cytokine family; RBD—receptor-binding domain; RSV—human respiratory syncytial virus (F viral protein coat antigen); SARS-CoV-2—severe acute respiratory syndrome coronavirus 2; SJIA—active systemic juvenile idiopathic arthritis; Sp2/0—BALB/c mouse spleen cells fused with P3 myeloma. Cells do not secrete Ig, are resistant to 8-azaguanine, and are HAT-sensitive; TNP—tumor necrosis factor; VEGF—vascular endothelial growth factor (a subfamily of growth factors; includes VEGF-A); VEGFR2—vascular endothelial growth factor receptor 2, also known as KDR (kinase insert domain-containing receptor), FLK1 (fetal liver kinase 1), or CD309. 1 Note added in press: Approved by the FDA 17 December 2021. ↓ decrease.

Table 2. Therapeutic monoclonal antibodies for cancer therapy currently marketed with regulatory approval from the U.S. FDA or EMA or both (as at December 2021).

| Monoclonal Antibody INN and Trade Name | Type of mAb | Target | Approved Indications |
|----------------------------------------|-------------|--------|----------------------|
| Rat mouse chimera (-axomab)            | Rat IgG2b/Mouse IgG2a bispecific | EpCAM/CD3 | Malignant ascites |
| Catumaxomab (Removab®)                |             |        |                      |
| Mouse (-omab)                          |             |        |                      |
| Blinatumomab (Blincyto®)               | Mouse scFv-H bispecific | CD19/CD3 epsilon | Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia |
| Monoclonal Antibody INN and Trade Name | Type of mAb | Target | Approved Indications |
|---------------------------------------|-------------|--------|---------------------|
| Ibritumomab tiuxetan (Zevalin<sup>®</sup>) | Mouse IgG1 | CD20   | Non-HL              |
| Moxetumomab pasudox-tdfk (Lumoxiti<sup>®</sup>) | ADC immunotoxin. Mouse single chain variable domain (scFv) | CD22   | HCL                |
| **Human-mouse chimeric (-ximab)**       |             |        |                     |
| Brentuximab vedotin (Adcetris<sup>®</sup>) | Chimeric IgG1 | CD30   | HL after failure of stem cell transplant or chemotherapy; sALCL after failure of chemotherapy; post auto-HSCT consolidation treatment for HL |
| Cetuximab (Erbitux<sup>®</sup>)         | Chimeric IgG1 | EFG    | Colorectal and head and neck cancers |
| Dinutuximab (Unituxin<sup>®</sup>)      | Chimeric IgG1 | GD2    | Pediatric patients with high-risk neuroblastoma |
| Isatuximab-irfc (Sarclisa<sup>®</sup>)  | Chimeric IgG1 with 2 identical H and κ L chains | CD38   | MM               |
| Margetuximab-cmkb (Margenza<sup>®</sup>) | Chimeric IgG1 | HER2   | HER2-positive breast cancer |
| Rituximab (Rituxan<sup>®</sup>; MabThera<sup>®</sup>) | Chimeric IgG1 | CD20   | Non-HL; CLL; rheumatoid arthritis; Wegener’s granulomatosis; microscopic polyangiitis |
| Siltuximab (Sylvant<sup>®</sup>)        | Chimeric IgG1 | IL-6   | Multicentric Castelman’s disease in patients negative for HIV and HHV-8 |
| **Humanized (-zumab)**                  |             |        |                     |
| Ado-trastuzumab emtansine (Kadcyla<sup>®</sup>) | ADC. Humanized IgG1 | HER2   | HER2-positive breast cancer in patients who previously received trastuzumab or a taxane |
| Alemtuzumab (Campath<sup>®</sup>; MabCampath<sup>®</sup>) | Humanized IgG1 | CD52   | Campath, MabCampath: B cell CLL |
| Atezolizumab (Tecentriq<sup>®</sup>)    | Humanised IgG1 | PD-L1  | MUC; NSCLC         |
| Bevacizumab (Avastin<sup>®</sup>)       | Humanized IgG1 | VEGF-A | Metastatic colorectal cancer; non-squamous NSCLC; metastatic breast cancer; ovarian cancer; glioblastoma Endometrial cancer |
| Dostarlimab-gxly (Jemperli<sup>®</sup>) | Humanized IgG4 | PD-1   |                     |
| Elotuzumab (Empliciti<sup>®</sup>)      | Humanised IgG1 | SLAMF7 | MM                |
| Fam-trastuzumab deruxtecan-nxki (Enheru<sup>®</sup>) | ADC. Humanised IgG1 | HER2   | HER2-positive breast, gastric, and GE adenocarcinomas |
| Gemtuzumab ozogamicin (Mylotarg<sup>®</sup>) | ADC. Humanized IgG4 | CD33   | AML               |
| Inotuzumab ozogamicin (Besponsa<sup>®</sup>) | ADC. Humanized IgG4 | CD22   | ALL               |
Table 2. Cont.

| Monoclonal Antibody INN and Trade Name | Type of mAb | Target | Approved Indications |
|----------------------------------------|-------------|--------|----------------------|
| Loncastumab tesirine-lpyl (Zynlonta<sup>®</sup>) | ADC. Humanized IgG1 | CD19 with tesirine cytotoxic agent | LBCL including DLBCL |
| Mogamulizumab-kpkc (Poteligeo<sup>®</sup>) | Humanized IgG1 | CCR4 | Mycosis fungoides; Sézary syndrome |
| Naxitamab-gqgk (Danyelza<sup>®</sup>) | Humanized IgG1 | GD2 | Neuroblastoma—antibody given in combination with GM-CSF |
| Obinutuzumab (Gazyva<sup>®</sup>; Gazyvaro<sup>®</sup>) | Humanized IgG1 | CD20 | In combination with chlorambucil for previously untreated CLL |
| Pembrolizumab (Keytruda<sup>®</sup>) | Humanized IgG4 | PD-1 | Unresectable or metastatic melanoma; refractory metastatic NSCLC tumors that express PD-L1 |
| Pertuzumab (Perjeta<sup>®</sup>) | Humanized IgG1 | HER2 | Combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer |
| Polatuzumab vedotin-piiq (Polivy<sup>®</sup>) | ADC. Humanized IgG1 | CD79b | Diffuse large B cell lymphoma |
| Sacituzumab govitecan-hziy (Trodelvy<sup>®</sup>) | ADC. Humanized IgG1 | Trop-2 with topoisomerase inhibitor | mTNBC |
| Tafasitamab-cxix (Monjuvi<sup>®</sup>) | Humanized IgG1/2 with hybrid Fc-modified domain | CD19 | DLBCL |
| Trastuzumab (Herceptin<sup>®</sup>) | Humanized IgG1 | HER2 | Breast cancer overexpressing HER2, metastatic gastric or GE junction adenocarcinoma overexpressing HER2 |
| Fully human (-umab) | | | |
| Amivantamab-vmjw (Rybrevent<sup>®</sup>) | Bi-specific low fucose human IgG1-based antibody | EGFR and c-MET receptors | NSCLC |
| Avelumab (Bavencio<sup>®</sup>) | Human IgG1 | PD-L1 | MCC; UC; RCC |
| Belantamab mafodotin-blmf (Blenrep<sup>®</sup>) | ADC afucosylated IgG1 | BCMA with MMAF microtubule inhibitor | MM |
| Cemiplimab-rwlc (Libtayo<sup>®</sup>) | Human IgG4 | PD-1 | CSCC |
| Daratumumab (Darzalex<sup>®</sup>) | Human IgG1 | CD38 | MM |
| Denosumab (Prolia<sup>®</sup>; Xgeva<sup>®</sup>) | Human IgG2 | RANKL | Bone loss. Prolia: for osteoporosis and to increase bone mass; Xgeva: for bone metastases from solid tumors and giant cell tumor of bone |
| Durvalumab (Imfinzi<sup>®</sup>) | Human IgG1 | PD-L1 | UC |
| Enfortumab-vedotin-ejfv (Padcev<sup>®</sup>) | ADC human IgG1 | Nectin-4 with MMAE microtubule inhibitor | UC |
| Ipilimumab (Yervoy<sup>®</sup>) | Human IgG1 | CTLA-4 | Metastatic melanoma |
Table 2. Cont.

| Monoclonal Antibody INN and Trade Name | Type of mAb | Target | Approved Indications |
|----------------------------------------|-------------|--------|----------------------|
| Necitumumab (Portrazza®)               | Human IgG1  | EGFR   | Squamous NSCLC        |
| Nivolumab (OPDIVO®)                    | Human IgG4  | PD-1   | Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600-positive, a BRAF inhibitor; NSCLC |
| Ofatumumab (Arzerra®)                  | Human IgG1  | CD20   | CLL refractory to fludarabine and alemtuzumab |
| Olaratumab (Lartruvo®)                 | Human IgG1  | PDGFR-α| Soft tissue sarcoma   |
| Panitumumab (Vectibix®)                | Human IgG2  | EGFR   | Metastatic colorectal cancer |
| Ramucirumab (Cyramza®)                 | Human IgG1  | VEGFR2 | Gastric or GE junction adenocarcinoma; metastatic NSCLC with docetaxel after platinum therapy; HCC; with FOLFIRI for metastatic colorectal cancer |
| Tisotum vedotin-tftv (Tivdak®)          | ADC human IgG1 | TF with MMAE microtubule inhibitor | Cervical cancer |

ADC—antibody drug conjugate; ALL—acute lymphoblastic leukemia; auto-HSCT—autologous hematopoietic stem cell transplantation; BRAF—proto-oncogene B-Raf; C5—complement component 5; CLL—chronic lymphocytic leukemia; CTLA-4—cytotoxic T lymphocyte-associated antigen 4 or CD152; CSCC—cutaneous squamous cell carcinoma; DLBCL—diffuse large B cell lymphoma; EGFR—epidermal growth factor receptor; EMA—European Medicines Agency; EpCAM—epithelial cell adhesion molecule; FDA—U.S. Food and Drug Administration; FOLFIRI—combination of folinic acid (leucovorin), fluorouracil, and irinotecan; CD2—glycolipid disialoganglioside on neuroblastoma, central nervous system, and peripheral nerve cells; GE—gastroesophageal; HCC—hepatocellular carcinoma; HCL—hairy cell leukemia; HER2—human epidermal growth factor receptor 2, also known as HER2/neu, ErbB2, CD340, p185, or EGFR2; HL—Hodgkin lymphoma; IPP—International Nonproprietary Name; LBL—large B cell lymphoma; MCC—Merkel cell carcinoma; MM—multiple myeloma; MMAE—cytotoxic agent monomethyl auristatin E; MMAF—cytotoxic agent monomethyl auristatin F; mTNBC—metastatic triple-negative breast cancer; MUC—metastatic urothelial carcinoma; NSCLC—non-small cell lung cancer; PD-1—programmed cell death protein 1 or CD279; PD-L1—programmed cell death protein ligand 1; RANKL—receptor activator of nuclear factor kappa-B ligand (CD254), a member of the TNF cytokine family; RCC—renal cell carcinoma; sALCL—systemic anaplastic large cell lymphoma; teserine—also known as SG3249, a pyrrolobenzodiazepine dimer; TF—tissue factor, platelet tissue factor, factor III, CD142; Trop-2—trophoblast cell surface antigen-2; UC—urothelial carcinoma; VEGF—vascular endothelial growth factor (a subfamily of growth factors; includes VEGF-A); VEGFR2—vascular endothelial growth factor receptor 2, also known as KDR (kinase insert domain-containing receptor), FLK1 (fetal liver kinase 1), or CD309.

With the steady increase in the identification and association of biomarker targets [3,17] for an expanding range of diseases, a total of 77 different targets have thus far been utilized in the preparation of the 110 currently approved mAbs with some targets complementary to more than one mAb (Table 3). In particular, there are 29 targets for the 46 different mAb cancer therapies (Table 2) and a collective of 48 targets for a diverse range of 66 mAbs for non-cancer disorders, including 27 inflammatory and/or immune disorders and 39 other diseases/applications (Table 1). For the mAbs used for non-cancer therapies, 14 different targets have been employed two or more times (Table 3). For example, TNF as target has been utilized for four mAbs—adalimumab, certolizumab pegol, golimumab, and infliximab—each used in the treatments of inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, and Crohn’s disease. IL-6R serves as target for three different mAbs—sarilumab and tocilizumab, each used to treat rheumatoid arthritis, and satralizumab-mwge, indicated for a quite different condition, neuromyelitis optica spectrum disorder (Tables 1 and 3). For the treatment of cancers, eight different targets are utilized for more than one mAb. The targets HER2, EGFR, programmed
cell death protein 1 PD-1, and its ligand PD-L1 have been used as complementary targets for, respectively, five, four, three, and four different mAbs (Tables 2 and 3).

### Table 3. Targets with more than one complementary approved therapeutic monoclonal antibody.

| Target | Monoclonal Antibodies |
|--------|------------------------|
| TNF    | Adalimumab; certolizumab pegol; golimumab; infliximab |
| PCSK9  | Alirocumab; evolocumab |
| EBOV GP1 | Ansuvimab-zykl; atoltivimab; mafitivimab; odesivimab-ebgn |
| IL-2 receptor α chain (CD25) | Basiliximab; daclizumab |
| VEGF-A | Brolocizumab-dbll; ranibizumab |
| ACE2 RBD of SARS-CoV-2 | Casirivimab + imdevimab; regdanvirimab; Sotrovimab |
| Complement C5 | Eculizumab; ravulizumab-cvvz |
| CGRP   | Êptinezumab-jjmr; fremanezumab-vfrm; galcanezumab-gnlm |
| IL-17A | Ixekizumab; secukinumab |
| IL-5   | Mepolizumab; reslizumab |
| α4 integrin | Natalizumab; vedolizumab |
| Bacillus anthracis | Obiltoxaximab; raxibacumab |
| IL-23 p19 | Risankizumab-zaa; tildrakizumab-asmn |
| IL-6R  | Sarilumab; satralizumab-mwge; tocilizumab |

**Monoclonal antibodies for non-cancer therapy**

**Monoclonal antibodies for cancer therapy**

For expansion of target abbreviations, see Tables 1 and 2.

### 4. Adverse Events to Monoclonal Antibody Therapy

Despite their target specificity, their low tendency for drug–drug interactions, and their generally better patient tolerance than small molecule drugs, mAbs are, unsurprisingly, not free of adverse effects, which may manifest as immune, non-immune, or direct cytotoxic reactions. Tables 4 and 5 summarize adverse events associated with mAbs used for non-cancer and cancer therapies, respectively. For all mAbs, there is the possibility of injection site reactions, infusion reactions, hypersensitivity, and immunogenicity, although these effects are more likely with some mAbs than others. Many of the approved mAbs are subject to warnings for “hypersensitivity”, often without further qualification, which is generally unhelpful given the loose usage of this term and the fact that it often has a different meaning to clinicians and investigators in different branches of medicine [18,19].
Immunogenicity is always a concern even with fully human antibodies since anti-idiotype responses can occur [3,20].

Adverse events, divided into immune, that is true hypersensitivities, and non-immune, are herein considered.

Table 4. Adverse events associated with approved 1 monoclonal antibodies used for non-cancer therapies (as at December 2021).

| Monoclonal Antibody 2 | Target 3 | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events 4, Serious and Common |
|-----------------------|----------|-------------------------------------------------|------------------------------------------|
| Abciximab (ReoPro®)   | Glycoprotein IIb/IIIa | Increased risk of bleeding; thrombocytopenia | Systemic: Bleeding; intracranial hemorrhage or stroke; GI; CV; anemia; NS; respiratory; urinary disorders
Cutaneous: Pruritus; generalized exanthema |
| Adalimumab (Humira®)  | TNF      | **Boxed warning**: Serious infections; malignancy Other: Anaphylaxis, serious allergic reactions; hepatitis B reactivation; demyelinating disease; cytopenias; heart failure; lupus-like syndrome Systemic: Infections; isr; ILD; sarcoidosis; liver failure Cutaneous: SJS; EM; psoriasis; cutaneous vasculitis; alopecia |
| Aducanumab-avwa (Aduhelm®) | Amyloid beta | Amyloid-related imaging abnormalities (ARIA); hypersensitivity Systemic: Headache; ARIA-oedema, -headache, -H microhemorrhage, -H superficial siderosis, fall |
| Alemtuzumab (Lemtrada®) | CD52     | **Boxed warning**: Autoimmunity; IRs; malignancies Other: Other immune cytopenias; glomerular nephropathies; thyroid disorders; delay therapy in cases of infections; pneumonitis Systemic: Headache; pyrexia; nausea; UTI; herpes virus infection; extremity and back pain; dizziness; flushing; cough; chills; vomiting; dyspnea Cutaneous: Rash; urticaria; pruritus; dermatitis |
| Alirocumab (Praluent®) | PCSK9    | Allergic reactions (pruritus, urticaria, rash) including some serious (including hypersensitivity vasculitis) Systemic: Nasopharyngitis; isr; influenza; URTI; cough; sinusitis; bronchitis; diarrhea; myalgia; muscle spasms; musculoskeletal pain; liver enzyme abnormalities |
| Anifrolumab-fnia (Saphnelo®) | IFNAR   | Serious infections; hypersensitivity; malignancy; avoid live attenuated vaccines and other biological therapies Systemic: Nasopharyngitis; URTI; IR; bronchitis; herpes zoster; cough |
| Ansuvimab-zykl (Ebanga®) | EBOV GP1 | Hypersensitivity; IR Systemic: Pyrexia; tachycardia; diarrhea; vomiting; hypotension; tachypnoea; chills |
| Atoltivimab, Maftivimab, and Odesivimab-ebgn (Inmazeb®) | EBOV GP1 | Hypersensitivity; IR Systemic: Pyrexia; chills; tachycardia; tachypnoea; vomiting |
| Monoclonal Antibody ² INN and Trade Names | Target ³ | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events ⁴, Serious and Common |
|------------------------------------------|----------|------------------------------------------------|------------------------------------------|
| Basiliximab (Simulect®) IL-2 receptor α-chain (CD25) | *Boxed warning*: General risk of immunosuppressive therapy | *Systemic*: GI; viral infection; peripheral oedema; UTI; URTI; dyspnea; wound complications; hypertension; anemia; hypo- and hyperkalemia and hyperuricemia; headache; tremor | *Cutaneous*: Rash; pruritus; hypertrichosis |
| Belimumab (Benlysta®) BLYS | Mortality; serious infection; malignancy; hypersensitivity including anaphylaxis; IR; depression; immunization | *Systemic*: Nausea; diarrhea; pyrexia; pain in extremity; bronchitis; depression; migraine | *Cutaneous*: Rash; pruritus |
| Benralizumab (Frasenra®) IL-5Rx | Hypersensitivity; helminth infections—treat prior; decrease steroids gradually | | |
| Bezlotoxumab (Zinplava®) *Clostridium difficile* toxin B | Heart failure | *Systemic*: Nausea; pyrexia; headache | |
| Bimekizumab (Bimzelx®) IL-17A, IL-17F, IL-17AF | Infections; pre-evaluation for tuberculosis; IBD; avoid live vaccines; hypersensitivity | *Systemic*: Infections and infestations, nervous system disorders; isr | *Cutaneous*: Dermatitis; acne; eczema |
| Brodalumab (Siliq®, Kyntheum®, Lumicef®) IL-17RA | *Boxed warning*: Suicidal ideation and behavior. | *Systemic*: Arthralgia; headache; fatigue; diarrhea; oropharyngeal pain; nausea; myalgia; isr; influenza; neutropenia; tinea infections | |
| Brolucizumab-dbll (Beovu®) VEGF-A | Endophthalmitis and retinal detachment; risk of arterial thromboembolic events; increase in intraocular pressure | *Systemic*: Conjunctival hemorrhage; eye pain; vitreous floaters; cataracts; blurred vision | |
| Burosumab-twza (Crysvita®) FGF23 | Hypersensitivity; isr; hyperphosphatemia and risk of nephrocalcinosis | *Systemic*: Headache; isr; vomiting; pyrexia; pain in extremity; decreased vitamin D | |
| Canakinumab (Ilaris®) IL-1β | Increased risk of serious infections; immunization; MAS; hypersensitivity; immunosuppression | *Systemic*: CAPS—Nasopharyngitis; diarrhea; influenza; headache; nausea; dizziness/vertigo; SJIA, URTI, isr, abdominal pain | |
| Caplacizumab-yhdp (Cablivi®) von Willebrand factor | Bleeding | *Systemic*: Epistaxis; gingival bleeding; headache; isr | |
| Casirivimab + Imdevimab (REGEN-COV®; Ronapreve®) mAbs bind to SARS-CoV-2 spike protein RBD preventing binding to the ACE2 receptor | Hypersensitivity including anaphylaxis; IR | - | |
| Monoclonal Antibody | INN and Trade Names | Target | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events |
|---------------------|---------------------|--------|-------------------------------------------------|----------------------|
| Certolizumab pegol (Cimzia®) | TNF | **Boxed warning:** Serious infections; lymphoma and other malignancies | **Systemic:** URTI; cardiac disorders; eye disorders; isr; hepatitis and ↑ liver enzymes; nephrotic syndrome; renal failure; thrombophlebitis; vasculitis | **Serious and Common** |
| Crizanlizumab-tmca (Adakveo®) | P-selectin | **Boxed warning:** Hepatic injury including autoimmune hepatitis and other immune-mediated disorders | **Systemic:** Nasopharyngitis; URTI; oropharyngeal pain; bronchitis; eczema; depression; influenza. **Cutaneous:** Dermatitis, rash |
| Daclizumab (Zinbryta®) | IL-2 receptor α-chain (CD25) | Hypersensitivity; hypocalcemia; serious infections; osteonecrosis of jaw; atypical femoral fractures; severe bone, joint, muscle pain; suppression of bone turnover; dermatologic reactions | **Systemic:** Post-menopausal osteoporosis—back, extremity and musculoskeletal pain; hypercholesterolemia; cystitis; male osteoporosis—back pain; arthralgia; nasopharyngitis **Cutaneous:** Rash; pruritus; dermatis; eczema |
| Denosumab (Prolia®) | RANKL | Hypersensitivity; conjunctivitis and keratitis; eosinophilic conditions; helminth infections—treat prior; decrease steroids gradually | **Systemic:** Conjunctivitis; blepharitis; eye pruritus; herpes infections; keratitis; dry eye; oropharyngeal pain; isr; eosinophilia |
| Dupilumab (Dupixent®) | IL-4Rx | **Boxed warning:** Serious meningococcal infection | **Systemic:** PNH—headache; nasopharyngitis; back pain; nausea; AHUS—hypertension; URTI; GI; abdominal pain; anemia; cough; pyrexia; peripheral edema **Cutaneous:** Rash; pruritus |
| Eculizumab (Soliris®) | Complement C5 | Hypersensitivity; mAb interference with coagulation tests | **Systemic:** Arthralgia; isr; headache |
| Efgartigimod-alfa-fcab (Vyvgart®) | Neonatal Fc receptor FcRn | See reference below | See reference below |
| Emepalumab-lzsg (Gamifant®) | IFNy | Infections; IR; avoid live vaccines | **Systemic:** Infections; pyrexia; hypertension; IR |
| Emicizumab-kxwh (Hemlibra®) | Factors IXa & X | **Boxed warning:** Thrombotic microangiopathy and thromboembolism. **Other:** mAb interference with coagulation tests | **Systemic:** Arthralgia; isr; headache |
| Eptinezumab-jjmr (Vyepti®) | CGRP | Hypersensitivity | **Systemic:** Nasopharyngitis; hypersensitivity |
| Erenumab-zoeo (Aimoig®) | CGRP Receptor | - | **Systemic:** Constipation; isr |
| Monoclonal Antibody 2 | Target 3 | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events 4, Serious and Common |
|----------------------|----------|-------------------------------------------------|------------------------------------------|
| Evinacumab-dgnb (Evkeeza®) | ANGPTL3 | Serious hypersensitivity; embryo-fetal toxicity | Systemic: Nasopharyngitis; influenza-like illness; dizziness; rhinorrhea; nausea |
| Evolocumab (Repatha®) | PCSK9 | Patients with renal and hepatic impairments have not yet been adequately studied; cover of prefilled syringe and pen contain latex which may cause allergic reactions | Systemic: Nasopharyngitis; isr; influenza; URTI; back pain; arthralgia; hypertension; nausea |
| Fremanezumab-vfrm (Ajovy®) | CGRP | Hypersensitivity | Systemic: isr |
| Galcanezumab-gnlm (Emgality®) | CGRP | Hypersensitivity | Systemic: isr |
| Golimumab (Simponi®) | TNF | Boxed warning: Serious infections; lymphoma, and other malignancies Other: Invasive fungal infections; heart failure; hepatitis B reactivation; demyelinating disease; hypersensitivity | Systemic: URTI; viral infections; bronchitis; ↑ liver enzymes; sarcoidosis; ILD; paresthesia Cutaneous: Skin exfoliation; rash |
| Guselkumab (Tremfya®) | IL-23 | Infections; prior evaluation for TB | Systemic: URTI; isr; arthralgia; headache; diarrhea; tinea; gastroenteritis; herpes simplex infections |
| Ilalizumab-uiyk (Trogarzo®) | CD4 | IRIS | Systemic: Diarrhea, nausea; dizziness. Cutaneous: Rash |
| Idarucizumab (Praxbind®) | Dabigatran | Thromboembolic risk; hypersensitivity; risk of adverse reaction in patients with hereditary fructose intolerance; reappearance of bleeding | Systemic: Headache; hypokalemia; delirium; pneumonia; constipation; pyrexia |
| Inebilizumab-cdon (Uplizna®) | CD19 | IR; infections; monitor immunoglobulin levels; fetal risk | Systemic: Urinary tract infection; arthralgia |
| Infliximab (Remicade®) | TNF | Boxed warning: Serious infections; malignancy Other: Hepatitis B reactivation; hepatotoxicity; cytopenias; demyelinating disease; lupus-like syndrome | Systemic: Infections; pancytopenia; anemia; cellulitis; serum sickness; thrombophlebitis; intestinal obstruction; ILD; anaphylaxis; IRs Cutaneous: Cutaneous vasculitis; SJS; EM; psoriasis; |
| Ixekizumab (Taltz®) | IL-17A | Infections: TB—evaluate prior; hypersensitivity; inflammatory bowel disease | Systemic: URTI; isr; nausea; tinea infections |
| Lanadelumab-flyo (Takhzyro®) | Plasma kallikrein | Hypersensitivity | Systemic: URTI; isr; headache; diarrhea; dizziness; myalgia Cutaneous: Rash |
### Table 4. Cont.

| Monoclonal Antibody ² | INN and Trade Names | Target ³ | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events ⁴, Serious and Common |
|----------------------|---------------------|----------|--------------------------------------------------|------------------------------------------|
| **Mepolizumab (Nucala®)** | IL-5 | | Hypersensitivity; helminth infections—treat prior; herpes zoster infections—consider prior vaccination; decrease steroids gradually; not to be used for bronchospasm or status asthmaticus | Systemic: Headache; isr; back pain; fatigue |
| **Natalizumab (Tysabri®)** | α4 integrin (binds to α4β1 and α4β7 integrins) | *Boxed warning*: PML | Systemic: MS—headache; fatigue; arthralgia; urinary tract infection; URTI; gastroenteritis; vaginitis; diarrhea. CD—headache; URTI; nausea | Cutaneous: Rash; urticaria |
| **Obiltoxaximab (Anthim®)** | Bacillus anthracis PA | *Boxed warning*: Hypersensitivity and anaphylaxis | Systemic: URTI; headache; pruritus; IR pain, swelling, bruise | Cutaneous: Urticaria |
| **Ocrelizumab (Ocrevus®)** | CD20 | Infecion; IR; increased risk of malignancy | Systemic: Allergic asthma—arthralgia; pain; dizziness; fracture; earache. CIU—nausea; pharyngitis; URTI; sinusitis; arthralgia; headache; cough; virus infections | Cutaneous: Pruritus; dermatitis. |
| **Omalizumab (Xolair®)** | IgE | Anaphylaxis; malignancy; acute asthma; decrease CSs gradually; eosinophilia; serum sickness-like reaction; parasitic infection | Systemic: isr; pyrexia; apnea; cough; dizziness thrombocytopenia | Cutaneous: Rash; itching; erythema |
| **Palivisumab (Synagis®)** | RSVF | Anaphylaxis; delay administration during moderate–severe infections; give with caution in cases of thrombocytopenia or coagulation disorders | Systemic: Conjunctival hemorrhage; eye pain; vitreous floaters; cataracts | |
| **Ranibizumab (Lucentis®)** | VEGF-A | Endophthalmitis and retinal detachment, increase in intraocular pressure and risk of arterial thromboembolic events after intravitreal injection | Systemic: Pain in extremity; somnolence; headache; URTI; nausea; cough; arthralgias. Cutaneous: Rash; pruritus; urticaria | |
| **Ravulizumab-cwvz (Ultomiris®)** | Complement C5 | *Boxed warning*: Serious meningococcal infections | Systemic: URTI; headache; diarrhea; nausea | |
| **Raxibacumab (ABthrax®)** | Bacillus anthracis PA | IR | Systemic: Pain in extremity; somnolence; headache; URTI; nausea; cough; arthralgias. Cutaneous: Rash; pruritus; urticaria | |
| **Regdanvirimab (Regkirona®)** | Binds to SARS-CoV-2 spike protein RBD preventing binding to ACE2 receptor | Hypersensitivity including anaphylaxis; IR | – | |
Table 4. Cont.

| Monoclonal Antibody ² INN and Trade Names | Target ³ | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events ⁴, Serious and Common |
|------------------------------------------|---------|-----------------------------------------------|-----------------------------------------|
| Reslizumab (Cinqair®)                     | IL-5    | Boxed warning: Anaphylaxis Other: Helminth infections—treat prior; decrease steroids gradually; malignancy | Systemic: Oropharyngeal pain |
| Risankizumab-rzza (Skyrizi®)              | IL-23 p19 | Infections; prior evaluation for TB; hypersensitivity | Systemic: URTI; isr; diarrhea |
| Romosozumab-aqqg (Evenity®)               | Sclerostin | Boxed warning: Potential risk of myocardial infarction, stroke, and cardiovascular death Other: Cardiac events; hypersensitivity; hypocalcemia; atypical femoral fracture | Systemic: Arthralgia; headache |
| Satralizumab-mwge (Enspryng®)             | IL-6R   | Infections; elevated liver enzymes (ALT, AST); decreased neutrophils | Systemic: Nasopharyngitis; headache; URTI; gastritis; arthralgia; extremity pain; fatigue; nausea Cutaneous: Rash |
| Sarilumab (Kevzara®)                      | IL-6R   | Boxed warning: Risk of serious infection Other: GI perforation; avoid live vaccines; hypersensitivity; neutropenia; thrombocytopenia | Systemic: increased ALT; isr; URTI; urinary tract infections |
| Secukinumab (Cosentyx®)                   | IL-17A  | Infections; tuberculosis activation; exacerbation of Crohn’s disease; hypersensitivity; avoid live vaccines | Systemic: Nasopharyngitis; diarrhea; URTI; rhinitis Cutaneous: Urticaria |
| Sotrovimab (Xevudy®) ⁶                    | Spike protein RBD of SARS-CoV-2 | Hypersensitivity reactions including anaphylaxis | – |
| Teprotumumab-trbw (Tepezza®)              | IGF-1R  | IR; exacerbation of pre-existing inflammatory bowel disease; hyperglycemia | Systemic: Muscle spasm; nausea; alopecia; diarrhea; fatigue; hyperglycemia; hearing impairment; dry skin; dysgeusia; headache |
| Tezepelumab-ekko (Tezspire®) ⁷            | Thymic stromal lymphopoietin | Hypersensitivity; acute asthma and deteriorating disease; reduction of corticosteroid dosage; parasite infection; live attenuated virus vaccines ⁷ | Systemic: Pharyngitis; arthralgia; back pain ⁷ |
| Tildrakizumab-asmn (Ilumetri®; Ilumya®)   | IL-23 p19 | Infections; prior evaluation for TB; hypersensitivity | Systemic: URTI; isr; diarrhea |
| Tocilizumab (Actemra®; RoActemra®)        | IL-6R   | Boxed warning: Serious infections Other: GI perforation; avoid live vaccines; hypersensitivity; laboratory monitoring | Systemic: Nasopharyngitis; nausea; ↑ liver enzymes; IR; hypertension; thrombocytopenia; neutropenia; headache Cutaneous: Dermatologic reactions |
Table 4. Cont.

| Monoclonal Antibody 2 | INN and Trade Names | Target 3 | Warnings, Precautions, Risks and Safety Concerns | Other Adverse Events 4, Serious and Common |
|-----------------------|---------------------|----------|-------------------------------------------------|------------------------------------------|
| Tralokinumab (Adtralza®) | IL-13 | Hypersensitivity; conjunctivitis; helminth infection; avoid live and live attenuated vaccines | Systemic: URTI; conjunctivitis; eosinophilia; isr |
| Ustekinumab (Stelara®) | IL-12, IL-23 | Infections; tuberculosis; RPLS; malignancies; anaphylaxis; avoid live vaccines | Systemic: Nasopharyngitis; headache; dental infections; URTI; isr; arthralgia; GI Cutaneous: Pruritus |
| Vedolizumab (Entyvio®) | α4β7 integrin | Hypersensitivity/IR; infections; PML; liver injury | Systemic: Headache; arthralgia; nausea; pyrexia; URTI; cough; bronchitis; influenza; back pain; pain in extremities; nasopharyngitis Cutaneous: Rash; pruritus |

ACE2—angiotensin-converting enzyme 2; AHUS—atypical hemolytic uremic syndrome; ANGPTL3—angioptelin-like 3; BlyS—B lymphocyte stimulator, also known as B cell-activating factor, BAFF; C5—complement component 5; CAPS—cryopyrin-associated periodic syndrome; CD—Crohn’s disease; CIU—chronic idiopathic urticaria; COVID—Coronavirus disease; CSs—corticosteroids; CV—cardiovascular; EBOV—Zaire ebolavirus; EM—erythema multiforme; GI—gastrointestinal; GP1—glycoprotein 1 of EBOV; HSTC—hematopoietic stem cell transplantation; IBD—inflammatory bowel disease; IFNAR—subunit I type I interferon receptor; IGF-1R—insulin-like growth factor receptor-1; ILD—interstitial lung disease; IR—infusion reaction; IRIS—immune reconstitution inflammatory syndrome; isr—injection site reaction; MAS—macrophage activation syndrome; MS—multiple sclerosis; NS—nervous system; PA—protective antigen of B. anthracis toxin; PCSK9—proprotein convertase subtilisin/kexin type 9; PML—progressive multifocal leukoencephalopathy; PNH—paroxysmal nocturnal hemoglobinuria; RANKL—receptor activator of nuclear factor kappa-B ligand (CD254); RBD—receptor binding domain; REMS—Risk Evaluation Mitigation Strategy; RSVF—human respiratory syncytial virus (F protein coat antigen); SARS-CoV-2—severe acute respiratory syndrome coronavirus 2; SJIA—active systemic juvenile idiopathic arthritis; SJIS—Stevens–Johnson syndrome; URTI—upper respiratory tract infection; UTI—urinary tract infection; VEGF-A—vascular endothelial growth factor A. 1 Approved by the FDA or EMA or both. 2 Monoclonal antibodies are listed in alphabetical order. 3 Specificity of antibody. 4 Adverse events in addition to those mentioned as occurring, or potentially likely to occur, and shown in column 3. 5 Approved by the FDA on 17 December 2021. For safety data and adverse events, see Howard, J.F; Bril, V.; Vu, T.; et al. [21]. 6 Note added in press: Approved by the EMA on 17 December 2021. For safety data and adverse events, see Menzies-Gow, A.; Colice G, Griffiths, J.M.; et al. [22] and Menzies-Gow, A.; Corren, J.; Bourdin, A.; et al. [23]. ↑ increase.

Table 5. Adverse events associated with approved 1 monoclonal antibodies used for cancer therapy (as at December 2021).

| Monoclonal Antibody 2 | INN and Trade Names | Target 3 | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events 4, Serious and Common |
|-----------------------|---------------------|----------|-------------------------------------------------|------------------------------------------|
| Ado-trastuzumab emtansine (Kadcyla®) | HER2 | Boxed warning: Hepatotoxicity; cardiac toxicity; embryo-fetal toxicity Other: IR; pulmonary toxicity; extravasation; hemorrhage; thrombocytopenia; neurotoxicity | Systemic: Pulmonary events; fetal harm; LVD; hypersensitivity/IR; nausea; fatigue; anemia; headache; musculoskeletal pain; increased transaminases; constipation Cutaneous: Rash; pruritus |
| Alemtuzumab (Campath®; MabCampath®) | CD52 | Boxed warning: Cytopenias; IR; immunosuppression/infections Other: Immunization | Systemic: Pulmonary events; immunogenicity; cardiac events; diarrhea; nausea; emesis; insomnia Cutaneous: Rash; urticaria; erythema; pruritus |
| Amivantamab-vmjw (Rybrevant®) | EGFR and c-MET receptors | ILD/pneumonitis; IR; dermatologic (including acneiform dermatitis and TEN); ocular toxicity; embryo-fetal toxicity | Systemic: IK; paronychia; musculoskeletal pain; dyspnea; nausea; fatigue; edema; stomatitis; cough; constipation; vomiting Cutaneous: Rash |
Table 5. Cont.

| Monoclonal Antibody \ INN and Trade Names | Target \ Target | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events 4; Serious and Common |
|------------------------------------------|----------------|--------------------------------------------------|------------------------------------------|
| **Atezolizumab (Tecentriq®)**            | PD-L1          | Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, thyroid disorders, adrenal insufficiency, diabetes mellitus); embryo-fetal toxicity | Systemic: IR; fatigue; nausea; infections; urinary tract infections; decreased appetite; diarrhea; pyrexia; constipation; dyspnea. Cutaneous: Rash; pruritus |
| **Avelumab (Bavencio®)**                | PD-L1          | Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction; IR | Systemic: Fatigue; musculoskeletal pain; diarrhea; nausea; decreased appetite; peripheral edema; urinary tract infection Cutaneous: Rash; pruritus |
| **Belantamab mafodotan-blmf (Blenrep®)** | BCMA with MMAF  | Boxed warning: Ocular toxicity Other: Thrombocytopenia; IR; embryo-fetal toxicity | Systemic: Keratopathy; decreased visual acuity, nausea; blurred vision; pyrexia; IR; fatigue; decreased platelets, lymphocytes, hemoglobin; increased creatinine, GGT |
| **Bevacizumab (Avastin®)**              | VEGF-A         | Boxed warning: GI perforation; surgery/wound healing; hemorrhage Other: Non-GI fistula; RPLS; IR; CHF; hypertension; arterial/venous thromboembolism; eye disorders; proteinuria; neutropenia/infections; ONJ | Systemic: Pulmonary events; epistaxis; headache; rectal hemorrhage; dry skin; necrotizing fascitis; taste alteration; lacrimation disorder; ovarian failure Cutaneous: Exfoliative dermatitis; alopecia |
| **Blinatumomab (Blincyto®)**            | CD19/CD3 epsilon | Boxed warning: CRS; neurological toxicities Other: Infections; neutropenia and febrile neutropenia; TLS; elevated liver enzymes; leukoencephalopathy | Systemic: HLH; pyrexia; lymphopenia; leukopenia; chills; headache; CNS symptoms (disorientation, confusion, tremor, speech disorders); hypokalemia; pneumonia; sepsis; constipation, peripheral edema Cutaneous: Rash |
| **Brentuximab vedotin(Adcetris®)**      | CD-30          | Boxed warning: PML Other: Peripheral neuropathy; IR and anaphylaxis; neutropenia; infections; fetal harm; hepatotoxicity; TLS; SJS | Systemic: Cytopenias; immunogenicity; URTI; pyrexia; nausea; vomiting; fatigue; cough; anaphylaxis Cutaneous: Rash; pruritus; SJS; alopecia |
| **Catumaxomab (Removab®)**             | EpCAM/CD3     | Monitor and evaluate for: CRS; SIRS; HAMA/HARA; GI hemorrhage; hepatic disorders; abdominal infection; ileus/intestinal perforation; decreased lymphocyte count | Systemic: Cytopenias; hepatotoxicity; abdominal disorders; pyrexia; chills; nausea; vomiting; infections; immunogenicity; dyspnea Cutaneous: Rash; erythema; allergic dermatitis; hyperhidrosis; pruritus |
| **Cemiplimab-rwlc (Libtayo®)**         | PD-1           | Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions; IR; embryo-fetal toxicity | Systemic: Diarrhea; fatigue; nausea; constipation; musculoskeletal pain Cutaneous: Rash; pruritus |
| Monoclonal Antibody ² INN and Trade Names | Target ³ | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events ⁴; Serious and Common |
|------------------------------------------|----------|------------------------------------------------|------------------------------------------|
| Cetuximab (Erbitux®)                     | EFGR     | Boxed warning: Serious IR and cardiopulmonary arrest. Other: Pulmonary toxicity; dermatologic toxicity; hypomagnesemia | Systemic: Electrolyte imbalance; infection; GI; anaphylaxis; headache; diarrhea Cutaneous: Acneiform rash; nail changes; xeroderma; paronychial inflammation; pruritus |
| Daratumumab (Darzalex®)                 | CD38     | IR; interference with serological testing; neutropenia; thrombocytopenia | Systemic: Neutropenia; thrombocytopenia; fatigue; nausea; diarrhea; constipation; vomiting; muscle spasms; arthralgia; back pain; pyrexia; chills; dizziness; insomnia; cough; dyspnea; peripheral edema; peripheral sensory neuropathy; URTI |
| Denosumab (Prolia®; Xgeva®)             | RANKL    | Hypocalcemia; ONJ; embryo-fetal toxicity | Systemic: Osteomyelitis; hypophosphatemia; dyspnea; fatigue/asthenia; back pain; nausea; extremity pain Cutaneous: Rash; pruritus; dermatitis; eczema |
| Dinutuximab (Unituxin®)                 | GD2      | Boxed warning: Serious IR; neuropathy Other: CLS and hypotension; infection; RPLS; neurological disorders of eye; BMS; electrolyte abnormalities; AHUS; embryo-fetal toxicity | Systemic: Hypokalemia; pain; fever; hypocalcemia; hypotonatremia; anemia; thrombocytopenia; lymphopenia; neutropenia; increased AST, ALT; GI Cutaneous: Urticaria |
| Dostarlimab-gxly (Jemperli®)            | PD-1     | Immune-mediated colitis, pneumonitis, hepatitis, endocrinopathies, nephritis, dermatologic adverse reactions; IR; complications of allogeneic HSCT after PD-1/L-1–blocking antibody; embryo-fetal toxicity | Systemic: Fatigue/asthenia; nausea; diarrhea; anemia |
| Durvalumab (Imfinzi®)                   | PD-L1    | Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies; dermatologic reactions; embryo-fetal toxicity; infections; IR | Systemic: Fatigue; musculoskeletal pain; diarrhea; nausea; decreased appetite; peripheral edema; urinary tract infection; pneumonitis; dyspnea; URTI; cough Cutaneous: Rash; pruritus |
| Elotuzumab (Empliciti®)                 | SLAMF7   | IR; infections; second primary malignancies; hepatotoxicity; interference in monitoring M-protein impacting determination of complete response in patients with IgGκ myeloma protein | Systemic: Fatigue; diarrhea; pyrexia; constipation; cough; peripheral neuropathy; nasopharyngitis; URTI; decreased appetite; pneumonia |
| Enfortumab-vedotin-ejfv (Padcev®)       | Nectin-4 with MMAE microtubule inhibitor | Hyperglycemia; peripheral neuropathy; ocular disorders; skin reactions; infusion site extravasation; embryo-fetal toxicity | Systemic: Fatigue; peripheral neuropathy; decreased appetite; rash; alopecia; nausea; dysgeusia; diarrhea; dry eye Cutaneous: Pruritus; dry skin |
| Monoclonal Antibody 2 INN and Trade Names | Target 3 | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events 4: Serious and Common |
|------------------------------------------|----------|------------------------------------------------|------------------------------------------|
| Fam-trastuzumab deruxtecan-nxki (Enhertu®) | HER2     | *Boxed warning:* ILD and pneumonitis; embryo-fetal toxicity  
*Other:* Neutropenia; LVD | *Systemic:* Decreased hemoglobin, white blood cells, neutrophils, lymphocytes, platelets; nausea; vomiting; constipation; fatigue; decreased appetite; anemia; diarrhea; hypokalemia; pyrexia; alopecia; increased blood bilirubin, aspartate aminotransferase, AP, alanine aminotransferase |
| Gemtuzumab ozogamicin (Mylotarg®)       | CD33     | *Boxed warning:* Hepatotoxicity including severe or fatal hepatic veno-occlusive disease  
*Other:* IR including anaphylaxis; hemorrhage; embryo-fetal toxicity | *Systemic:* Hemorrhage; infection; fever; nausea; vomiting; constipation; headache; increased ALT, AST; mucositis  
*Cutaneous:* Rash |
| Ibritumomab tiuxetan (Zevalin®)         | CD20     | *Boxed warning:* Serious IR; severe cytopenias; severe mucocutaneous and cutaneous reactions  
*Other:* MDS and AML; extravasation; immunization | *Systemic:* Infections; asthenia; musculoskeletal symptoms; GI; hemorrhage; hypersensitivity  
*Cutaneous:* Exfoliative dermatitis; bullous dermatitis; EM; SJS; TEN |
| Inotuzumab ozogamicin (Besponsa®)       | CD22     | *Boxed warning:* Hepatotoxicity including hepatic veno-occlusive disease; increased risk of post-transplant non-relapse mortality  
*Other:* myelosuppression; embryo-fetal toxicity; QT interval prolongation | *Systemic:* IR; cytopenias; nausea; fatigue; hemorrhage; pyrexia; infection; headache; febrile neutropenia; increased transaminases; hyperbilirubinemia |
| Ipilimumab (Yervoy®)                    | CTLA-4   | *Boxed warning:* Immune-mediated adverse reactions | *Systemic:* Diarrhea; fatigue; colitis  
*Cutaneous:* Rash; pruritus; dermatitis |
| Isatuximab-irfc (Sarclisa®)             | CD38     | IR; neutropenia; second primary malignancies; indirect antiglobulin test and interference with serum electrophoresis and immunofixation tests | *Systemic:* Neutropenia; IR; pneumonia; URTI; diarrhea; anemia; lymphopenia; thrombocytopenia |
| Loncastumab tesirine-lpyl (Zynlonta®)   | CD19 with teserine cytotoxic agent | Effusions (pericardial, pleural, ascites); embryo-fetal toxicity; myelosuppression; infections; cutaneous reactions (including photosensitivity) | *Systemic:* Thrombocytopenia; increased gamma-glutamyltransferase; neutropenia; nausea; anemia; hyperglycemia; transaminase elevation; fatigue; hypoalbuminemia; edema; musculoskeletal pain  
*Cutaneous:* Rash |
| Margetuximab-cmkb (Margenza®)           | HER2     | *Boxed warning:* LVD; embryo-fetal toxicity | *Systemic:* Fatigue/asthenia; nausea; diarrhea; vomiting; constipation; IR; headache; pyrexia; alopecia; abdominal pain; peripheral neuropathy; arthralgia/myalgia; cough; decreased appetite; dyspnea; extremity pain  
*Cutaneous:* PPE |
| Mogamulizumab-kpkc (Poteligeo®)         | CCR4     | Dermatologic toxicity; IR; infections; autoimmune reactions; HSCT complications | *Systemic:* IR; diarrhea; fatigue; URTI; musculoskeletal pain  
*Cutaneous:* Rash |
| Monoclonal Antibody ² | Target ³ | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events ⁴; Serious and Common |
|----------------------|----------|-------------------------------------------------|------------------------------------------|
| Moxetumomab pasudox-tdfk (Lumoxiti®) | CD22 | **Boxed warning:** CLS; hemolytic uremic syndrome  
**Other:** Renal toxicity; electrolyte abnormalities; IR | **Systemic:** Edema; nausea; fatigue; headache; pyrexia; constipation; diarrhea; anemia; increased creatinine, ALT, AST; hypophosphatemia; hypocalcemia |
| Naxitamab-gqgk (Danyelza®) | GD2 | **Boxed warning:** Serious IR; neurotoxicity including RPLS | **Systemic:** IR; isr; pain; tachycardia; vomiting; cough; nausea; diarrhea; decreased appetite; hypertension; fatigue; peripheral neuropathy; edema; urticaria; pyrexia; headache; anxiety; irritability; decreased lymphocytes; neutrophils, hemoglobin, platelets, K, Ca, Na, glucose, albumin, phosphate; increased alanine aminotransferase  
Cutaneous: EM |
| Necitumumab (Portrazza®) | EGFR | **Boxed warning:** Cardiopulmonary arrest; hypo-magnesemia  
**Other:** Venous, arterial thromboembolic events; dermatologic toxicities; embry-o-fetal toxicity; ↑ toxicity, mortality in patients with non-squamous NSCLC; IR | **Systemic:** Diarrhea; vomiting  
Cutaneous: Rash; dermatitis acniform |
| Nivolumab (OPDIVO®) | PD-1 | Immune-mediated adverse reactions; embry-o-fetal toxicity | **Systemic:** Increased ALT, AST, AP; hyponatremia; hyper- and hypokalemia; hyper- and hypocalcemia; lymphopenia; fatigue; asthenia; musculoskeletal and abdominal pain; dyspnea; cough;GI.  
Cutaneous: Rash; pruritus |
| Obinutuzumab (Gazyva®; Gazyvaro®) | CD20 | **Boxed warning:** Hepatitis B virus reactivation; PML.  
**Other:** IR; TLS; neutropenia; thrombocytopenia; infections; immunization | **Systemic:** Anemia; pyrexia; musculoskeletal disorders; headache; cough |
| Ofatumumab (Arzerra®) | CD20 | IR; Hepatitis B virus reactivation; PML; cytopenias intestinal obstruction; immunization | **Systemic:** Infections; pneumonia; neutropenia; pyrexia; dyspnea; cough; diarrhea; URTI; nausea; fatigue; bronchitis  
Cutaneous: Rash; urticaria; hyperhidrosis. |
| Olaratumab (Lartruvo®) | PDGFR-α | IR; embry-o-fetal toxicity | **Systemic:** Olaratumab + doxorubicin: fatigue; musculoskeletal pain; diarrhea; decreased appetite; headache; neuropathy; cytopenias; hyperglycemia; elevated aPTT; hypokalemia; hypophosphatemia  
Cutaneous: Alopecia |
### Table 5. Cont.

| Monoclonal Antibody **| INN and Trade Names | Target ** | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events **<sup>4</sup>: Serious and Common |
|----------------------|----------------------|-----------|--------------------------------------------------|----------------------------------------------------------|
| Panitumumab (Vectibix®) | EGFR | **Boxed warning**: Dermatologic toxicity; IR  
**Other**: Increased toxicity with bevacizumab and chemotherapy; pulmonary toxicities; electrolyte depletion; ocular events | **Systemic**: Pulmonary events; pulmonary embolism; GI; fatigue; abdominal pain; hypomagnesemia  
**Cutaneous**: Rash; dermatitis ‘acneiform’; erythema; exfoliation; paronychia; skin fissures; photosensitivity; xerosis; pruritus |
| Pembrolizumab (Keytruda®) | PD-1 | Immune-mediated adverse reactions; embryo-fetal toxicity | **Systemic**: Fatigue; peripheral edema; chills; pyrexia; renal failure; cellulitis; decreased appetite; dyspnea; arthralgia; nausea; diarrhea; cough  
**Cutaneous**: Rash; pruritus; vitiligo |
| Pertuzumab (Perjeta®) | HER2 | **Boxed warning**: Cardiomyopathy; embryo-fetal toxicity.  
**Other**: IR; hypersensitivity/anaphylaxis | **Systemic**: Neutropenias; LVD; peripheral neuropathy; fatigue; GI; asthenia  
**Cutaneous**: Rash; paronychia; pruritus; alopecia; PPE (in combination therapy) |
| Polatuzumab vedotin-piiq (Polivy®) | CD79b | Peripheral neuropathy; myelosuppression and related reactions; infections; IR; TLS; PML; hepatotoxicity; embryo-fetal toxicity | **Systemic**: Cytopenia; fatigue; decreased appetite; diarrhea; pyrexia; pneumonia |
| Ramucirumab (Cyramza®) | VEGFR2 | **Boxed warning**: Hemorrhage; GI perforation; impaired wound healing.  
**Other**: Atrial thromboembolic events; IR; RPLS; hypertension; deterioration in patients with cirrhosis; proteinuria including nephrotic syndrome; thyroid dysfunction; embryo-fetal risk | **Systemic**: Hypertension; diastolic and systolic blood pressure; headache; hypertension; hypotension; proteinuria; renal impairment; stomatitis; immunogenicity |
| Rituximab (Rituxan®; MabThera®) | CD20 | **Boxed warning**: Fatal IRs; TLS; potentially fatal PML and severe mucocutaneous reactions  
**Other**: hepatitis B virus reactivation; infections; cardiac arrhythmias; bowel obstruction and perforation  
**Boxed warning**: Severe neutropenia; severe diarrhea  
**Other**: Hypersensitivity; nausea/vomiting; risk of neutropenia increased in individuals with reduced uridine diphosphate-glucuronosyl transferase 1A1; embryo-fetal toxicity | **Systemic**: Pulmonary events; renal toxicity; neutropenias; serum sickness; anaphylaxis; fever; lymphopenia; chills; asthenia  
**Cutaneous**: Paraneoplastic pemphigus; lichenoid dermatitis; vesiculobullous dermatitis; SJS; TEN  
**Systemic**: Nausea; neutropenia; diarrhea; fatigue; anemia; vomiting; alopecia; constipation; decreased appetite; abdominal pain  
**Cutaneous**: Rash |
| Sacituzumab govitecan-hziy (Trodelvy®) | Trop-2 with topoisomerase inhibitor | | | |
| Siltuximab (Sylvant®) | IL-6 | Not for patients with severe infections or live vaccines; IR; cautionary use in patients with GI perforation risk | **Systemic**: Hyperuricemia; URTI; increased weight  
**Cutaneous**: Rash; pruritus |
| Monoclonal Antibody 2 | Target 3 | Warnings, Precautions, Risks, and Safety Concerns | Other Adverse Events 4 |
|----------------------|----------|-----------------------------------------------|-----------------------|
| Tafasitamab-cxix (Monjuvi®) | D19 | IR; myelosuppression; infections; embryo-fetal toxicity | Systemic: Neutropenia; fatigue; anemia; diarrhea; thrombocytopenia; cough; pyrexia; peripheral edema; URTI; decreased appetite |
| Tisotumab vedotin-tftv (Tivdak®) | TF with MMAE microtubule inhibitor | Boxed warning: Ocular toxicity  
Other: Ocular adverse reactions, e.g., conjunctival reactions, dry eyes, corneal reactions, blepharitis; ulcerative keratitis; peripheral neuropathy; pneumonitis; embryo-fetal toxicity | Systemic: Most serious: ileus; hemorrhage; pneumonia; sepsis; pyrexia; peripheral neuropathy; constipation. Most common: diarrhea; peripheral neuropathy; conjunctival and corneal reactions; fatigue; alopecia; epistaxis; decreased hemoglobin, lymphocytes, and leukocytes; increased creatinine; dry eye; prothrombin international normalized ratio; aPTT prolonged |
| Trastuzumab (Herceptin®) | HER2 | Boxed warning: Cardiomyopathy; IR; pulmonary toxicity  
Other: Exacerbation of chemotherapy-induced neutropenia; embryo-fetal toxicity | Systemic: Neutropenia; anemia; thrombocytopenia; pulmonary events; LVD; GI; chills; fever; URTI; anaphylaxis/angioedema; headache; cough; stomatitis; mucosal inflammation |

AHUS—atypical hemolytic syndrome; ALT—alanine transaminase; AML—acute myelogenous leukemia; AP—alkaline phosphatase; aPTT—activated partial thromboplastin time; AST—aspartate transaminase; BCMA—B cell maturation antigen; BMS—bone marrow suppression; CHF—congestive heart failure; CNS—central nervous system; CRIS—cytokine release syndrome; CTLA-4—cytotoxic T lymphocyte-associated antigen 4; DLBCL—diffuse large B cell lymphoma; EGFR—epidermal growth factor receptor (HER1, ErbB-1); EM—erythema multiforme; EpCAM—epithelial cell adhesion molecule; GD2—disialoganglioside expressed on tumors of neuroectodermal origin; GGT—gamma-glutamyl transferase; GI—gastrointestine/gastrointestinal symptoms, e.g., nausea, diarrhea, vomiting, constipation; GM-CSF—granulocyte-macrophage colony-stimulating factor; HAMA—human antimouse antibody; HARA—human antirat antibody; HER2—human epidermal growth factor 2, also known as Neu, ErbB2, CD340, or p185; HLH—hemophagocytic lymphohistiocytosis; IR—infusion reactions; isr—injection site reaction; ILD—interstitial lung disease; LBCL—large B cell lymphoma; LVD—left ventricular dysfunction; MDAE—monomethyl auristatin E; MMAE—monomethyl auristatin F; MDS—myelodysplastic syndrome; mTNBC—metastatic triple-negative breast cancer; ONJ—osteonecrosis of the jaw; PD-1—programmed cell death protein 1; PD-L1; PDGFRA—platelet-derived growth factor receptor A; PML—progressive multifocal leukoencephalopathy; PPE—palmar plantar erythrodysaesthesia; RANKL—receptor activator of nuclear factor kappa-B ligand (CD254); RPLS—reversible posterior leukoencephalopathy syndrome; SIRS—systemic inflammatory response syndrome; SJS—Stevens—Johnson syndrome; TEN—toxic epidermal necrolysis; teserine—also known as SG3249, a pyrrolobenzodiazepine dimer; TF—tissue factor, platelet tissue factor, factor III, CD142; TLS—tumor lysis syndrome; Trop2—trophoblast cell surface antigen-2; URTI—upper respiratory tract infection; VEGF—vascular endothelial growth factor; VEGFR-2—vascular endothelial growth factor receptor 2. 1 Approved by the FDA or EMA or both. 2 Monoclonal antibodies are listed in alphabetical order. 3 Specificity of antibody. 4 Adverse events in addition to those mentioned as warnings and precautions in column 3. ↑ increase.

### 4.1. Immune-Mediated Adverse Responses (Hypersensitivities) to Approved Monoclonal Antibodies

Collectively, patient responses to mAbs cover the full range of hypersensitivities from types I to IV (Box 1) [19] with the type I IgE-antibody-mediated hypersensitivity responses—anaphylaxis; urticaria (e.g., to ofatumumab and alemtuzumab); and, rarely, angioedema (e.g., with trastuzumab) occasionally seen. Chimeric mAbs with mouse and/or rat sequences (abciximab, basiliximab, blinatumomab, brentuximab vedotin, catumaxomab, cetuximab, dinutuximab, infliximab, obinutuzumab, rituximab, and siltuximab) are considered to be the highest risk for type I reactions. Overall, however, reports of type I hy-
persensitivities are relatively rare, and perhaps less than expected, with only two FDA black box warnings issued thus far (for the humanized mAbs reslizumab and obiltoxaximab) and two FDA warning/precaution for palivizumab and brentuximab vedotin. Table 6 lists 19 mAbs with warnings for, and reports of, anaphylaxis, with 5 employed in cancer therapy (Table 5) and 14 for other disorders (Table 4). Severe infusion reactions that occur with some mAbs and which show some similar symptoms to anaphylaxis (see Section 4.2) can sometimes make distinguishing the two difficult and lead to doubts about the true incidence of anaphylaxis.

Box 1. Hypersensitivity reactions, known and some suspected, to approved monoclonal antibodies used for therapy.

- **Type I hypersensitivity:** Warnings for, and reports of, anaphylaxis account for ≈18% of mAbs, 14 used for non-cancer indications and 5 for cancer indications. Reslizumab and obiltoxaximab are covered by a black box warning for anaphylaxis. Urticaria occurs more often with the non-cancer mAbs.
- **Serious infusion reactions** with signs and symptoms resembling, and sometimes confused with anaphylaxis, occur with some mAbs, for example, alemtuzumab, cetuximab, dinutuximab, ibritumomab tiuxetan, naxitamab-ggkg, panitumumab, rituximab, trastuzumab, and vedolizumab. Cytokine release appears to be involved.
- There is as yet no good evidence that many cytopenias are type II hypersensitivities, but these may occur with, for example, abciximab, alemtuzumab for multiple sclerosis and rituximab. Autoimmune hemolytic anemia may be induced by alemtuzumab and rituximab and rituximab-induced early- and late-onset neutropenia may be immune-mediated.
- **Type III hypersensitivities**, serum sickness-like reactions, cutaneous vasculitis, and hypersensitivity pneumonitis (may be a combined type III and IV hypersensitivity) occur with, for example, infliximab, adalimumab, and alirocumab. Checkpoint inhibitors including ipilimumab, nivolumab, and avelumab (Table 5) may also induce hypersensitivity pneumonitis. Chimeric mAbs (e.g., rituximab) and the humanized mAb omalizumab may cause a serum sickness-like reaction.
- **Type IV hypersensitivities**: Rare Stevens–Johnson syndrome reactions have been reported to adalimumab, brentuximab vedotin, infliximab, and rituximab; toxic epidermal necrolysis has been induced by ibritumomab tiuxetan and rituximab. Adalimumab, ibritumomab tiuxetan, infliximab, and naxitamab-ggkg have been implicated in cases of erythema multiforme (EM). Paraneoplastic pemphigus, lichenoid dermatitis, and vesiculobullous dermatitis have occurred after rituximab. Dermatitis may occur after some mAbs, e.g., bevacizumab, catumaxomab, denosumab, and panitumumab. Immune-mediated cutaneous reactions induced by, e.g., cemiplimab-rwlc and durvalumab may be type IV hypersensitivities but mechanisms are not yet unequivocally established. Skin manifestations of rash and pruritus, often seen after many mAbs (Tables 4 and 5), are generally not true hypersensitivity reactions.

There are a number of reports of mAb-induced cytopenias suggesting an underlying immune mechanism [19], but because of the lack of proper investigations, there are few convincing reports of the involvement of mAbs in type II hypersensitivity responses (Box 1). Thrombocytopenia after abciximab treatment [24,25] and cases of alemtuzumab-induced immune thrombocytopenia [26,27], neutropenia [27], autoimmune hemolytic anemia [28,29], and pure red cell aplasia [27] provide perhaps the best examples of immune-mediated true hypersensitivity responses. Apart from abciximab and alemtuzumab, rituximab has been implicated in thrombocytopenia [30], anemia [30], severe autoimmune hemolytic anemia [31], and early-onset and late-onset forms of neutropenia [30,32,33]. Although early- and late-onset neutropenia are well-known side effects of rituximab, the mechanisms have yet to be firmly established. Both forms are suspected examples of a mAb-induced type II hypersensitivity, although late-onset neutropenia may involve autoantibodies and appears to be due to a different mechanism than the early-onset form. Involvement of trastuzumab in severe thrombocytopenia has been reported [34]. See also the section on cytopenias below and Table 6.
Table 6. Individual approved monoclonal antibodies associated with adverse events affecting different organs and tissues.

| Monoclonal Antibodies for non-cancer therapy |
|---------------------------------------------|
| Anaphylaxis 1 | Infusion Reactions | Cytopenias | Pulmonary Adverse Events 2 | Cardiac Adverse Events | Hepatotoxicity 2 | Other Immune-Mediated Reactions 3 | Embryo-Fetal Toxicity | Dermatologic Toxicity 3 |
|----------------|-------------------|------------|---------------------------|----------------------|-----------------|----------------------------------|----------------------|------------------------|
| Adalimumab | Anifrolumab fnia | Ansvimab-zykl | Abciximab | Adalimumab | Adalimumab | Adalimumab | Adalimumab | Abciximab |
| Belimumab | Casrivimab+ | Indevimab | Alemtuzumab | Belimumab | Casirivimab+ | Imdevimab | Crizanizumab-tmca | Belimumab |
| Casrivimab+ | Indevimab | Infliximab | Abciximab | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab |
| Certolizumab pegol | Evacucumab-dgmb | Infliximab | Abciximab | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab |
| Emapalumab-lgg | Inebilizumab-cdon | Infliximab | Abciximab | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab |
| Fingolimod | Golimumab | Infliximab | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Golimumab | Infliximab | Palivizumab | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inquinub | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
| Inubicumab | Inubimab | Inflorida | Adalimumab | Alemtuzumab | Belimumab | Casirivimab+ | Indevimab | Inebilizumab-cdon |
Table 6. Cont.

| Anaphylaxis  
| Monoclonal Antibodies for cancer therapy |
|---|---|---|---|---|---|---|
| Infusion Reactions | Pulmonary Adverse Events | Cardiac Adverse Events | Hepatotoxicity | Other Immune-Mediated Reactions | Embryo-Fetal Toxicity | Dermatologic Toxicity |
| Brentuximab vedotin | Naxitamab-gqgk | Ofatumumab | Rituximab | | | |
| Cetuximab | Alemtuzumab | Catumaxomab | Gemtuzumab | | | |
| Ozoagamicin | Bevacizumab | Deruxtecan-nxki | Ibritumomab | | | |
| Pertuzumab | Margetuximab-cmbk | Ipilimumab | Nivolumab | | | |
| Trastuzumab | Atezolizumab | Nvivomab | Ozogamicin | | | |

For infusion reactions, cytopenias, pulmonary events, and dermatologic toxicity, alemtuzumab as Lemtrada® and Campath® are counted as one mAb not two; likewise, denosumab as Prolia® and Xgeva® are counted as one mAb in inducing dermatologic toxicity.  

1 A type I immediate hypersensitivity.  

2 Includes some mAb-induced hypersensitivities.  

3 mAbs including, and in addition to, those clearly identified as inducing an adverse event via a type I, II, III, or IV hypersensitivity mechanism.  

4 A combination of two mAbs directed to the spike protein receptor binding domain of SARS-CoV-2.  

5 As Lemtrada®.  

6 As Campath®.  

7 As Xgeva®.  

8 As Prolia®.  

9 As Campath®.
Hypersensitivity (cutaneous) vasculitis (Figure 2), serum sickness, and hypersensitivity pneumonitis are examples of type III hypersensitivities induced by mAbs (Box 1, Table 5). Apart from the fully human mAbs adalimumab and alirocumab (the latter subject to a warning), for possible hypersensitivity vasculitis, again, the chimeric antibodies, such as rituximab and infliximab, are the biggest cause of reactions. For example, cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis is known [35], and there are a number of reports of rituximab-induced vasculitis [36,37] and serum sickness [38–40]. In fact, rituximab-induced serum sickness is said to occur in up to 20% of treated patients [41]. Checkpoint inhibitors ipilimumab, nivolumab, pembrolizumab, cemiplimab-rwlc, atezolizumab, avelumab, and durvalumab (Table 5) may cause hypersensitivity pneumonitis, generally thought to be a combined type III and IV hypersensitivity in a Th1/Th17 response [42–44]. As well as the adverse pulmonary reactions (Tables 5 and 6), the checkpoint inhibitors may also provoke immune-mediated colitis, endocrinopathies, hepatitis, nephritis, and thyroiditis, reactions that might involve a type III hypersensitivity mechanism (Table 6).

Almost 40% of the 110 approved mAbs are associated with some sorts of adverse cutaneous effects, including type IV hypersensitivities [19] with rare cases of life-threatening cutaneous toxidermias (Tables 4–6, Box 1). Ibritumomab has an FDA boxed warning for severe cutaneous and mucocutaneous reactions, which includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) (Figure 3), exfoliative dermatitis, and bullous dermatitis. Warnings and precautions apply to brentuximab vedotin for SJS; rituximab has been involved in cases of SJS, TEN, paraneoplastic pemphigus, lichenoid dermatitis, and vesiculobullous dermatitis; and EM has occurred with naxitamab-gqgk therapy. EM, SJS, and psoriasis have been reported for adalimumab. EGFR-targeted mAbs are known for so-called dermatologic acneiform toxicities that are not immune-mediated (see below, Section 4.2, Cutaneous reactions).
4.2. Non-Immune-Mediated Adverse Responses to Approved Monoclonal Antibodies

As mentioned above, despite the specific targeting of mAbs to a particular disease-/disorder-associated tissue(s), the range and number of adverse events during or following therapy can sometimes be large and diverse. As summarized and discussed in Tables 4–6 and Box 2, many of these events do not have an immune basis or such a basis has yet to be convincingly demonstrated, either because sufficient investigation has yet to be undertaken or because of the clinical and laboratory difficulties involved in defining a precise mechanism(s). The list of recorded mAb-induced non-immune events is extensive and includes injection site reactions, infusion reactions, cytopenias, lung and liver injuries, heart effects, dermatologic toxicities, embryo and fetal toxicities, and a number of potentially life-threatening syndromes occurring with low frequency (Table 6, Box 2). It should be pointed out, however, that within some of these categories, it might be argued that there is, or may be, an immunological component with the involvement of cells and/or cytokines normally present in many inflammatory and immunological reactions.

Injection site reactions are very common, and when the preferred terms used in the Federal Adverse Event (FAERS) reporting system to describe such reactions are considered, namely, irritation, erythema, rash, bruising, swelling, induration, extravasation, reactions, pruritus, urticaria, hemorrhage, hematoma, and pain, it becomes apparent as to why such patient reactions are seen so regularly. In any injected population, it is to be expected that at least some individuals will respond with at least one of the above adverse effects. In the post-marketing period, the larger the population injected, the wider the collective list of adverse effects seen. The preferred terms listed are from the Medical Dictionary for Regulatory Activities (MedDRA; http://www.meddra.org/ accessed on 14 December 2021). Of the 66 approved mAbs for non-cancer therapy surveyed here, the FDA in its warnings, precautions, and lists of adverse reactions mentions injection site reactions as an adverse event for 24 (≈37%).

Figure 3. Erythema multiforme with circumscribed bullous lesions. Image courtesy of Dr Adrian Mar.
Box 2. Non-immune-mediated adverse events to monoclonal antibodies (mAbs).

- Infusion reactions. Usually mild–moderate or controllable by premedication. Fatal reactions can occur. Reactions have been recorded for almost 50% of approved mAbs. FDA boxed warnings for infusion reactions apply to 8 mAbs used for cancer therapy and 1 mAb used for other therapies.

- Cytopenia: Mechanisms of mAb-induced thrombocytopenia, neutropenia, lymphopenia, and hemolytic anemia are often not investigated/established. Cytopenia seen in more than 30% of the mAbs, especially those used in cancer therapy. Some may be immune-mediated.

- mAb-induced lung disease: Pathogenesis and pathophysiology are generally not known. At least 21 mAbs implicated. Some reactions are known, or suspected, to be immune-mediated.

- Cardiac events: Mechanisms mostly obscure. At least 20 mAbs implicated.

- Liver events: At least 22 mAbs implicated. Immune-mediated hepatitis is seen but other mechanisms often not well understood.

- Dermatologic toxicities: 39 (~36%) of the mAbs elicited adverse cutaneous reactions of different severity from mild to severe. Rash and/or pruritus are common and were not included in the assessments. Apart from severe toxidermias (see text), papulopustular (acneiform) skin eruptions occur in response to EGFR-targeted antibodies, in particular, cetuximab, necitumumab, and panitumumab. Adverse reactions were seen in ~29% of the non-cancer group and 50% of the mAbs used for cancer therapy.

- Embryo-fetal toxicity is recognized for 27 (~25%) of the mAbs, including eight antibody–drug conjugates.

- Cytokine release syndrome (CRS): The distinguishing features between CRS and infusion reactions are often not clear. mAbs implicated include blinatumomab and catumaxomab.

- Tumor lysis syndrome (TLS): Anti-cancer mAbs may destroy large numbers of cells in a short period of time. Seen with brentuximab vedotin, blinatumomab, rituximab, and polatuzumab vedotin-piql.

- Progressive multifocal leukoencephalopathy (PML): Rare but occasionally seen after mAbs directed to B cells, e.g., brentuximab vedotin, rituximab, obinutuzumab, vedolizumab, polatuzumab vedotin-piql, and natalizumab.

- Other syndromes of poorly understood pathogenesis: Reversible posterior leukoencephalopathy syndrome (RPLS) (cases reported after, e.g., bevacizumb and ramucirumb); immune reconstitution inflammatory syndrome (IRIS) (natalizumab); systemic inflammatory response syndrome (SIRS) (catumaxomab, eculizumab); capillary leak syndrome (CLS) (bevacizumab, dinutuximab); macrophage activation syndrome (MAS) (canakinumab).

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Infusion reactions [3,19] to mAbs are common, usually with mild to moderate ‘flu’-like symptoms, but serious, potentially fatal reactions can occur. Table 6 shows that infusion reactions are known for 53 of the 110 approved mAbs (Tables 4 and 5). Reactions may resemble anaphylaxis, and hypotension, cardiac arrest, urticaria, rash and pruritus may occur, usually after the first or second infusion, but IgE antibody reactions generally have a faster onset (often within minutes) and effects are more severe. The cytokines tumor necrosis factor (TNF) and IL-6, as well as high counts of circulating lymphocytes (e.g., >50 × 10⁹/L) are thought to be involved [45]. The highest incidence of reactions occurs with human–rodent chimeric antibodies, e.g., rituximab and infliximab, and some humanized mAbs such as alemtuzumab, ocrelizumab, and trastuzumab. Table 6 lists the 53 mAbs shown to provoke infusion reactions. Rituximab and trastuzumab show the highest incidence of reactions with incidences for first infusion reactions of ~77% and ~40%, respectively. Premedication may be necessary in order to avoid or lessen reactions, for example, as sometimes found necessary with elotuzumab infused for multiple myeloma [46]. Overall, mAbs involved show a two to one infusion reaction ratio of mAbs for cancer compared to those for other indications. Eight mAbs for cancer indications carry a black box warning for infusion reactions, while 22 are subject to a warnings and precautions notice. The corresponding warnings for mAbs used for non-cancer therapies are one and nine, respectively.
Cytopenias commonly occur during and/or following mAb therapy, especially as a result of anti-cancer therapies. Of 34 mAbs implicated in the induction of cytopenias, 24 (≈71%) are anti-cancer agents and 10 (≈29%) relate to other indications (Tables 4–6). FDA boxed warnings have been issued for three mAbs, namely, for sacituzumab govetizy-induced severe neutropenia and for cytopenia following ibritumomab tiuxetan and alemtuzumab, while FDA general warnings and precautions apply to 21 other mAbs listed in Table 7. In addition, other warnings of adverse events apply to brodalumab for neutropenia; to tocilizumab for neutropenia and thrombocytopenia; and to different cytopenias, namely, lymphocytopenia, for a high proportion of anti-neoplastic mAbs (Tables 4 and 5). Note that because mechanisms of mAb-induced thrombocytopenia, neutropenia, lymphocytopenia, anemia, and what is often simply termed ‘cytopenia’ are often not investigated, some events may, in fact, be immune-mediated.

Table 7. Approved monoclonal antibodies subject to FDA warnings and precautions for cytopenias.

| Cytopenia          | Thrombocytopenia | Neutropenia | Lymphocytopenia |
|--------------------|------------------|-------------|-----------------|
| Adalimumab         | Abciximab        | Bevacizumab | Catumaxomab     |
| Alemtuzumab 1      | Ado-trastuzumab emtansine | Blinatumomab |
| Certolizumab pegol| Belantamab mafodoton-blmf | Brentuximab vedotin |
| Ibritumomab tiuxetan 1 | Daratumumab | Daratumumab |
| Infliximab         | Palivisumab      | Fam-trastuzumab Deruxtecan-nxki |
| Ofatumumab         | Sarilumab        | Isatuximab-irfc |
| Obinutuzumab       |                  |             |
| Sacituzumab govitecan-hziy 1 | Sarilumab | |
| Sarilumab          |                  |             |
| Satralizumab-mwge  |                  |             |
| Trastuzumab        |                  |             |

1 Subject to boxed warning.

Mab-induced pulmonary adverse events comprise a heterogeneous group of disorders, many of which remain poorly understood mechanistically. Of the 21 mAbs (counting alemtuzumab as Lemtrada® and Campath® as one mAb) listed in Table 6 and Box 3 (see also Tables 4 and 5), immune-mediated or hypersensitivity pneumonitis is recognized as an important adverse event for an increasing number of mAbs, particularly checkpoint inhibitors [42–44,47]. This condition is now considered to be a combined type III and IV hypersensitivity in a Th1/Th17 response. Pneumonitis associated with checkpoint inhibitors is a rare, potentially fatal immune disease with an incidence of 2–5% [48]. Interestingly, the incidence is higher in non-small cell lung cancer than in melanoma [49]. For rituximab, while early-onset organizing pneumonia may be a hypersensitivity reaction, its prognosis is poorer than the late-onset form [50], which may be either a toxicity or due to immune restoration. Acute respiratory distress syndrome (ARDS) [51], seen for example with rituximab, trastuzumab, and ado-trastuzumab, may result from the release of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-8, which are elevated both in bronchoalveolar lavage fluid and circulating plasma in ARDS patients [52]. Rituximab, alemtuzumab, trastuzumab, and panitumumab are responsible for the most severe and widest range of adverse lung events (Box 3).

Adverse cardiac events have occurred with at least 20 of the 110 approved mAbs (Tables 4–6 and 8) in a range of effects, including cardiomyopathy, myocardial infarction, cardiac arrhythmias, cardiopulmonary arrest, congestive heart failure, left ventricular...
dysfunction (LVD), decreased left ventricular ejection fraction (LVED), and QT interval prolongation (Table 8). FDA black box warnings apply to necitumumab for cardiopulmonary arrest; romosozumab-aqqg for the risk of myocardial infarction, cardiac events, stroke, and cardiovascular death; ado-trastuzumab emtansine for cardiac toxicity; margetuximab-cmkb for LVD; and pertuzumab and trastuzumab, each for cardiomyopathy. Patients given mAbs targeted to HER2, namely, trastuzumab, ado-trastuzumab emtansine, and pertuzumab, show an increased risk of decreased LVED, especially if also given anthracyclines. Trastuzumab increases the risk of myocardial infarction 4–6 times, and again, the risk is highest when anthracyclines are also administered. Fam-trastuzumab deruxtecan-nxki carries a warning for LVD. Kounis and coworkers [53] believe that it is likely that many of the cardiac toxicities associated with mAbs used in cancer therapy share the same pathophysiology with Kounis syndrome. Suggested possible mAb involvements include -ximabs (e.g., rituximab, cetuximab, brentuximab); -zumabs (alemtuzumab, bevacizumab, trastuzumab, pertuzumab); -umabs (ipilimumab, panitumumab); and -omabs (catumaxomab, ibrutimomab).

**Box 3.** Pulmonary adverse events caused by approved monoclonal antibodies.

| Mouse antibodies | Human-mouse chimeric antibodies | Humanised antibodies | Fully human antibodies |
|------------------|---------------------------------|----------------------|------------------------|
| Ibrutumomab tiuxetan: hypersensitivity bronchospasm | Cetuximab: interstitial pneumonitis | Ado-trastuzumab: interstitial lung disease, pneumonitis, ARDS, dyspnea, pulmonary infiltrates, radiation pneumonitis | Adalimumab: interstitial lung disease |
| Infliximab: interstitial lung disease | Rituximab: ARDS, BOOP, bronchospasm, diffuse alveolar hemorrhage, immune-mediated (hypersensitivity) pneumonitis | Atezolizumab: pneumonitis, bronchospasm, diffuse alveolar hemorrhage, pulmonary infection | Avelumab: immune-mediated pneumonitis |
| | | Amivantamab-vmjw: interstitial lung disease, pneumonitis | Cemiplimab-rwlc: immune-mediated pneumonitis |
| | | Atezolizumab: immune-mediated pneumonitis, dyspnea | Durvalumab: immune-mediated pneumonitis, dyspnea |
| | | Bevacizumab: anaphylaxis/bronchospasm, pulmonary hemorrhage from tumor site | Golimumab: interstitial lung disease |
| | | Dostarlimab-gxly: immune-mediated pneumonitis | Ipilimumab: immune-mediated pneumonitis, dyspnea |
| | | Fam-trastuzumab deruxtecan-nxki: interstitial lung disease, pneumonitis | Nivolumab: immune-mediated pneumonitis, dyspnea |
| | | Pembrolizumab: immune-mediated pneumonitis, dyspnea | Panitumumab: immune-mediated pneumonitis, lung infiltrates, pneumonitis, pulmonary fibrosis |
| | | Trastuzumab: ARDS, BOOP, dyspnea, interstitial pneumonitis, pleural effusions, pulmonary infiltrates/fibrosis/edema | Tisotumab vedotin-tftv: pneumonitis |

ARDS—acute respiratory distress syndrome; BOOP—bronchiolitis obliterans organizing pneumonia; ‘pneumonitis’ is used when the mechanism remains uncertain.
Table 8. Cardiac adverse events caused by approved monoclonal antibodies used for therapy.

| Monoclonal Antibody | Cardiac Adverse Events |
|---------------------|------------------------|
| Adalimumab          | Heart failure          |
| Ado-trastuzumab emtansine ¹ | Decreased LVEF |
| Alemtuzumab         | Cardiomyopathy, decreased LVEF, cardiac arrhythmias associated with infusions |
| Bevacizumab         | CHF: incidence of grade 3 reaction for LVD 1% |
| Bezlotoxumab        | Heart failure          |
| Brentuximab vedotin | Supraventricular arrhythmia in systemic anaplastic large cell lymphoma |
| Certolizumab pegol  | Heart failure          |
| Cetuximab           | Cardiopulmonary arrest/sudden death |
| Fam-trastuzumab deruxtecan-nxki | LVD |
| Golimumab           | Heart failure          |
| Ibrutumomab tiuxetan| Cardiac arrest related to infusions |
| Inotuzumab ozogamicin| QT interval prolongation |
| Margetuximab-cmkb ¹| LVD                    |
| Necitumumab ¹       | Cardiopulmonary arrest |
| Obinutuzumab        | Worsening of preexisting cardiac conditions leading to fatal cardiac events |
| Pertuzumab ¹        | Cardiomyopathy manifesting as CHF and decreased LVEF |
| Ramucirumab         | Serious, sometimes fatal, myocardial infarction |
| Rituximab           | Cardiac arrhythmias and angina, fatal cardiac failure |
| Romosozumab-aqgg ¹  | Myocardial infarction, cardiac events, cardiovascular death |
| Trastuzumab ¹       | Cardiomyopathy manifesting as CHF and decreased LVEF |

CHF—congestive heart failure; LVD—left ventricular dysfunction; LVEF—left ventricular ejection fraction. ¹ FDA boxed warnings apply.

As occurs with mAb-induced pulmonary adverse events, checkpoint inhibitors, both PD-L1- and PD-l-targeted mAbs, may elicit immune adverse reactions in the liver in the form of immune-mediated hepatitis. Another immune-based adverse effect may occur with the CD25 (IL-2R α-chain)-targeted mAb daclizumab, which is subject to an FDA box warning for hepatic injury including via an autoimmune mechanism. Other mAb-provoked adverse liver injuries include direct toxicities and reactivation of hepatitis (Tables 4–6 and 9). FDA warnings and precautions for non-immune mAb-induced liver injury apply to adalimumab, certolizumab pegol, evolocumab, golimumab, infliximab, natalizumab, vedolizumab, brentuximab vedotin, catumaxomab, cemiplimab-rwlc, elotuzumab, ofatumumab, polatuzumab vedotin-piöq, and rituximab. Four mAbs are subject to boxed warnings, gemtuzumab ozogamicin and inotuzumab ozogamicin for hepatotoxicity, including severe or fatal hepatic veno-occlusive disease; ado-trastuzumab emtansine for hepatotoxicity; and obinutuzumab for hepatitis B reactivation (Table 9). Three of these four mAbs are antibody–drug conjugates, suggesting involvement of the attached toxin in the severe hepatotoxicities. A warning applies to satralizumab-mwge for elevated liver enzymes ALT and AST.
Table 9. Liver adverse events induced by approved monoclonal antibodies used for therapy.

| Monoclonal Antibody      | Liver Adverse Events                                      |
|--------------------------|----------------------------------------------------------|
| Adalimumab               | Reactivates hepatitis B; liver failure                    |
| Ado-trastuzumab          | Hepatotoxicity                                           |
| Atezolizumab             | Immune-mediated hepatitis                                 |
| Avelumab                 | Immune-mediated hepatitis                                 |
| Brentuximab vedotin      | Hepatotoxicity                                           |
| Catumaxomab              | Hepatic disorders—hepatotoxicity                          |
| Cemiplimab-rwlc          | Immune-mediated hepatitis                                 |
| Certolizumab pegol       | Reactivates hepatitis B                                   |
| Daclizumab               | Hepatic injury including autoimmune hepatitis             |
| Dostarlimab-gxly         | Immune-mediated hepatitis                                 |
| Durvalumab               | Immune-mediated hepatitis                                 |
| Elotuzumab               | Hepatotoxicity                                           |
| Evolocumab               | Hepatic impairment                                       |
| Gemtuzumab ozogamicin    | Hepatotoxicity including severe or fatal hepatic veno-occlusive disease |
| Golimumab                | Reactivates hepatitis B                                   |
| Infliximab               | Hepatotoxicity                                           |
| Inotuzumab ozogamicin    | Hepatotoxicity including severe or fatal hepatic veno-occlusive disease |
| Natalizumab              | Hepatotoxicity                                           |
| Obinutuzumab             | Reactivates hepatitis B                                   |
| Ofatumumab               | Reactivates hepatitis B                                   |
| Polatuzumab vedotin-piiq | Hepatotoxicity                                           |
| Rituximab                | Reactivates hepatitis B                                   |
| Vedolizumab              | Possibility of liver injury suggested by elevated levels of transaminase and/or bilirubin |

Cutaneous reactions have been associated with at least 39 of the 110 different mAbs (≈36%, counting alemtuzumab and denosumab each only once) (Table 6). As discussed above, some of these reactions are true type IV hypersensitivities, and there are a few recorded examples of type I reactions such as urticaria (e.g., alirocumab), but mechanisms remain to be established for many of the other adverse events (Tables 4 and 5, Box 2). FDA warnings and precautions for dermatologic toxicity/reactions have been issued for cemiplimab-rwlc, cetuximab, denosumab, dostarlimab-gxly, durvalumab, enfortumab vedotin-ejfv, and mogamulizumab-kpc. It is not clear whether or not at least some of the skin reactions following checkpoint inhibitors (cemiplimab-rwlc, dostarlimab-gxly, durvalumab) are immune-mediated. Skin reactions to loncastumab tesirine-lpyl may also demonstrate photosensitivity. Antibodies targeted to EGFR, namely, amivantamab-vmjw, cetuximab, necitumumab, and panitumumab, are known to produce, and are subject to, FDA warnings for papulopustular (acneiform) skin eruptions (Figure 4) [54] and mucocutaneous reactions (mucositis, xerosis, paronychia, fissures, palmar-plantar rash, skin hyperpigmentation, and others), both of which are not immune-mediated. In addition, panitumumab carries an FDA black box warning for dermatologic toxicity and has been implicated in cases of erythema, exfoliation, paronychia, skin fissures, photosensitivity, xerosis, and pruritus.
4.3. Rare Syndromes Associated with Monoclonal Antibody Therapy

Some rare, potentially life-threatening syndromes (Box 4) may occur with low frequency following the administration of some mAbs. **Cytokine release syndrome (CRS)** [55] shows similarities to severe infusion reactions in that both are related to a high lymphocyte count; counts greater than $50 \times 10^9/L$ are associated with CRS and the release of TNF and IL-6. Symptoms include fever, chills, hypotension, nausea, vomiting, dyspnea, and an increase in liver enzymes. Rituximab is a well-known cause of CRS; other implicated mAbs are alemtuzumab, blinatumomab, and catumaxomab. **Hemophagocytic lymphohistiocytosis (HLH)** [56] is a rare, highly inflammatory disorder resembling cytokine storm involving proliferation of activated T cells and macrophages with the release of large amounts of cytokines, particularly IFN gamma, TNF, and GM-CSF. IL-1 and IL-6 released from activated macrophages are responsible for the inflammatory response, tissue damage, and symptoms of HLH. Two forms of HLH are known, primary, or familial, HLH and
secondary, or acquired, HLH that occurs after malignancy, infection, or immunodeficiency. Blinatumomab is well known to be a rare cause and, more recently, immune checkpoint inhibitors avelumab, ipilimumab, and nivolumab have been rarely implicated. In the immune reconstitution inflammatory syndrome (IRIS) [57], also called immune recovery syndrome, restoration of immunity is, paradoxically, accompanied by deterioration of a known or new condition. Examples of the syndrome are seen in AIDS and tuberculosis. The pathogenesis of the condition is poorly understood. MAbs implicated in IRIS are adalimumab, ibalizumab-uiyk, infliximab, and natalizumab. Macrophage activation syndrome (MAS) [58] resembles HLH, but the name is traditionally reserved for the HLH-like inflammatory reaction seen in at least 10% of patients with rheumatologic diseases, in particular systemic juvenile idiopathic arthritis (SJIA). MAS, which can be rapidly fatal, is mediated by an uncontrolled proliferation of T cells and macrophages exhibiting hemophagocytic activity [59]. MAbs known to precipitate the syndrome include alemtuzumab, canakinumab, and tocilizumab. Progressive multifocal leukoencephalopathy (PML) [60] is a rare, usually fatal demyelinating disease characterized by inflammation and progressive brain damage. It is caused by infection with the normally harmless JC virus that becomes lethaly active in immunosuppressed patients, in some autoimmune diseases, and in patients receiving chemotherapy, including some biologics. MAbs involved include belimumab, brentuximab vedotin, infliximab, eculizumab, natalizumab, ofatumumab, polatuzumab vedotin-piiq, rituximab, and vedolizumab. In reversible posterior encephalopathy syndrome (RPLS), also called posterior reversible encephalopathy syndrome (PRES [61]), edematous changes occur in the brain perhaps as a result of systemic hypertension leading to hypoxia and vasogenic edema. However, some cases of RPLS appear to occur in the absence of hypertension and others in the absence of inflammation. MAbs associated with RPLS include bevacizumab, certolizumab pegol, infliximab, dinutuximab, naxitamab-gqgk, ramucirumab, rituximab, and ustekinumab. Systemic capillary leak syndrome (SCLS) [62], also known simply as capillary leak syndrome, vascular leak syndrome, and Clarkson’s disease, has symptoms of body weight increase, malaise, weakness, pyrexia, myalgia, abdominal pain/vomiting, and diarrhea. An increase in vascular permeability and extravasation of fluids leads to peripheral and interstitial edema and, in severe form, pulmonary and cardiovascular failure. MAbs reported to be associated with SLS include alemtuzumab, basiliximab, bevacizumab, catumaxomab, dinutuximab, the immune checkpoint inhibitor nivolumab, and rituximab. Systemic inflammatory response syndrome (SIRS) [63], related to sepsis, can cause organ dysfunction and failure. It may be caused by infection or have a noninfectious basis such as trauma, pancreatitis, ischemia, anaphylaxis, or treatment with a biologic agent. The condition proceeds via activation of an inflammatory cascade of cytokines including TNF; IFN gamma; and IL-1, -6, and -8. SIRS has been reported following catumaxomab and eculizumab. Tumor lysis syndrome (TLS) [64] occurs most often in patients with leukemia and high-grade lymphomas where there are large numbers of cancer cells. Death of the cells results in marked ionic imbalance due to hypercalcemia, hyperkalemia, hyperphosphatemia, and hyperuricemia. This can lead to renal failure, cardiac arrhythmias, seizures, and death. The mAbs most often associated with TLS are alemtuzumab, blinatumomab, brentuximab vedotin, ipilimumab, obinutuzumab, polatuzumab vedotin-piiq, and rituximab (Box 4).
Box 4. Monoclonal antibodies associated with rare syndromes.

- **Cytokine release syndrome (CRS)**
  - Alemtuzumab; blinatumomab; catumaxomab; rituximab
- **Hemophagocytic lymphohistiocytosis (HLH)**
  - Alemtuzumab; avelumab; blinatumomab; ipilimumab; nivolumab
- **Immune reconstitution inflammatory syndrome (IRIS)**
  - Adalimumab; ibalizumab-uiyk; infliximab; natalizumab
- **Macrophage activation syndrome (MAS)**
  - Alemtuzumab; canakinumab; tocilizumab
- **Progressive multifocal leukoencephalopathy (PML)**
  - Belimumab; brentuximab vedotin; infliximab; eculizumab; natalizumab; ocrelizumab; ofatumumab; polatuzumab vedotin-piq; rituximab; vedolizumab
- **Reversible posterior encephalopathy syndrome (RPLS)**
  - Bevacizumab; certolizumab pegol; infliximab; dinutuximab; naxitamab-ggk; ramucirumab; rituximab; ustekinumab
- **Systemic capillary leak syndrome (SCLS)**
  - Alemtuzumab; basiliximab; bevacizumab; catumaxomab; dinutuximab; nivolumab; rituximab
- **Systemic inflammatory response syndrome (SIRS)**
  - Catumaxomab; eculizumab
- **Tumor lysis syndrome (TLS)**
  - Alemtuzumab; blinatumomab; brentuximab vedotin; ipilimumab; obinutuzumab; polatuzumab vedotin-piq; rituximab

5. Concluding Remarks

At the beginning of 2022, the catalog of mAbs approved for therapy by the FDA and/or EMA consisted of 66 approved for non-cancer indications and 46 for cancer therapy. Unsurprisingly because of their clinical success, the number of approved mAbs continues to expand, for example, in the 17 year period 1997–2013, 34 mAbs were approved, whereas in the 7 years of 2014–2020, the approved total was 61 (Figure 5) [65]. From 1997 until the present time (December 2021), 110 mAbs have received approval from the FDA and/or EMA (Figure 5). In 2021, 14 products were approved: aducanumab, amivantamab, anifrolumab, bimekizumab, casirivimab + imdevimab; dostarlimab-gxly, efgartigimod-alfa-fcab, evinacumab, loncastuximab teserenine-lpyl, regdanvimab, sotrovimab, tezepelumab-ekko, tisotumab vedotin, and tralokinumab. Approved by the EMA, casirivimab + imdevimab, regdanvimab, and sotrovimab are the first three preparations for the treatment of COVID-19, each targeted to the spike protein receptor-binding domain of SARS-CoV-2 (Table 1). It is clear that from information on the numbers of mAbs already undergoing clinical assessment, as well as some already marketed for other indications with the view of repurposing for the treatment of COVID-19, further approvals of mAb preparations to treat this disease are imminent [65]. In late December 2021, efgartigimod-alfa-fcab indicated for myasthenia gravis and tezepelumab-ekko for severe asthma were approved by the FDA.

In the next few years, research and clinical progress in disease pathogenesis and the identification of new disease biomarker targets, together with ongoing orphan drug development programs, will continue an inevitable expansion of the list of approved mAbs. Aspects of this expansion of great interest include a growing list of new indications; further mechanistic insights into the interplay between antibodies, cells, cytokines, chemokines, receptor interactions and downstream signaling; the appearance of new, and some unexpected, adverse events; and progress in understanding and treating such events.
Figure 5. Numbers of mAbs approved by the FDA and/or EMA during the 24 year period 1997–2020. Biosimilar and Fc fusion proteins are not included. Note that in 2021, 14 mAb products were approved.

*: Data publicly available as of 25 November 2020. From Kaplon, H.; Reichert, J.M. Antibodies to watch in 2021. Mabs 2021, 13, e1860476, doi.org/10.1080/19420862.2020.1860476 [65], an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0) (accessed on 14 December 2021).

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