Specific targeting of tumor cells without inflicting collateral damage on normal healthy cells has been, and remains, a long-standing aim in cancer therapy. In attempts to destroy rapidly dividing malignant cells, the mainstay of therapy has been the administration of small cytotoxic molecules used with, or without, radiation therapy. This rather crude and non-discriminatory approach of killing rapidly dividing cells often adversely affects some normal, healthy cells such as mucosal lining cells and those in the bone marrow and hair follicles. Frequent consequences of this approach using agents demonstrating non-specific toxicity are patients with poor tolerance of the chemo- and radiation therapies, delays, interruptions or discontinuation of therapy, and sometimes poor survival outcomes.

Here, targeted drugs have been divided into the natural or synthetic “small” molecules (i.e., generally MW ≤ 1 kDa; often called “chemotherapy” drugs) and the biologics. Note that the macrolide mammalian (mechanistic) target of rapamycin (mTOR) inhibitors, sirolimus (also known as rapamycin), temsirolimus, and everolimus, have molecular weights of ~1000 Da. The small molecules are almost always of nonbiologic origin whereas the biologics in the main are particular monoclonal antibodies (mAbs) and a few recombinant fusion proteins, for example, aflibercept.

14.1 Targeted Small Molecule Drugs for Cancer Therapy

Effective targeting of tumor cells without accompanying toxicity has started to be realized with the introduction of signal transduction therapies and monoclonal antibodies (mAbs). The principle of signal transduction therapy is shown diagrammatically in Fig. 14.1. Signal transduction involves the utilization of biochemically induced signals generated by a range of large and small molecules such as growth factors, neurotransmitters, hormones, cytokines, chemokines, and ATP, to produce a wide variety of cell responses like cell division, metabolic changes, gene expression, and cell death. Signal transduction therapy then depends on identifying signaling proteins and their altered pathways. The first example of understanding and applying a signaling network to design and employ targeted drugs was the use of the estrogen receptor antagonist tamoxifen for the treatment of some estrogen-dependent breast cancers. The first signaling
proteins to be utilized as targets for a new generation of unique anticancer drugs were protein kinases.

### 14.1.1 Signal Transduction and Protein Kinases

Kinases and phosphatases are enzymes that modulate activities of proteins in the cell. Kinases transfer a $\gamma$-phosphate group (PO$_3^{2-}$) from adenosine triphosphate to the hydroxyl group of tyrosine on signal transduction molecules (proteins), thus maintaining cellular functions, while phosphatases remove phosphate groups reversing the actions. The reactants, products, and stoichiometric numbers for the protein kinase-catalyzed reaction is:

$$\text{MgATP}^+ + \text{protein} - \text{O:} + \text{H} \rightarrow \text{protein} - \text{O:PO}_3^{2-} + \text{MgADP} + H^+$$

Tyrosine kinases can be classified as receptor and non-receptor kinases. Approximately 538 kinases encoded in the human genome promote cell proliferation, survival, and migration, but overexpression, dysregulation, and mutations of protein kinases involve them in the pathogenesis of many diseases including an association with oncogenesis. As a consequence of genetic mutations and chromosome reshuffling, many human malignancies are now known to be associated with the actions and dysfunctions of protein and lipid kinases and malfunctioning phosphatases. According to Manning et al. (The protein kinase complement of the human genome. Science 2002;298:1912), the human protein kinase super family consists of 518 enzymes, classified as 385 protein-serine/threonine kinases, 90 (58 receptor and 32 non-receptor) protein-tyrosine kinases, and 43 protein-tyrosine kinase-like enzymes. At March 2019, the US FDA had approved 48 small molecule protein kinase inhibitors directed against about 20 different protein kinases: 25 inhibitors of receptor protein-tyrosine kinases, 10 inhibitors of non-receptor protein-tyrosine kinases, and 13 inhibitors of protein-serine/threonine tyrosine kinases. Forty-three of the 48 kinase inhibitors are directed toward malignancies (36 solid tumors, 7 non-solid tumors). Eighteen are multitarget inhibitors.
14.1.1.1 Tyrosine Kinases and the Philadelphia Chromosome

The original targeting strategy for cancer therapies was based on the instability of the cancer genome compared to the normal cell. The Philadelphia translocation t(9;22)(q34;q11) or Philadelphia chromosome is a chromosomal defect resulting in gene fusion of the BCR and ABL genes. The BCR (breakpoint cluster region) gene is on chromosome 22 (region q11) and the ABL (so named because the Abelson leukemia virus has a similar protein) tyrosine kinase gene is on chromosome 9 (region q34). The resultant fusion gene is the BCR-ABL oncogene. The Philadelphia chromosome is a cytogenetic abnormality seen in 95% of chronic myeloid leukemia (CML) patients and 15–30% of adults with acute lymphoblastic leukemia (ALL) but absent from nonmalignant cells. Tyrosine kinases were implicated as oncogenes in some animal tumors induced by retroviruses more than 30 years ago. The oncogene BCR-ABL results in the expression of two forms of tyrosine kinases and a large increase in myeloid cell numbers. The BCR-ABL mutation is present in the great majority of CML patients, the Bcr-Abl fusion protein is unique to leukemic cells but absent from nonmalignant cells, it is expressed in high levels, and its tyrosine kinase activity is essential in the induction of leukemia. CML cells show absolute dependence (“oncogene addiction”) on the kinase activity of protein Bcr-Abl, and this dependence was first exploited by the development of the drug imatinib (Gleevec®) which inhibits both the Abl and Bcr-tyrosine kinases and has been successful in treating CML. In fact, the extraordinary interest in and development of protein kinase inhibitors was stimulated by the 2001 regulatory approval of imatinib for the treatment of Philadelphia chromosome-positive CML.

Besides imatinib, nilotinib is another protein tyrosine kinase inhibitor targeting Bcr-Abl. In CML cases resistant to imatinib, broader spectrum tyrosine kinases such as dasatinib (Sprycel®), which blocks both Bcr-Abl, Src, and other tyrosine kinases, may be used (Table 14.1). Inhibitors of receptor tyrosine kinases targeting epidermal growth factor receptor (EGFR; ErbB1; HER1; a member of the ErbB family of receptors), vascular endothelial growth factor receptors (VEGFRs), and platelet-derived growth factor receptors (PDGFRs) have also found use in the clinic as effective targeted antitumor drugs. Elevated EGFR tyrosine kinase activity is found in most solid tumors. The following is a list of the percentage expression of EGFR by some common human cancers: nonsmall cell lung cancer 40–80, head and neck 80–100, gastric 33–81, colorectal 25–100, pancreatic 30–50, ovarian 35–70, breast 15–37, prostate 40–90, and glioma 40–92%. Some receptor tyrosine kinase inhibitors include gefitinib and erlotinib (both inhibitors of EGFR), lapatinib (inhibits ErbB1 and ErbB2), vatalanib (inhibits VEGFR-1 and VEGFR-2), sorafenib (inhibits VEGFR, PDGFR, and c-Kit [CD117]), and sunitinib with a broad spectrum activity targeting VEGFR, PDGFR, FGFR, FLT3, and c-Kit. Other targeting strategies summarized in Table 14.1 that interfere with signal transduction include the mTOR serine/threonine kinase inhibitors that target the Raptor complex; lipid kinase inhibitors (e.g., idelalisib, a phosphoinositide 3-kinase delta isoform [PI3Kδ] inhibitor); histone deacetylase inhibitors (drug examples include romidepsin and vorinostat) that arrest the cell cycle; the PML-RARα oncoprotein (arsenic trioxide); and drugs (e.g., bexarotene) binding to retinoid receptors. Still other targeting strategies are represented by pralatrexate, a folate analog that accumulates in cancer cells overexpressing protein RFC-1, and proteasome inhibitors such as bortezomib and carfilzomib are active against the cells of multiple myeloma and mantle cell lymphomas in perhaps the most fascinating of all the current targeted mechanisms (Table 14.1). These drugs inhibit proteasomes by binding to proteolytic catalytic sites in the 20S proteasome core (see below). This is thought to prevent degradation of pro-apoptotic factors permitting killing of cancer cells.

14.1.1.2 Imatinib Mesylate

Imatinib mesylate (4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[(4-(3-15pyridinyl)-2-pyrimidinyl)amino]-phenyl]benzamide methanesulfonate) (Fig. 14.2) is a protein tyrosine
Table 14.1 Classification of targeted chemotherapeutic drugs used for cancers and their hypersensitivity/adverse reactions

| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/adverse reactions |
|---|---|---|---|
| **Non-receptor tyrosine kinase inhibitors** | | | |
| Bosutinib (Bosulif)° | Ph+CML² | Targets Abl and Src kinases inhibiting autophosphorylation of both | Anaphylaxis, thrombo, neutron, anemia, edema, hepatotox, pneumonia, pyrexia, cough, GI, renal toxicity, eff | Rash, pruritus |
| Crizotinib (Xalkori)° | NSCLC | Inhibits tyr kinase activity of fusion protein EML4-ALK° | Pneumonitis, edema, neuropathy, est, arthralgia, vision disorders, cough, dyspnea, QT prolongation, GI | Rash, pruritus, stomatitis |
| Dasatinib (Sprycel)° | Ph+ALL, Ph+CML, Ph+CML resistant to imatinib | Inhibits Bcr-Abl, Src, c-Kit⁴, ephrin (EphA2), and other tyr kinases (PDGFRβ)° | Abnormal platelets, neutron, anemia, tls, peripheral edema, pleural effusion, pah, GI, CV, QT prolongation, dyspnea, eff | Rash, pruritus, xerosis, alopecia, urticarial, nail disorders, pigm, panniculitis, dermatitis |
| Imatinib (Gleevec)° | Ph+CML, Ph+ALL, HES/CEL, MDS/MPD, ASM, DFSP, GISTPh+CML | Blocks Bcr-Abl tyr kinase from phosphorylating | Thrombo, neutron, anemia, edema, eff, hypersens pneum, hepatotox, tls, GI, hypothyroidism | Rash, pruritus, angioedema, vasculitis, hyper-pigm, dress, agep, sjs, erythema multiforme |
| Nilotinib (Tasigna)° | Ph+CML resistant to imatinib | Inhibits Bcr-Abl, c-Kit⁴, EphA3⁹, EphA8³, PDGFRβ° and other tyr kinases | Thrombo, neutron, leuko, anemia, tls, edema, hepatotox, GI, pneumonia, dyspnea, QT prolongation, pancreatitis | Rash, pruritus, erythema, eczema, urticarial, alopecia, xerosis, ecchymosis |
| Ponatinib (Iclusig)° | CML, Ph+ALL | Targets pan Bcr-Abl | Thrombo, neutron, anemia, leuko, RPLS, hepatotox, CV, tls, pancreatitis, GI, eff, hypertension, neuropathy, hemorrhage | Rash, xerosis |

**Signal transduction inhibitors**

| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/adverse reactions |
|---|---|---|---|
| Erlotinib (Tarceva)° | NSCLC, pancreatic cancer | EGFR; inhibitor – binds to ATP binding site of receptor interrupting signal cascade | Hepatotox, ild, thrombo, anemia, renal disorders, GI perforation, ocular disorders | Rash, pruritus, ppr, xerosis; hyper-pigm, hfsr, digital fissures, alopecia, paronychia, eyelid/brow changes, bullous reactions |
| Gefitinib (Iressa)° | NSCLC | EGFR inhibitor | GI perforation, ild, ocular disorders, hemorrhage, eff | Stomatitis, hfsr, ppr, pruritus, nail and hair disorders, ocular disorders |
| Lapatinib (Tykerb)° | Metastatic breast cancer | Inhibits tyr kinase activity of HER² and EGFR | Anaphylaxis, cardiac tox, hepatotox, ild, GI, QT prolongation, diarrhea | Rash, hfsr, pruritus, xerosis, paronychia, nail disorders, alopecia |
| Drug               | Indications                        | Functions and Side Effects                                                                                                                                 |
|--------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Pazopanib**      | RCC, STS                          | Inhibits several tyrosine kinases including VEGFRs, PDGFRs, FGFRs, and c-Kit. Heptotoxicity, hypertension, QT prolongation, hemorrhage, hypothyroidism, rPLS, Ild, cardiac dysfunction. Hair, skin depigment, hFSR, exfoliative rash, nail disorders, xerosis, stomatitis, alopecia, mucositis. |
| **Regorafenib**    | CRC, GIST, HCC                    | Inhibits multiple kinases including VEGFRs 2 and 3, PDGFR, c-Kit, RET, RAF, and TIE2. Heptotoxicity, hypertension, hemorrhage, GI dysphonia, rPLS, infections. Rash, hFSR, xerosis, mucositis, desquamation, pruritus. |
| **Sorafenib**      | RCC, HCC, thyroid carcinoma        | Inhibits VEGFR2 and PDGFRβ signaling, blocking tumor angiogenesis. Blocks RAF kinase involved in cell growth and proliferation. Hemorrhage, cardiac toxicity, hypertension, GI flushing, thrombo, neuron, anemia, leuko, lympho, rPLS, eft. Rash, hFSR, desquamation, erythema, xerosis, pruritus, alopecia, ssh, facial acne, stomatitis, bullous eruptions. |
| **Sunitinib**      | RCC, GIST, PNET                    | Inhibits VEGFR2, PDGFR3, and c-Kit, inhibiting angiogenesis and cell proliferation. Inhibits phosphorylation of FLT3. Heptotoxicity, hypertension, CV, GI, QT prolongation, hemorrhage, thyroid dysfunction, fever, periph edema, dyspnea, ts, eft, hypoglycemia. Rash and acne (? ppr), xerosis, stomatitis, sjs, ten, erythema multiforme, necrotizing fasciitis. |
| **Vandetanib**     | MTC                               | Inhibits cell receptor tyrosine kinases VEGFR, EGFR, and RET. Hypertension, cardiac toxicity, QT prolongation, hemorrhage, Ild, rPLS, eft, rPLS, ischemic cerebrovascular events. Rash and acne (? ppr), xerosis, stomatitis, sjs. |
| **Lipid tyrosine kinase inhibitors** |                                       |                                                                                                                      |
| Idelalisib         | CLL*, SLL*, FL*                    | Inhibits PI3Kδ; and BCR, CXCR4 signaling. Anaphylaxis, eft, neuton, hepatotoxicity, intestinal perforation, diarrhea, colitis, infections, pneumonitis. Sjs, ten, other severe cutaneous reactions. |
| **mTOR serine/threonine kinase inhibitors** |                                       |                                                                                                                      |
| Everolimus         | RCC, breast cancer, PNET, SEGA, RA and TSC | Binds FK-binding protein FKBP12 and drug-protein complex inhibits mTOR. This blocks binding of regulatory-associating protein of mTOR causing dephosphorylation of S6K1 and apoptosis of cancer cells. Pneumonitis infections, ↓ platelets, neutrophils, HB and lymphocytes, renal failure, edema, oral ulcers, GI, fever, dyspnea, hyperglycemia, hyperlipidemia. Acneiform rash (? ppr), erythema, stomatitis, nail disorders, xerosis. |
| Temsirolimus       | RCC                               | Binds FK-binding protein FKBP12 and drug-protein complex inhibits mTOR. This blocks binding of regulatory-associating protein of mTOR causing dephosphorylation of S6K1 and apoptosis of cancer cells. Also inhibits tumor angiogenesis by reduced synthesis of VEGF. Renal failure, hir, Ild, thrombo, leuko, anemia, edema, GI, bowel perforation, eye disorders, hyperglycemia, hyperlipidemia. Rash (mpr, exfoliative dermatitis), nail disorders, pruritus, xerosis, acne (? ppr), stomatitis. |
| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/adverse reactions |
|---|---|---|---|
| **Histone deacetylase inhibitors** | | | |
| Romidepsin (Istodax)® | CTCL, PTCL | Inhibits histone deacetylase altering gene expression and causing cell cycle arrest and apoptosis | Thrombo, neutrophils, lymphocytes, anemia, QT prolongation, GI, dysgeusia, pyrexia | Exfol dermatitis, itching, pale skin |
| Vorinostat (Zolinza)® | CTCL | Induces growth arrest, differentiation or apoptosis due to accumulation of acetylated proteins incl BCL6, p53, and Hsp90ab | Thrombo, anemia, pulm embolism, trombosis, GI, dysgeusia | Exfol dermatitis, pruritus, alopecia |
| **Drugs that target the PML-RARα oncprotein** | | | |
| Tretinoin (all-trans retinoic acid; ATRA) (Vesanoid)® | APL | APL results from expression by NB4 cells of PML-RARA oncprotein which increases cell surface levels of plasminogen receptor S100A10 and fibrinolytic activity. ATRA down regulates S100A10 blocking fibrinolytic activity (and hence hemorrhage) | Retinoic acid syndrome (dyspnea, fever, periph edema, weight gain), cls, retinoid tox, respiratory and ear disorders | Erythema, xeroderma, photosens, itch, increased risk sunburn |
| Arsenic trioxide (Trisenox)® | APL | As₂O₃ binds to oncogenic fusion protein PML-RARA, induces increased interaction with a ubiquitin-like protein-modifier SUMO-conjugating enzyme UBC9, enhanced SUMOylation and degradation | Thrombo, neuron, hyperleukocytosis, anemia, hypertension, vasculitis, differentiation syndrome, dyspnea, QT prolongation, GI | Rash, erythema, pruritus, facial edema, ecchymosis |
| **Drugs binding to retinoid receptors** | | | |
| Bexarotene (Targretin)® | CTCL | Synthetic retinoic acid deriv. Binds and activates retinoid X receptors inducing changes in gene expression, decreased cell proliferation, apoptosis of some cancer cell types and tumor regression | Hyperlipidemia, pancreatitis, neutrophils, hypothyroidism, hepatotox, cholestasis, limit vitamin A intake, photosensitivity, hypoglycemia risk in diabetics | Vesicular bullous rash, ppr, mpr, acne, keratitis, conjunctivitis, corneal lesions, alopecia, skin nodules, photosens, xerosis |
### Proteasome inhibitors

| Drug                  | Disease(s) | Effect | Side Effects | Common Adverse Effects |
|-----------------------|------------|--------|--------------|------------------------|
| Bortezomib (Velcade)® | MM, MCL    | Inhibits proteasomes by binding via its β atom to β-subunit chymotrypsin and caspase catalytic sites – may suppress degradation of pro-apoptotic factors allowing for killing of neoplastic cells | Periph neuropathy, GI, thrombo, neutro, leuko, anemia, hypotension, cardiac disorders, ards, rpls, tls, hepatic events, pyrexia, dyspnea, pneumonia, eft | Rash<sup>ab</sup>, pruritus, erythema, urticarial, facial edema, eczema, vasculitis, ten, Sweet’s-like syndrome |
| Carfilzomib (Kyprolis)® | MM | Binds to and inhibits chymotrypsin-like activity of the 20S proteasome | Cardiac disorders, pulm hypertension, dyspnea, infusion reactions, tls, thrombo, anemia, neutro, hepatotox, periph neuropathy | Rash, urticarial, itch<sup>c</sup> |

### Hormones, hormone analogs, and hormone antagonists

#### Inhibitors of hormone synthesis

| Hormone Inhibitors | Disease(s) | Effect | Side Effects | Common Adverse Effects |
|--------------------|------------|--------|--------------|------------------------|
| **Aromatase inhibitors** | | | | |
| Anastrozole (Arimidex)® | Breast cancer. Post- menopausal women with hormone receptor positive | Binds reversibly to aromatase preventing conversion of androgens to estrogens | Hot flushes, arthritis, arthralgia, dyspnea, osteoporosis, hypertension, GI | Rash, pruritus, mpr, cutaneous vasculitis, lupus erythematosus, erythema nodosum, erythema multiforme, sj <sup>s</sup> |
| Exemestane (Aromasin)® | Breast cancer. Post- menopausal women | Irreversible aromatase inactivator. Permanently binds the enzyme preventing conversion of androgens to estrogens | Anaphylaxis, hot flushes, arthralgia, dyspnea, decreased bone density, eft | Rash, urticarial, pruritus, cutaneous vasculitis, erythema multiforme, agep, alopecia, dermatitis |
| Letrozole (Femara)® | Breast cancer. Post- menopausal women | As for anastrozole | Anaphylaxis, flushing, dyspnea, GI, eft, diaphoresis, arthralgia, hypertension, periph edema, decreased bone density | Angioedema, rash, erythema multiforme, ten, alopecia |
| **Gonadotropin-releasing hormone analogs (GnRH agonists)** | | | | |
| Goserelin (Zoladex)® | Prostate cancer, breast cancer | Synthetic analog of GnRH. Binds to receptors for GnRH leading to initial increase in Gn and then receptor down-regulation and reduction in hormone levels | Anaphylaxis, hot flushes, didf, anemia, osteoporosis, vaginitis | Rash, itching, rpcs, acne, seborrhea, alopecia |
| Leuprolide (Leuprolrelin) (Lupron)® | Prostate cancer, breast cancer | As for goserelin | Anaphylaxis, hot flushes, didf, thrombo, anemia, leuko, periph edema | Rash, injection site granuloma, pruritus, xerosis, ecchymosis, photosens, pigm |

(continued)
**Table 14.1 (continued)**

| Drug generic and trade names and classification based on mechanism | Hormone receptor antagonists | Selective estrogen receptor modulators (SERMs) |
|---|---|---|
| Cancer indications | Breast cancer (estrogen receptor-positive) | Breast cancer (estrogen receptor-positive) |
| Mechanism(s)$\textsuperscript{a}$ of action | Competitive antagonist of estrogen receptor, inhibiting breast cancer cells requiring estrogen to grow; anti-angiogenic effect | Competitive antagonist of estrogen receptor, inhibiting breast cancer cells requiring estrogen to grow; anti-angiogenic effect |
| Hypersensitivity$\textsuperscript{b}$/adverse$\textsuperscript{c}$ reactions | Hot flushes, vaginal discharge, reduced vision, thrombosis, eft, liver effects, uterine effects, interstitial pneumonia | Hot flushes, vaginal discharge, reduced vision, thrombosis, eft, liver effects, uterine effects, interstitial pneumonia |
| | Pruritus vulvae, urticarial, angioedema, vasculitis$\textsuperscript{d}$, erythema multiforme, bullous pemphigoid, sjs | Pruritus vulvae, urticarial, angioedema, vasculitis$\textsuperscript{d}$, erythema multiforme, bullous pemphigoid, sjs |

**Androgen blockade** (anti-androgens)

| Drug | Bicalutamide (Casodex)$\textsuperscript{b}$ |
|---|---|
| Cancer indications | Prostate metastatic cancer |
| Mechanism(s)$\textsuperscript{a}$ of action | Binds to androgen receptor preventing its activation and accelerates degradation of the receptor |
| Hypersensitivity$\textsuperscript{b}$/adverse$\textsuperscript{c}$ reactions | Hot flushes, hepatic injury/failure, thrombo, interstitial pneumonia, gynecomastia |
| | Urticaria, angioedema, pruritus, alopecia |

**Targeted anti-folate drug**

| Drug | Pralatrexate (Folotyn)$\textsuperscript{b}$ |
|---|---|
| Cancer indications | PTCL |
| Mechanism(s)$\textsuperscript{a}$ of action | Folate analog antimetabolite accumulates in cancer cells which overexpress the protein RFC-1$\textsuperscript{a}$ and interferes with DNA synthesis and leading to cell death |
| Hypersensitivity$\textsuperscript{b}$/adverse$\textsuperscript{c}$ reactions | Thrombo, febrile neuron, anemia, mucositis, pyrexia, dyspnea, fetal harm, tls |
| | Rash, pruritus, exfoliation, ulceration, ten |

From Baldo BA, Pham NH. Adverse reactions to targeted and non-targeted chemotherapeutic drugs with emphasis on hypersensitivity responses and the invasive metastatic switch. *Cancer Metastasis Rev.* 2013;32:723–76. Adapted and reproduced with permission from Springer + Business Media

$\textsuperscript{a}$Some drugs exert their action(s) by more than one mechanism and might therefore be classified into more than one category. The classification shown is deemed to be the most appropriate one

$\textsuperscript{b}$Reactions known, or suspected, of having an immunological basis
Reactions such as weakness, fatigue, headache etc. and GI symptoms like nausea, vomiting, diarrhea, constipation, appetite reduction, dyspepsia etc. are not recorded here since they are common to so many of the drugs. Where such reactions are important, they are referred to collectively as “GI”.

Philadelphia chromosome-positive

Proto-oncogene c-Kit, mast/stem cell growth factor receptor (SCFR). Also called tyrosine-protein kinase Kit or CD117

Belongs to ephrin receptor family of tyrosine kinases

Ph+ used to treat refractory CML including patients with T3151 "gatekeeper" mutation

EGFR, epidermal growth factor receptor

HER2, human epidermal growth factor receptor 2 (also known as Neu, ErB-2, CD340, p185)

VEGFR, vascular endothelial growth factor receptor

FGFR2, fibroblast growth factor receptor 2

RET (rearranged during transfection) proto-oncogene on chromosome 10

The enzyme RAF proto-oncogene ser/threo-protein kinase (also called c-Raf or Raf-1). Functions in MAPK/ERK signal transduction pathway

TIE2, angiopoietin receptor that binds angiopoietin growth factor required for angiogenesis

30–60% of patients

FLT3, CD135; Fms-like tyrosine kinase; receptor-type tyrosine protein kinase FLT3

15–20% of patients

Avoid coadministration of CYP3A inducers and substrates

In combination with rituximab

Relapsed

Blocks P110δ isoform of phosphoinositide-3-kinase

Subject of FDA Boxed Warning

Exfoliative dermatitis, rash (erythematous, generalized, macular, papular, macropapular, pruritic, exfoliative

May occur on first and subsequent infusions. Reactions include flushing, chest pain, dyspnea, hypotension, apnea, and anaphylaxis. Allergic/hypersensitivity reactions occur in ~9% of patients (FDA)

7% of patients

BCL6 protein – zinc finger transcription factor, a sequence-specific repressor of transcription. p53 (tumor protein 53), a tumor suppressor protein that regulates the cell cycle.

Hsp90, heat shock protein 90, a molecular chaperone assisting protein folding and stabilizes some proteins in tumor growth

PML-RARA, promyelocytic leukemia retinoic acid receptor α oncogene fusion protein

Incidence 8–18%

Skin and subcutaneous tissue adverse events in phase 2 trial on 526 patients with MM = 36%. Discontinuations due to these adverse events = 1%

Incidence 8–18%

Also called luteinizing hormone

In 2006, NCI stated that raloxifene was as effective as tamoxifen in reducing the incidence of breast cancer in post-menopausal women at increased risk

19% of treated patients experience skin reactions

RFC-1, reduced folate carrier type I
kinase inhibitor with specific activity for the receptor tyrosine kinase domains in c-Abl, Bcr-Abl, PDGF-R, and c-Kit. Crystallographic studies have contributed greatly to explaining the mechanism of action of imatinib. Imatinib interrupts the oncogenic signaling pathway of Bcr-Abl tyrosine kinase (Fig. 14.3) by targeting the inactive conformation of the Abl kinase. The catalytic domain of Abl is bi-lobal, made up of an N-terminal lobe (N-lobe) and a larger C-terminal lobe (C-lobe). ATP binds in the cleft between the two lobes, linking them, while the peptide substrate binds mainly to the C-lobe. The C-lobe has an “activation loop” (AL) that has a central role in activation of the kinase. In the active state, the AL is in an extended conformation which, together with catalytic Mg$^{2+}$, forms part of the platform for binding the peptide substrate. The AL has a different conformation in the inactive kinase and cannot coordinate the Mg$^{2+}$. Imatinib binds to the inactive state of the Abl kinase which leads to the AL blocking the binding of the peptide substrate.

Imatinib mesylate and some other targeted tyrosine kinase inhibitors are generally well tolerated with less severe systemic effects, especially when compared to most cytotoxic chemotherapies. Dermatologic reactions are the main adverse responses to many of the targeted drugs including gefitinib, lapatinib, erlotinib, regorafenib, pazopanib, sorafenib, and sunitinib (Sect. 14.1.1.3). The most common non-hematologic adverse reactions to the drug include superficial edema, especially periorbital edema, nausea, vomiting, diarrhea, muscle cramps,
myalgia, arthralgia, fatigue, abdominal pain, headache, and, most common of all, cutaneous reactions. Patients receiving standard dose imatinib therapy in the chronic phase of chronic myeloid leukemia experience neutropenia in 35–45% of cases, thrombocytopenia in 20% of cases, and anemia in 10% of cases. Although most cutaneous reactions are mild and dose dependent, severe reactions such as Stevens-Johnson syndrome (SJS), exfoliative dermatitis, toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Other severe reactions to the drug include rare cases of acute generalized exanthematous pustulosis (AGEP), nearly 20 cases of lichenoid drug eruptions of the skin or oral mucosa, vasculitis, pityriasis rosea-like eruption, palmoplantar hyperkeratosis, and exacerbation of psoriasis. For mild to moderate rashes, antihistamines or, if necessary, topical or short-course corticosteroids can be used.

For severe skin reactions, the following management schedule has proved effective for achieving tolerance of therapeutic dosages of imatinib even after severe cutaneous reactions to the drug: prednisolone 1 mg/kg per day, tapered to 20 mg per day over several weeks along with the gradual reintroduction of imatinib (100 mg per day increased by 100 mg per week) given as the prednisolone dose is tapered off. This, of course, is only continued if the skin manifestations do not recur.

Oral desensitization to imatinib in patients with recurrent rash induced by the drug has been reported. Ten patients were subjected to a 4 h dosage procedure beginning with a dose of 10 ng followed by increases every 15 min. Four patients experienced no recurrence of rash after desensitization, four had recurrent rash that resolved after corticosteroid/antihistamine administration, and two patients each developed a rash and were unable to resume imatinib therapy.

14.1.1.3 Gefitinib, Erlotinib, and Other Kinase Inhibitors: Adverse Events

Gefitinib and erlotinib are derivatives of 4-aminooquinazoline (Fig. 14.2). Both drugs are EGFR inhibitors, inhibiting the receptor’s tyrosine kinase domain by binding to the ATP-binding site of the enzyme. Approved by the FDA in 2003, gefitinib is indicated for locally advanced or metastatic nonsmall cell lung cancer with activated mutations of EGFR tyrosine kinase. EGFR is overexpressed by the cells of some cancers such as lung and breast leading to uncontrolled cell proliferation, the blocking of apoptosis, and increased production of angiogenic factors and metastasis. The mutations also incur increased sensitivity to tyrosine kinase inhibitors like gefitinib, but no clinically beneficial activity of the drug is shown in patients with EGFR-negative tumors. The most frequent adverse reactions to gefitinib, that is, reactions occurring in more than 20% of patients, are diarrhea and skin reactions. Reactions may be categorized by the affected organ: skin reactions like hand-foot skin reaction, pruritus, erythema, and papulopustular rash (Fig. 14.4) are common as are nail disorders, while bullous eruptions (erythema multiforme, SJS, and TEN) are rare. Note that hand-foot skin reaction (Fig. 14.5) should not be confused with hand-foot syndrome or acral erythema (Chap. 15, Sects. 15.2 and 15.2.5.1) seen during the administration of some cytotoxic anticancer drugs such as 5-fluorouracil and doxorubicin. Hand-foot skin reaction is distinguished by localized blisters or hyperkeratosis, whereas hand-foot syndrome shows diffuse, symmetrical erythematous, and edematous lesions on the palms and soles. Ocular (conjunctivitis, blepharitis) and gastrointestinal disorders, vascular effects (hemorrhage), and renal and urinary disorders are also common side effects of gefitinib. Interstitial lung disease has been found in 1.3% of patients, often of severe grade and occasionally fatal.

Erlotinib is an EGFR type I receptor (HER1/EGFR) tyrosine kinase inhibitor. These receptors are involved in the control of cell divisions and proliferation and by inhibiting their functions. Erlotinib limits tumor cell division and metastasis and may even help in initiating apoptotic cell death. A randomized, placebo-controlled, double-blind trial carried out by a National Cancer Institute of Canada Clinical Trials Group revealed that the main adverse responses to erlotinib were rash, fatigue, anorexia, diarrhea, nausea, ocular effects, infec-
tion, vomiting, and stomatitis. Rash and diarrhea were the main reasons for dose reduction and interruption of treatment. In a 2009 warning, the FDA referred to rare serious gastrointestinal, skin, and ocular disorders in some patients taking erlotinib. As with other tyrosine kinase inhibitors, papulopustular rash, hand-foot skin reaction, and pigmentary changes are commonly seen. Serious eye conditions include corneal lesions, some patients develop gastrointestinal perforations, and rare bullous and exfoliative skin reactions, some leading to death, have occurred.

Second-generation Bcr-Abl inhibitors such as dasatinib and nilotinib may cause a pruritic skin rash with incidences of 23% and 34%, respectively. The pathogenesis is not well understood although it has been suggested that some kinases, with a role in epidermal homeostasis (e.g., PDGFR, RAS/RAF, Src family) and drug-
induced decrease in TGF-β-stimulated collagen production, are involved. The third-generation Bcr-Abl inhibitor ponatinib is associated with hyperkeratotic rashes in about 40% of treated patients. BRAF inhibitors, vemurafenib and dabrafenib, cause keratosis pilaris-like rashes in 10–55% of treated patients and a Grover’s disease-type rash in up to 27% of patients. Grover’s disease is seen as an erythematous, polymorphic, pruritic, crusted papulovesicular eruption occurring mostly on the trunk. Such reactions occur more rarely with sorafenib and regorafenib. Interestingly, there are some rare reports of Grover’s disease associated with mAb immune checkpoint inhibitor therapy including anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab) and anti-programmed cell death-ligand 1 (PD-L1 (pembrolizumab) blockade (Sect. 14.2.1). The lipid tyrosine kinase PI3K P110δ inhibitor idelalisib occasionally induces a pityriasis rubra pilaris-like rash. Multikinase inhibitors like sorafenib and sunitinib frequently exhibit skin toxicity and produce fever, edema, and occasionally inflammatory actinic keratosis and bullous manifestations (Table 14.1).

The inclusion of reactions to 17 kinase inhibiting drugs demonstrates the current importance of tyrosine and serine/threonine kinase inhibitors for the targeted treatment of an expanding range of tumors (Table 14.1). While the aim of signal transduction therapy is to kill the cancer cells with minimal collateral damage, even a quick glance at the catalog of side effects in the table shows that, just as with the non-targeted drugs (but less so), cutaneous, gastrointestinal, and hematopoietic cells are often still affected. Cytotoxic effects such as anemia, thrombocytopenia, and neutropenia occur less often and usually with less severity than with, say, antimetabolites and alkylating agents, but a number of the targeted agents show their own fairly unusual effects including a lengthened QT interval, hand-foot skin reaction, and papulopustular rash. Inhibition of the EGFR in skin often produces xerosis, skin fissures, nail alterations, paronychia (Fig. 14.6), periungual ulcers, and pruritus.

Fig. 14.6 Paronychia after treatment with lapatinib, a dual tyrosine kinase inhibitor which inhibits the HER2/neu and epidermal growth factor receptor (EGFR) pathways (see Table 14.1). (From Fabbrocini G, Cameli N, Romano MC, et al. Chemotherapy and skin reactions. J Exp Clin Cancer Res. 2012:31:50. https://doi.org/10.1186/1756-9966-31-50, an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0))

14.1.2 Proteasome Inhibitors

The ubiquitin-proteasome system has a central role in the turnover of proteins – in the regulation of cellular proteins involved in growth and survival and in the destruction of defective proteins. The proteasome consists of a hollow cylindrical or barrel-like 20S (0.7 MDa) proteolytic core capped at one or both ends by a 19S (0.9 MDa) regulatory particle or activator. These structures make up the single-capped proteasome complex or 30S double-capped form (Fig. 14.7). Note that the enzymically active double-capped proteasome complex, which is thought to be the functional unit in the cell, is usually referred to as the 26S (2.5 MDa) proteasome even though physicochemical analysis has revealed that the correct sedimentation coefficient is ~30S. The ~26S form probably represents the single-capped proteolytic core. Proteins that are defective in some
way, for example, due to aging, incorrect folding, etc., are tagged by ubiquitin and directed to the proteasome for degradation via the endoplasmic reticulum degradation pathway. Cell-cycle progression is dependent on the ubiquitin-proteasome pathway with its three proteolytic activities in the proteasome that are mediated by three β-subunits in the core: β2 trypsin-like, β5 chymotrypsin-like, and so-called arm (pink). The 20S proteolytic core may be capped at one or both ends by a 19S regulatory particle. Proteasomes are thus referred to as single-capped (sedimentation coefficient ~26S) or double-capped (~30S). In the literature, the term 26S proteasome is often used incorrectly when referring to the double-capped form. The double-capped complex is thought to be the functional proteasome unit in the cell.

**Fig. 14.7** Diagrammatic representation of the proteasome and its role in protein degradation via the ubiquitin-proteasome pathway. After being tagged with ubiquitin and unfolded for degradation on the 19S regulatory particles which aid the opening of a proteolytic gate in the 20S core, proteins are degraded into small peptides in the barrel-shaped core where β1 caspase-, β2 trypsin-, and β5 chymotrypsin-like activities reside. Regulatory particles are composed of a base (dark blue), lid (yellow-brown), and so-called arm (pink). The 20S proteolytic core may be capped at one or both ends by a 19S regulatory particle. Proteasomes are thus referred to as single-capped (sedimentation coefficient ~26S) or double-capped (~30S). In the literature, the term 26S proteasome is often used incorrectly when referring to the double-capped form. The double-capped complex is thought to be the functional proteasome unit in the cell.
like, and β1 caspase-like activities. Proteolytic activity of each of these subunits is associated with the N-terminal threonine residues in peptide bond hydrolysis. Cancer cells show higher proteasome activity than normal cells. Inhibition of proteasome function leads to intracellular accumulation of unwanted proteins and ultimately cell death, and, here too, cancer cells are more sensitive to the apoptosis-promoting effects of inhibition than normal cells. Proteasome inhibitors can induce apoptosis in leukemia- and lymphoma-derived cells without causing the death of non-transformed cells. Multiple myeloma cells synthesize and secrete large amounts of immunoglobulin, and this high rate of biosynthesis is thought to increase the sensitivity of the synthesized proteins to proteasome inhibitors by, for example, inducing the immunoglobulins into the unfolded state.

14.1.2.1 Bortezomib

Most proteasome inhibitors are short peptides that serve as protein substrates in the proteasome 20S core where they target the active site threonine residues. Bortezomib, an N-protected dipetide that contains a boron atom (Fig. 14.8), was the first proteasome inhibitor to be introduced into the clinic and is approved for treating relapsed multiple myeloma and mantle cell lymphoma. The drug inhibits proteasomes by binding with high affinity via the boron atom to the β-subunit chymotrypsin- and caspase-like proteolytic catalytic sites. It has little effect on the trypsin-like activity. Apoptosis is normally suppressed in mantle cell lines and myeloma cells, but proteasome inhibition may overcome this suppression and activate cell death. Bortezomib suppresses tumor growth and spread and angiogenesis through multiple mechanisms, and, in addition to directly inducing apoptosis of tumor cells, it mediates a myriad of biological effects including reduced adherence of myeloma cells to bone marrow cells, prevention of IL-6 production and signaling in myeloma cells, interference with the production of pro-angiogenic factors, and suppression of nuclear-factor-κ-light chain-enhancer (NF-κB). Bortezomib gained regulatory approval in 2003, and its success has proved...
a stimulant in attempts to understand the molecular mechanisms underlying its clinical effectiveness and identifying new drugs acting on the same pathway.

Gastrointestinal symptoms, thrombocytopenia, neutropenia, peripheral neuropathy, neuropathic pain, and fatigue are the most common side effects of bortezomib, and adverse cutaneous reactions to the drug are numerous (Table 14.1). Rash (often pruritic) is frequently reported in more than 10% of patients (an incidence of 8–18% has been stated), and pruritus, erythema, urticaria, periorbital edema, and eczema are commonly seen. Bortezomib has been associated with cases of drug-induced Sweet’s syndrome-like reactions (Fig. 14.9) or acute febrile neutrophilic dermatosis, a rare variant of this uncommon skin disease characterized by fever, an elevated neutrophil count, and erythematous lesions infiltrated by neutrophils. Besides Sweet’s syndrome, reported cutaneous adverse drug reactions to bortezomib include ulceration, leukocytoclastic vasculitis, morbilliform exanthema, folliculitis-like rash, erythematous nodules and plaques, and perivascular dermatitis. Histological examination of a bortezomib-induced skin eruption showed a clinical picture similar to Sweet’s syndrome but which differed by the presence of a significant number of CD30+ lymphocytes. The presence of these cells, which are seen during some treatments of blood malignancies, is not understood. Ocular symptoms are said to be common but rarely reported with bortezomib therapy. Cases with meibomitis, multiple chalazions, and blepharitis after treatment have been described. A separate 2016 report described 24 cases of bortezomib-related chalazia, usually multiple and involving the upper eyelid. The mean duration of therapy before the onset of chalazia was a little more than 3 months.

Subcutaneous infusion of bortezomib at 1 mg/ml as an alternative to intravenous administration (2.5 mg/ml) was recently approved by the US Food and Drug Administration (FDA). This has proved a more convenient and less toxic route of administration and seems likely to become the standard form of the drug’s delivery.

14.1.2.2 Second-Generation Proteasome Inhibitors

Carfilzomib, a tetrapeptide epoxycetone (Fig. 14.8), is structurally and mechanistically different to bortezomib. It irreversibly binds to and inhibits chymotryptase activity but has less activity toward the other two enzymatic actions. The drug was approved by the FDA in 2012 for patients with relapsed and refractory multiple myeloma. It leads to cell cycle arrest and induces apoptosis in multiple myeloma, other hemato-

![Fig. 14.9](image-url) Bortezomib-induced Sweet’s syndrome. The patient presented with sudden onset of painful round erythematous and edematous plaques on the head, neck, and trunk. Skin biopsies confirmed the clinical diagnosis of Sweet’s syndrome, with neutrophilic infiltration of the dermis. (From Knoops L, Jacquemain A, Tennstedt D, et al. Bortezomib-induced Sweet’s syndrome. Brit J Haematol. 2005;131:142, reproduced with permission from John Wiley and Sons)
logic malignancies, and some solid tumors. A potentially very important property is the drug’s activity against primary multiple myeloma cells and cell lines resistant to bortezomib. Adverse reactions noted so far include pulmonary hypertension, dyspnea, cardiac toxicities, cytopenias, infusion reactions (Sect. 14.2.2.6), venous thrombosis, hemorrhage, tumor lysis syndrome (Sect. 14.2.2.7), hepatotoxicity, posterior reversible encephalopathy syndrome, acute renal failure, rash, and urticaria (Table 14.1). In one study, peripheral neuropathy was observed in 12.4% of patients. Several studies have shown a 5–12% incidence of cardiac events in patients given carfilzomib.

Like bortezomib, ixazomib (MLN9708, Ninlaro®) (used as the citrate) is also a peptide boronate (Fig. 14.8), but it is orally active, shows greater tissue penetration, and has a shorter half-life (18 versus 110 min). The drug is primarily an inhibitor of the chymotrypsin-like activity (β5) of the 20S proteasome core, and, like bortezomib, it inhibits NF-κB activation and has antitumor activity in multiple myeloma and some other hematologic malignancies. Besides common adverse reactions of diarrhea, nausea, and peripheral edema, FDA warnings and precautions for the drug relate to thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy, hepatotoxicity, and cutaneous reactions, the most common of which are macular and maculopapular rash.

Still in clinical development, the orally active proteasome non-peptide inhibitor salinosporamide A, derived from natural sources, is a γ-lactam-β-lactone bicyclic compound (Fig. 14.8). Also known as marizomib, the drug is obtained from Salinispora tropica, a bacterium found in ocean sediments. Marizomib is an irreversible proteasome inhibitor that shows little effect on the caspase-like activity but inhibits chymotrypsin- and trypsin-like protease activities. Preclinical studies have demonstrated antitumor activity in models for multiple myeloma, hematologic malignancies, and solid tumors, and, importantly, marizomib does not show cross-resistance with other proteasome inhibitors. Phase I studies demonstrated relatively low toxic effects and no evidence of neuropathy or thrombocytopenia.

With structural similarities to carfilzomib, and similar to that compound and bortezomib, orally active aprozomib (Fig. 14.8) is highly selective to the β5 subunit of the 20S proteasome. Two early phase studies indicated what was said to be a tolerable safety profile with a low incidence of neuropathy, but diarrhea, nausea, and vomiting were a concern.

Besides peptide boronates like bortezomib, other synthetic compounds tested as proteasome inhibitors include peptide aldehydes, peptide epoxyketones, and peptide vinyl sulfones.

### 14.1.3 Adverse Events Associated with Other Small Targeted Drugs

**Serine/threonine mTOR kinase** belongs to the phosphoinositide 3-kinase (PI3K)-related family. Used in oncology and as an immunosuppressive agent in organ transplants, mTOR inhibitor drugs are associated with a considerable number of adverse events (Table 14.1). Prominent among these effects are interstitial lung disease, more common in oncology than transplantation, with up to 14% of renal cell carcinoma patients given everolimus developing pneumonitis. mTOR-associated stomatitis, thought to be the result of toxic effects on the oral and nasal mucous membranes and manifesting as oral ulceration and distinct from mucositis seen during chemotherapy, is a common dose-limiting effect. Other potentially serious adverse responses to the drugs include hyperglycemia and new-onset diabetes mellitus, hyperlipidemia with increased levels of cholesterol and triglycerides common in up to 75% of patients, and reproduction effects producing decreased fertility, low sperm counts, sex hormone dysfunction, and high rates of ovarian cysts.

**Human histone deacetylases (HDACs)** are grouped into three classes, class I, class II, and class IV, with each class differing in location, enzyme activity, and substrate specificity. HDAC class I includes isoenzymes HDACs 1, 2, 3, and 8; HDAC class II includes HDACs 4, 5, 6, 7, 9, and 10. HDACs 1, 2, 3, and 6 are highly expressed
in different combinations of a number of cancers including breast, prostate, lung, colon, gastric, cervical, and esophageal cancers. Inhibition of classes I and II produces apoptosis of a wide range of tumor cells. HDAC inhibitors (HDACIs) lead to differentiation, cell-cycle arrest, and inhibition of migration, invasion, and angiogenesis in many different cancer cells. Some HDACIs are effective against different tumors either alone or in combination with other drugs or radiotherapy. In addition to romidepsin (approved for the treatment of cutaneous and peripheral T cell lymphomas), and vorinostat (approved for cutaneous T cell lymphoma) (Table 14.1), two other drugs that inhibit the HDAC isoenzyme, belinostat (Beleodaq®) and panobinostat (Farydak®), are approved for cancer therapy by the FDA. Belinostat was approved by the FDA in 2014 for the treatment of peripheral T cell lymphoma, while in 2015 panobinostat was approved for multiple myeloma in combination with bortezomib and dexamethasone.

Myelosuppression involving thrombocytopenia, leukopenia, and anemia induced by all four of the above HDACIs is a frequent and often severe adverse event sometimes leading to serious hemorrhage and infection. Cardiac effects may occur, especially with QTc prolongation induced by vorinostat; hepatic effects may be seen, usually as raised serum transaminases and/or bilirubin; and gastrointestinal effects of nausea, vomiting, and diarrhea may be severe, especially with panobinostat which now has an FDA Boxed Warning for diarrhea. Specific adverse effects listed for the four HDCAIs are romidepsin, infections and tumor lysis syndrome; vorinostat, pulmonary embolism, deep vein thrombosis, and hyperglycemia; belinostat, infections and tumor lysis syndrome; panobinostat, hemorrhage and cardiac ischemia. Post-marketing data from the EMA’s EudraVigilance database of 455 reports of adverse events to panobinostat (the only HDACI approved by the EMA) revealed diarrhea as the most reported event (93 cases), followed by myelosuppression (81 cases, made up of thrombocytopenia 60, anemia 12, and neutropenia 9 cases), and cardiac/ECG effects (30 cases).

Acute promyelocytic leukemia (PML), which accounts for 10–15% of acute myeloid leukemia, is characterized by the translocation t(15;17). Expression of the PML/RARA oncprotein is diagnostic of the disease and downregulated in response to all-trans retinoic acid (tRA; ATRA; tretinoin). Arsenic trioxide induces apoptosis and partial differentiation at high and low concentrations, respectively. Approved for PML cases resistant to tRA, arsenic trioxide targets the PML moiety of PML/RARA protein, inducing a complete remission rate in 85–90% of patients with newly diagnosed or relapsed PML. tRA induces terminal differentiation of acute promyelocytic leukemia cells by binding PML/RARA protein via the ligand-binding domain of RARA, but the majority of patients do not achieve complete remission and relapse within a few months. Clinical trials have shown that most acute PML patients can be cured by combination therapy of tRA and arsenic trioxide. Retinoic acid syndrome is a potentially fatal side effect of acute PML treatment (Table 14.1). The syndrome occurs in about one quarter of acute promyelocytic leukemia patients treated with tRA and/or arsenic trioxide. Symptoms include fever, hypotension, weight gain, dyspnea with pulmonary infiltrates, pleuropericardial effusion, and renal failure. The realization that retinoic acid syndrome occurred in acute PML patients previously treated with arsenic trioxide but not in patients treated with tRA for other disorders led to the syndrome being termed differentiation syndrome. Some investigators have pointed out that the syndrome’s symptom complex most closely resembles capillary leak syndrome (Sect. 14.2.2.8) and systemic inflammatory response syndrome (Sect. 14.2.2.9). The most frequently reported adverse effects elicited by tRA are similar to those seen in patients taking high doses of vitamin A, namely, fever, skin, and mucous membrane dryness, nausea and vomiting, bone pain, ocular disorders, rash, pruritus, and mucositis (Table 14.1). Apart from differentiation syndrome, the most important and potentially serious adverse events following arsenic trioxide dosage are a number of cardiac conduction abnormalities including QTc interval prolongation and atrioventricular block.
Retinoids, structurally related to vitamin A, are a family of signaling molecules that regulate gene expression and influence, among other functions, vision, neural function, immunity, and cell proliferation and differentiation. Retinoic acid has an important role in cell development and differentiation and has found possible applications in cancer treatment suppressing breast, prostate, lung, ovarian, bladder, and skin cancers. Retinoic acid inhibits markers of cell proliferation including growth factors such as vascular endothelial growth factor (VEGF). In inhibiting tumor growth, angiogenesis, and metastasis, retinoic acid activates the retinoic acid receptor (RAR) or retinoic X receptor (RXR). As a result of the known anticancer activities of natural retinoids, synthetic retinoid receptor binders have been produced and investigated. The RXR synthetic agonist bexarotene, an oral retinoid therapy, is approved for the treatment of cutaneous T cell lymphoma (CTCL). Potential serious side effects of the drug (Table 14.1) in the treatment of CTCL include rapid elevation of lipids and hypothyroidism. Hypertriglyceridemia of all grades occurred in 79% of patients who received the drug in early stage CTCL; hypercholesterolemia was reported in 48% of patients and hypothyroidism in 40%. Hyperlipidemia is a concern because of the associated increased risk of cardiovascular events.

Like other systemic targeted therapies, hormone therapy for some cancers such as breast and prostate can be as potent and effective as many other cancer treatments. Blockage, inhibition, or inactivation of hormones gives rise to side effects relevant to the targeted hormone. For women, many of these effects are similar to those experienced during menopause when estrogen levels decline, for example, hot flashes, weight gain, vaginal dryness, night sweats, and headaches. Symptoms induced by the administered hormone or analog may cause nausea, muscle and joint pain, hair loss, blood clots, and an increased risk of some cancers, for example, endometrial cancer and cancer of the uterus. Side effects in males include tiredness, hot flashes, nausea, loss of sex drive, impotence, and breast tenderness. Due to a decrease in the body’s natural hormone levels, an increased risk of osteoporosis is possible for both sexes. A more complete list of hormone-related adverse effects including possible cutaneous reactions, some severe, is set out in Table 14.1.

14.2 Monoclonal Antibodies for Cancer Therapy

From their earliest examples, specifically targeted mAbs directed to selected antigens of many different tumors appeared to offer great promise for both patients and clinicians. Now, with 88 mAbs (April 2020) currently approved by the FDA and/or EMA, 36 or 41% are indicated for the treatment of human cancers covering hematologic, solid tumor, and cutaneous malignancies. The 36 mAbs currently approved by the FDA for cancer therapy are listed in Table 14.2 together with trade names, antibody subclass, extent of species recognition, antibody target, mechanism of action, and approved indications.

In achieving the wide and diverse coverage of a large variety of tumors, a range of different targets and mechanisms of action have been sought. Molecular mechanisms employing mAb-targeted therapies are predominately direct cytotoxic action against cancer cells, an effect on signaling pathways, or immune modulatory effects leading to the indirect destruction of cancer cells. For a still small but increasing number of approved mAbs, a direct cytotoxic action is achieved by using an antibody-drug conjugate (ADC) (Chap. 13, Sect. 13.1.5), whereby cell killing is effected by an attached bioactive payload of a potentially lethal toxin, drug, cytokine, or radionuclide. Figure 14.10 shows three examples of ADCs, gemtuzumab ozogamicin, ado-trastuzumab emtansine, and brentuximab vedotin, each summarized in Sect. 14.2.1. Examples of cell-destructive immune modulatory effects include antibody-dependent cell cytotoxicity (ADCC) and modulation of immune checkpoints by the targeting of inhibitory pathways regulating signaling between T cells and antigen-presenting cells. Specifically, 23 different targets have been utilized so far (including, at April 2020, Trop-2, targeted by sacituzumab govitecan-hziy [Table 14.2]) in obtaining the present battery of
| INN and trade name                  | Type of mAb                        | Cell line | Target | Mechanism of action                                                                 | Approved indications                                                                 |
|------------------------------------|------------------------------------|-----------|-------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| **Rat-mouse chimera (-axomab)**    |                                    |           |       |                                                                                  |                                                                                      |
| Catumaxomab (Removab®)             | Rat IgG2b/Mouse IgG2a bispecific   | Hybrid    | EpCAM/CD3 | Binds EpCAM, CD3 and FcγRs (via Fc) activating T and accessory cells at tumor site and leading to cell killing | Malignant ascites                                                                  |
| **Mouse (-omab)**                  |                                    |           |       |                                                                                  |                                                                                      |
| Blinatumomab (Blincyto®)           | Mouse scFvκ–H4V bispecific         | CHO       | CD19/CD3ε | Links CD19 on malignant B cells with CD3 in T cell receptor destroying tumor cell via perforin and granzymes | Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia |
| Ibritumomab tiuxetan (Zevalin®)    | Mouse IgG1κ                         | CHO       | CD20β   | Binds malignant B cells, β emissions induce cell damage                           | Non-HL                                                                              |
| Moxetumomab pasudotox-tdfk (Lumoxit®) | ADC immunotoxin. Mouse single chain variable domain (scFv) | E. coli  | CD22 | Binds CD22 on B cells, internalized, toxin inhibits protein synthesis leading to apoptotic cell death | HCL                                                                                 |
| **Human-mouse chimeric (-ximab)**  |                                    |           |       |                                                                                  |                                                                                      |
| Brentuximab vedotin (Adcetris®)     | Chimeric IgG1κ                      | CHO       | CD30β  | Binds to CD30 cells, released MMAE binds to and disrupts microtubules causing cell cycle arrest and apoptotic cell death | HL after failure of stem cell transplant or chemotherapy, sALCL after failure of chemotherapy, post auto-HSCT consolidation treatment for HL |
| Cetuximab (Erbitux®)               | Chimeric IgG1κ                      | Sp2/0 EGFR |        | Binds to EGFR blocking phosphorylation and activation of kinases inhibiting growth and survival of tumor cells | Colorectal and head and neck cancers                                                |
| Dinutuximab (Unituxin®)            | Chimeric IgG1κ                      | Sp2/0 GD2 |        | Binds cell surface GD2 on neuroblastoma cells and induces cell lysis by ADCC and CDC | Pediatric patients with high risk neuroblastomaa                                      |
| Rituximab (Rituxan®; MabThera®)    | Chimeric IgG1κ                      | CHO       | CD20   | Binds CD20 on B cells, Fc recruits effector functions CDC and ADCC                | Non-HL, CLL, rheumatoid arthritis, Wegener’s granulomatosis, microscopic polyangiitisa |
| Siltuximab (Sylvant®)              | Chimeric IgG1κ                      | CHO       | IL-6   | Binds to IL-6 preventing its overproduction and lessening symptoms of disease    | Multicentric Castleman’s disease in patients negative for HIV and HHV-8               |
| **Humanized (-zumab)**             |                                    |           |       |                                                                                  |                                                                                      |
| Alemtuzumab (Campath®; MabCampath®; Lemtrada®) | Humanized IgG1κ                 | CHO       | CD52α  | Binds CD52 on leukemic cells and induces antibody-dependent cell-mediated lysis | Campath, MabCampath: B cell CLL. Lemtrada: Multiple sclerosis                          |
| Drug Name               | Type                  | Target | Effect                                                                 | Indication                                                                                   |
|------------------------|-----------------------|--------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Atezolizumab           | Humanized IgG1κ       | CHO    | PD-L1 Binds PD-L1 blocking PD-1 and B7.1 releasing inhibition of immune response | MUC, NSCLC                                                                                  |
| Bevacizumab (Avastin®) | Humanized IgG1κ       | CHO    | VEGF-A Inhibits angiogenesis and metastatic disease progression by binding VEGF preventing interaction with its receptors | Metastatic colorectal cancer, non-squamous NSCLC, metastatic breast cancer, glioblastoma     |
| Elotuzumab (Empliciti®)| Humanized IgG1κ       | NSO    | SLAMF7+ Activates NK cells and targets SLAMF7 on myeloma cells mediating killing via NK cells and ADCC | MM                                                                                          |
| Gentuzumab ozogamicin (Mylotarg®) | ADC Humanized IgG4κ | NSO    | CD33 ADC Binds CD33 on tumor cells, internalized, released toxin induces DNA breaks, cell cycle arrest and apoptosis | AML                                                                                          |
| Inotuzumab ozogamicin (Besponsa®) | ADC Humanized IgG4κ | CHO    | CD22 ADC Binds CD22 on tumor cells, internalized, released toxin induces DNA breaks, cell cycle arrest and apoptosis | ALL                                                                                          |
| Mogamulizumab-kpke (Poteligeo®) | Humanized IgG1κ | CHO    | CCR4 Binding of defucosylated mAb to CCR4 on some T cells leads to ADCC-mediated depletion of targeted cells | Mycosis fungoides, Sézary syndrome                                                              |
| Obinutuzumab (Gazyva®; Gazyvaro®) | Humanized IgG1κ | CHO    | CD20 Mediates B cell lysis by CDC, ADCC, ADCP and by activating death signaling | In combination with chlorambucil for previously untreated CLL                                |
| Pembrolizumab (Keytruda®) | Humanized IgG4κ | CHO    | PD-1 Blocks receptor interaction of PD-L1 and PD-L2 preventing PD-1-mediated inhibition of antitumor immune response | Unresectable or metastatic melanoma, refractory metastatic NSCLC tumors that express PD-L1 |
| Pertuzumab (Perjeta®)  | Humanized IgG1κ       | CHO    | HER2 Prevents heterodimer formation and subsequent MAPK and PI3K signaling resulting in cell growth arrest and apoptosis | Combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer         |
| Polatuzumab vedotin-piiqi (Polivy®) | ADC Humanized IgG1 | CHO    | CD79b+ Binds CD79b on B cells, internalized, released toxin binds microtubules inhibiting cell division and inducing apoptosis | Diffuse large B cell lymphoma                                                               |
| Trastuzumab (Herceptin®) | Humanized IgG1κ       | CHO    | HER2 Blocks homodimerization of HER2 thus inhibiting HER2 receptor signaling. Mediates ADCC | Breast cancer overexpressing HER2, metastatic gastric or GE junction adenocarcinoma overexpressing HER2 |
| Ado-trastuzumab emtansine (Kadcyla®) | ADC Humanized IgG1κ | CHO    | HER2 See trastuzumab Also: Binds to tubulin after internalization disrupting microtubules and causing apoptotic cell death | HER2-positive breast cancer in patients who previously received trastuzumab or a taxane |

(continued)
| INN and trade name | Type of mAb | Cell line | Target | Mechanism of action | Approved indications |
|-------------------|-------------|-----------|--------|---------------------|---------------------|
| **Fully human (-umab)** | | | | | |
| Avelumab (Bavencio®) | Human IgG1\(\lambda\) | CHO | PD-L1 | Binds PD-L1 blocking PD-1 and B7.1 releasing inhibition of immune response and activating antitumor response | MCC; UC; RCC |
| Cemiplimab-rwlc (Libtayo®) | Human IgG4 | CHO | PD-1 | Binds PD-1 blocking interaction with PD-L1 and PD-L2 releasing inhibition of the immune and antitumor responses | CSCC |
| Daratumumab (Darzalex®) | Human IgG1\(\kappa\) | CHO | CD38\(\alpha\) | Binds CD38 on tumor cells and induces apoptosis by Fc-mediated cross-linking, ADCC, CDC, and ADCP \(\alpha\) | MM |
| Denosumab (Prolia®; Xgeva®) | Human IgG2\(\kappa\) | CHO | RANKL | Binds RANKL preventing receptor activation, osteoclast formation, bone resorption, osteolysis, and tumor growth | Bone loss. Prolia: For osteoporosis and to increase bone mass \(\beta\). Xgeva: For bone metastases from solid tumors and giant cell tumor of bone \(\alpha\) |
| Durvalumab (Imfinzi®) | Human IgG1\(\kappa\) | CHO | PD-L1 | Binds PD-L1 blocking PD-L1/PD-1 and PD-L1/CD80 interactions releasing inhibition of immune response and activating antitumor response without ADCC | UC |
| Ipilimumab (Yervoy®) | Human IgG1\(\kappa\) | CHO | CTLA-4 | Blocks interaction of CTLA-4 with its ligands \(\alpha\) augmenting T cell activation and antitumor response | Metastatic melanoma |
| Necitumumab (Portrazza®) | Human IgG1\(\kappa\) | NSO | EGFR | Blocks binding to EGFR ligands, internalized and induces ADCC in EGFR-expressing cells \(\alpha\) | Squamous NSCLC |
| Nivolumab (OPDIVO®) | Human IgG4\(\kappa\) | CHO | PD-1 | Blocks receptor interaction of PD-L1 and PD-L2 preventing PD-1-mediated inhibition of antitumor immune response | Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 positive, a BRAF inhibitor; NSCLC \(\alpha\) |
| Ofatumumab (Arzerra®) | Human IgG1\(\kappa\) | NSO | CD20 | Binds CD20 on B cells; Fc recruits effector functions CDC and ADCC | Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab |
| Olaratumab (Lartruvo®) | Human IgG1 | NSO | PDGFR-\(\alpha\) | Binds PDGFR-\(\alpha\) preventing binding to its ligands, receptor activation and signaling \(\alpha\) | Soft tissue sarcoma |
| Panitumumab (Vectibix®) | Human IgG2\(\kappa\) | CHO | EGFR | Binds to EGFR blocking phosphorylation and activation of kinases inhibiting growth and survival of tumor cells | Metastatic colorectal cancer \(\alpha\) |
Ramucirumab (Cyramza®)  Human IgG1κ  NSO  VEGFR2  Inhibits activation of VEGFR2 and hence ligand-induced proliferation and migration of endothelial cells  Gastric or GE junction adenocarcinoma, metastatic NSCLC with docetaxel after platinum therapy, HCC, with FOLFIRI for metastatic colorectal cancer

Note: In April 2020, sacituzumab govitecan-hziy (Trodelvy™), an ADC prepared by conjugating the toxic topoisomerase I inhibitor, govitecan (SN-38) to a humanized IgG1κ mAb against trophoblastic cell surface antigen-2 (Trop-2), was approved in the USA for the treatment of metastatic triple negative breast cancer. The CD38-targeted chimeric IgG1κ cytolytic mAb, isatuximab-irfc (Sarclisa®), was recently approved by the FDA for the treatment of multiple myeloma (See also Table 14.4).

ADC antibody-drug conjugate, ADCC antibody-dependent cell-mediated cytotoxicity, ADCP antibody-dependent cellular phagocytosis, ALL acute lymphoblastic leukemia, auto-HSCT autologous hematopoietic stem cell transplantation; BRAF proto-oncogene B-Raf, C5 complement component 5, CDC complement-dependent cytotoxicity, CHO Chinese hamster ovary cells, CLL chronic lymphocytic leukemia, CTLA-4 cytotoxic T lymphocyte-associated antigen 4 or CD152, CSCC cutaneous squamous cell carcinoma, EGF epidermal growth factor receptor, EMA European Medicines Agency, EpCAM epithelial cell adhesion molecule, FDA US Food and Drug Administration, FOLFIRI folinic acid (leucovorin), fluoropyrimidine, and irinotecan, GD2 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; HIV human immunodeficiency virus, HHV-8 human herpesvirus-8, HL Hodgkin lymphoma, IPP International Nonproprietary Name, MAPK mitogen-activated protein kinase, MCC Merkel cell carcinoma, MM multiple myeloma, MMAE cytotoxic agent monomethyl auristatin E, NK natural killer, NSCLC nonsmall cell lung cancer, NSO non-Ig-secreting, non-L chain-synthesizing, 8-azaguanine-resistant and HAT-sensitive mouse myeloma cell line; PD-1 programmed cell death protein 1 or CD279; PD-L1 programmed cell death protein ligand 1, PI3K phosphoinositide 3-kinase, 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, Sp2/0 BALB/c mouse spleen cells fused with P3 myeloma. Cells do not secrete Ig, are resistant to 8-aza-guanine and HAT-sensitive, 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.

Target specificity of mAb

*Registered by the EMA, Health Canada, and Ministry of Health, Israel but not the FDA

*A BITE (bispecific T cell-engaging) fusion protein

Two single chain variable fragments (scFv) each from an H and L chain to give four peptide chains linked to a single protein, MW ~54 kDa

CD19, a B cell antigen; CD3, part of the T cell receptor

Conjugated to the chelator triuexatan which links the radiosotope Yttrium-90 or Indium-111 Yttrium-90 or Indium-111

Expressed on B lymphocytes where it aids optimal B cell response to T-independent antigens. Encoded by the membrane-spanning MS4A1 gene

Attached truncated Pseudomonas exotoxin PE38 promotes ADP-ribosylation of elongation factor 2, inhibition of protein synthesis and apoptotic cell death

Conjugated to the cytotoxic agent monomethyl auristatin E (MMAE) via a protease-cleavable linker

CD30 is a cell membrane protein of the tumor necrosis receptor family expressed on activated T and B lymphocytes

In combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2 and 13-cis-retinoic acid

CD20 is expressed on >90% of non-Hodgkin lymphoma cells

In adults in combination with glucocorticoids

Also called giant lymph node hyperplasia and angiofollicular lymph node hyperplasia

CAMPATH-1 antigen. Present on mature lymphocytes, monocytes, and dendritic cells and is associated with some lymphomas

Withdrawn from the United States and Europe in 2012 and relaunched for multiple sclerosis (as Lemtrada®)

Without inducing ADCC

Signaling lymphocyte activation molecule family member 7

(continued)
Table 14.2 (continued)

| Drug Name | Description |
|-----------|-------------|
| Toxin N-acetyl-γ-calicheamicin linked to mAb by an acid-cleavable linker | Also in disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor. Note: The FDA states: “An improvement in survival or disease-related symptoms has not yet been established.” In June 2015, the FDA accepted for review the supplemental Biologics License Application for pembrolizumab for the treatment of advanced nonsmall cell lung cancer whose disease has progressed on or after platinum and EGFR therapy. |
| Also mediates ADCC | |
| Also in patients who have not yet received prior anti-HER2 therapy or chemotherapy for metastatic disease | |
| CD79b is a component of the B cell receptor | |
| An antibody-drug conjugate of trastuzumab linked to the maytansinoid cytotoxin DM1 or mertansine (N2′-diacetyl-N2′-(3-mercaptop-1-oxopropyl) maytansine. Also known as trastuzumab emtansine and T-DM1 | |
| Also induces ADCC | |
| CD38, cyclic ADP ribose hydrolase. Found on surface of CD4+, CD8+, B lymphocytes and NK cells. Functions in cell adhesion, signal transduction, and calcium signaling | |
| A subset of suppressor cells (CD38 + MDSCs), regulatory T cells (CD38 + Treg) and B cells (CD38 + Breg) are decreased by daratumumab | |
| Treatment of menopausal women at high risk of fracture, men receiving androgen deprivation for prostate cancer, and women at high risk of fracture receiving aromatase inhibitor therapy for breast cancer | |
| Not indicated for skeletal-related events in multiple myeloma | |
| Ligands for CTLA-4: B7-1/B7-2 (CD80/CD86) | |
| Expression and activation of EGFR has been correlated with malignant progression, induction of angiogenesis, and inhibition of apoptosis | |
| In March 2015, nivolumab was approved by the FDA for the treatment of patients with metastatic squamous nonsmall cell lung cancer with progression on or after platinum-based chemotherapy; approval was extended to non-squamous nonsmall cell lung cancer in October 2015 | |
| Olaratumab prevents binding of PDGFR-α to its ligands PDGF-AA and PDGF-BB and also prevents PDGF-AA, -BB, and -CC-induced reactivation and downstream PDGFR-α-signaling | |
| Panitumumab is not recommended for treatment of tumors with KRAS mutations in codon 12 or 13 | |
| Gastric or GE junction adenocarcinoma: As single agent or in combination with paclitaxel after prior fluoropyrimidine or platinum chemotherapy. Colorectal cancer: For patients with disease progression on or after bevacizumab, oxaliplatin, and fluoropyrimidine therapy. Also approved by the EMA as monotherapy and for use with paclitaxel for advanced gastric cancer or GE junction cancer | |
approved antibody preparations as efforts continue to further understand mechanisms underlying tumor growth, avoidance of immune recognition, and metastasis while extending the coverage of different neoplasms with new mAbs and improving on the effectiveness of existing agents.

### 14.2.1 Targets for Anticancer Monoclonal Antibodies

Following are summaries of individual targets of the 36 approved anticancer mAbs together with the rationale for their use (Table 14.2).

The trifunctional hybrid mAb *catumaxomab* is a dual specificity mouse-rat hybrid mAb (Removab®) composed of a mouse kappa light chain and IgG2a heavy chain and a rat lambda light chain and IgG2b heavy chain. Binding of the Fc region with Fcγ receptors provides a third functional binding site. The mouse Fab binds to EpCAM, the rat Fab binds to CD3, and the hybrid Fc fragment binds to FcγRI (CD64), FcγRIIa (CD32), and FcγRIIIa (CD16a) on macrophages, NK cells, dendritic cells and mononuclear cells. EpCAM (CD326) is a transmembrane glycoprotein, expressed on the surface of tumor cells. It promotes tumor growth and metastasis and is overexpressed on epithelial tumors of the gastrointestinal tract, esophagus, head, neck, lung, liver, kidney, ovary, pancreas, prostate, and a number of other organs and tissues. Overexpressed in advanced cases of cancer, EpCAM is also expressed on tumor cells in malignant effusions, hence its indication for malignant ascites. T cell-mediated killing, ADCC, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP) results from the trifunctional action of catumaxomab.

*Blinatumomab* (Blincyto®) (Table 14.2), used to treat acute lymphoblastic leukemia, is not a standard 2H and 2 L chain mAb but a so-called bispecific T-cell-engaging (BiTE) fusion protein. This antibody construct, a ~55 kDa protein derived from the linkage of four peptide chains from four different genes, is composed of two...
antibody single chain variable fragments each from an H and L chain. There are two binding specificities, one directed to the B cell antigen CD19 and the other to CD3, part of the T cell receptor. By linking malignant B cells to, and thus activating cytotoxic T cells, tumor cells are destroyed by apoptosis induced by released perforin and granzymes.

Monoclonal antibodies ibritumomab (Zevalin®), obinutuzumab (Gazyva®; Gazyvaro®), ofatumumab (Arzerra®), and rituximab (MabThera®; Rituxan®) (Table 14.2) target the human B lymphocyte-restricted differentiation antigen Bp35, or CD20, a 33–35 kDa transmembrane glycosylated phosphoprotein expressed on the surface of B cells (but not plasmablasts and mature plasma cells) at all stages of their development and also on B cell lymphomas, B cell chronic lymphocytic leukemia, hairy cell leukemia, and melanoma cancer stem cells. CD20 may be involved in transmembrane signaling controlling growth and cell death in some tumors, it is not normally shed from cells, it is internalized after binding to antibody, and due to its B cell expression in non-Hodgkin lymphoma and chronic lymphocytic leukemia, it has been exploited as a target for mAbs for the treatment of lymphomas.

Brentuximab vedotin (Adcetris®) (Table 14.2) is a chimeric mAb conjugated to the cytotoxic agent monomethyl auristatin E to form an ADC targeted to CD30 (TNFRSF8) (Fig. 14.10), a 120 kDa cell membrane glycoprotein of the tumor necrosis factor receptor family expressed on activated T and B lymphocytes. CD30, overexpressed in Hodgkin lymphoma, anaplastic large-cell lymphoma, cutaneous T cell lymphoma, and mediastinal B cell lymphoma, protects against autoimmunity by limiting CD8 T cells and by interaction with TRAF2 and TRAF5 (TNF receptor-associated factors 2 and 5), regulating apoptosis via (NF-κB) activation. Once linked to its target, the mAb’s attached toxin is internalized, disrupting microtubules in the lysosomes and inducing apoptosis.

Alemtuzumab (Campath®; MabCampath®), a humanized mAb with complementarity-determining regions from a rat mAb, is targeted to CD52 (Campath-1 antigen) (Table 14.2), a 21–28 kDa 12 amino acid glycoprotein of unknown function with a single N-linked oligosaccharide. CD52 is expressed on mature normal and malignant B and T lymphocytes, monocytes, macrophages, NK cells, a subpopulation of granulocytes, and dendritic cells as well as lymphoid and male sexual organs. Widely used for the treatment of B cell chronic lymphocytic leukemia resistant to alkylating agents until 2012, alemtuzumab exerts its anti-tumor action primarily by ADCC and with a contribution from CDC and induction of apoptosis. After being withdrawn and relaunched as Lemtrada® for multiple sclerosis, a small number of patients receive it through a specific access program, and some off-label cancer therapy usage remains.

Cetuximab (Erbitux®), panitumumab (Vectibix®), and necitumumab (Portrazza®) target epidermal growth factor receptor (EGFR, HER1, ErbB1), a transmembrane glycoprotein cell surface receptor and member of the ErbB family of receptors (Table 14.2). The ErbB family is a subfamily of closely related receptor tyrosine kinases, themselves important targets for cancer therapy because of their central role in growth factor signaling leading to cell proliferation, differentiation, and survival. In addition to the importance of EGFR in normal cellular functions and survival, EGFR may contribute to the development of cancerous cells through effects on angiogenesis, cell cycle progression, inhibition of apoptosis, and metastasis. EGFR and its ligands are associated with growth of cancer cells, and elevated EGFR tyrosine kinase activity is found in many solid tumors. Table 14.3 shows the percentages of overexpression of EGFR in some common human solid tumors. After receptor activation by binding its specific ligands and dimerization, the receptor-ligand complex is internalized, autophosphorylation occurs, and the tyrosine kinase signal transduction pathways lead to regulation of gene transcription involved with cell growth and survival, motility, and proliferation. The EGFR-binding mAbs bind the receptor on both normal and tumor cells, competitively inhibiting binding of the normal ligands. Ligand-induced autophosphorylation of
Bevacizumab (Avastin®) (Table 14.2) binds to, and inhibits, human vascular endothelial growth factor-A (VEGF-A), an important regulator of blood vessel formation in health and disease. Acting in endothelial cells through a family of related receptor tyrosine kinases, VEGF-A also has a major role in inducing angiogenesis and the pathogenesis of a wide range of human diseases including cancers. VEGF-A binds to receptors VEGFR-1 (also called Flt-1) and VEGFR-2 (KDR/Flk-1); VEGFR-1 recruits hematopoietic stem cells, while VEGFR-2 regulates vascular endothelial function. Increased expression of VEGF-A occurs in many human solid tumors, promoting angiogenesis and assisting aggressive tumor growth. By binding to VEGF-A, bevacizumab prevents both activation of VEGF-R2 and the generation of new tumor vasculature, depleting the blood supply necessary for tumors to grow and proliferate.

Ramucirumab (Cyramza®) (Table 14.2) has binding specificity for VEGFR-2 (CD309; also known as kinase insert domain-containing receptor KDR), the receptor mediating angiogenesis. VEGF-A and VEGFR-2 are often upregulated in cancers, and since uncontrolled angiogenesis is a major contributor to tumor growth, targeted inhibition of the development of blood vessels is a logical antitumor strategy. Ramucirumab targets VEGF-R2 with high affinity and thereby inhibits receptor activation and signaling, intracellular Ca²⁺ mobilization, proliferation and migration of endothelial cells, and tumor angiogenesis.

Pertuzumab (Perjeta®), trastuzumab (Herceptin®), and ado-trastuzumab emtansine (Kadcyla®) target Human epidermal growth factor receptor 2 or HER2 (also known as HER2/neu, ErbB2, CD340 and p185), a member of the erythroblastic leukemia viral oncogene (gene ErbB) family (Table 14.2). The structure of the HER2 receptor consists of an extracellular ligand-binding domain, a transmembrane spanning section, and an intracellular protein tyrosine kinase domain. An intracellular tyrosine kinase domain also exists for HER1 and HER4 but not HER3. HER2 is inactive in the monomeric state and needs to be in the dimeric or oligomeric state for activation. There is no known natural ligand for HER2. Activation of receptor kinase function proceeds mainly via ligand-mediated hetero- or homodimerization, but ligand-independent receptor activation can occur with activation being triggered by overexpression of HER2 and a high concentration of cell surface receptors that results in the formation of HER2/HER2 homodimers. Overexpression of HER2 leads to constitutive activation of the growth factor signaling pathways with a consequent favorable environment for breast cancer cell growth. For receptor dimerization, HER2 is the preferred and most important partner. HER3 has a high affinity for HER2, and the HER2/HER3 heterodimer appears to be the most potent in promoting the signal transduction process and tumor promotion. By blocking dimerization, pertuzumab and trastuzumab inhibit HER2 signaling, mediating ADCC. Like trastuzumab, the ADC ado trastuzumab emtansine inhibits HER2 signaling, mediating ADCC.

| Tumor                          | Percentage of tumors overexpressing EGFR |
|--------------------------------|-----------------------------------------|
| Breast                         | 15–37%                                  |
| Renal carcinoma                | 50–90                                   |
| Head and neck                  | 80–100                                  |
| Colorectal                     | 25–100                                  |
| Nonsmall cell lung carcinoma   | 40–80                                   |
| Pancreatic                     | 30–50                                   |
| Ovarian                        | 35–70                                   |
| Glioma                         | 40–92%                                  |
| Bladder                        | 31–48                                   |
| Gastric                        | 33–81                                   |
| Prostate                       | 40–90                                   |

From Baldo BA. Safety of biologics therapy. Monoclonal antibodies, cytokines, fusion proteins, hormones, enzymes, coagulation proteins, vaccines, botulinum toxins. Cham, Switzerland: Springer Nature; 2016. Reproduced with permission from Springer Nature

EGFR epidermal growth factor receptor

a Other percentages quoted, 14–91%

b 25–77% also quoted for colon cancer
c Other percentages quoted, 40–63%
ates ADCC, and inhibits overexpression of HER2. In addition, the ADC undergoes receptor-mediated internalization, lysosomal degradation, binding of the released thiol-containing maytansinoid toxin (Fig. 14.10) to microtubules, cell cycle arrest, and apoptotic death of the cell.

**Denosumab (Xgeva®; Prolia®)** (Table 14.2) is specific for receptor activator of nuclear factor kappa B ligand, otherwise known as RANKL, a cytokine and member of the tumor necrosis factor (TNF) family (also called TNFSF11) responsible for bone resorption. RANKL stimulates osteoclast formation, activation, adherence, survival, and ultimately resorption of bone, and its inhibition results in an increase in bone density, volume, and strength. Marketed under two trade names, denosumab as Prolia® has approved cancer use indications for the treatment of men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer and for the treatment of women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. As Xgeva®, denosumab is approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors and the treatment of giant cell tumor of the bone.

**Ipilimumab (Yervoy®)** (Table 14.2) binds the extracellular domain of the protein receptor, human cytotoxic T lymphocyte antigen 4 or CTLA-4 (also known as CD152), a member of the immunoglobulin superfamily. CTLA-4, expressed on the lymphocyte surface, has a critical role as an inhibitory regulator during the early stages of T cell expansion. When it competitively interacts with the B7 ligands on antigen presenting cells (see Chap 3, Sect. 3.2.1), interference with IL-2 secretion and receptor expression and downregulation of the T cell response results. When bound to the B7 complex (where it binds with greater affinity than CD28), CTLA-4 can be viewed as an immune “off” switch modulating over-activity of T cells and maintaining tolerance to self-antigens (Fig. 14.11). However, suppressing the immune response can allow cancer cells to be recognized as self and thus multiplying in the absence of antitumor immune challenge led to the strategy of blockade of the receptor by the anti-CTLA-4 immunostimulatory monoclonal antibody ipilimumab. The programmed death-1 receptor PD-1 acts as another important immune checkpoint. Binding of PD-1 to its ligands PD-L1 and PD-L2 suppresses T cell proliferation and activity allowing the tumor cells to avoid immune recognition and attack. Blocking at this second checkpoint by anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab results in the reactivation of T cells including those with specificity for the tumor cells. (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)

**Siltuximab (Sylvan®)** (Table 14.2) is a chimeric human-mouse mAb targeted to the soluble bioactive forms of interleukin-6 (IL-6). IL-6, produced...
by many different cells including lymphocytes, monocytes, fibroblasts, and endothelial and cancer cells, is a pleiotropic cytokine with a complex action producing both proinflammatory and anti-inflammatory effects. The balance between pro- and anti-inflammatory effects of IL-6 appears to be crucial in the pathogenesis and/or response to some diseases. In fact, increased levels of IL-6 are known to be associated with a variety of diseases including neoplasias. Cancers associated with increased production of IL-6 include renal cell carcinoma, prostate and bladder cancers, some neurologic cancers, and particularly multiple myeloma and the B cell lymphoproliferative disorder, Castleman’s disease. Castleman’s disease may be unicentric (localized) or multicentric. IL-6, produced in excess, has a central role in the latter form which is characterized by generalized lymphadenopathy with systemic symptoms and with its production of B lymphocytes, plasma cells, secretion of VEGF, and autoimmune reactions. IL-6 binds to its receptor IL-6R, but the resultant complex needs to associate with the protein gp130 (CD130), expressed on almost all cells, to initiate intracellular signaling. IL-6R is also found in soluble form (sIL-6R). The soluble receptor can bind IL-6, and, in a process called trans-signaling, cells expressing gp130, even in the absence of IL-6R, can respond to the complex of IL-6 – sIL-6R. Siltuximab blocks the binding of IL-6 to both the membrane-bound and soluble IL-6 receptors, thereby preventing the formation of the signaling complex with gp130 on the cell surface.

Monoclonal antibodies targeting programmed cell death protein 1 (PD-1): pembrolizumab (Keytruda®), nivolumab (Opdivo®), and cemiplimab-rwlc (Libtayo®) (Table 14.2). The programmed death-1 receptor PD-1 (CD279), a transmembrane protein receptor expressed on T cells during thymic development and on CD4+ and CD8+ T cells, B lymphocytes, NK cells, B cells, monocytes, and some dendritic cells, acts as an important immune checkpoint, playing a critical role in cancer immunology. Although PD-1 has two ligands, PD-L1 (CD130; B7-H1) and PD-L2 (CD273; B7-DC), the affinity of PD-L2 for PD-1 is three times higher than the affinity of PD-L1. PD-L1 is expressed on fewer cells, and cell types than PD-L2 and PD-L1 appears to be associated with increased aggressiveness of cancers and death. Like CTLA-4, PD-1 negatively regulates T cell activation. Signaling induced by the binding of PD-1 with its ligands suppresses T cell proliferation and activity. Upregulation of PD-L1 ligands occurs in some tumors. The binding of cancer cells, which often express PD-L1, induces receptor inhibitory signaling preventing expansion of activated T cells and allowing the tumor cells to avoid immune recognition and attack. Reversing such checkpoint inhibition can be achieved by selectively blocking the signaling pathway, reversing the checkpoint inhibition, and restoring the T cell-mediated response to the tumor. The mAbs pembrolizumab, nivolumab, and cemiplimab-rwlc bind to PD-1 and prevent interaction of the receptor with its ligands (Fig. 14.11).

PD-L1 may be expressed on tumor cells and can contribute to inhibition of the antitumor response. PD-L1 appears to be associated with increased aggressiveness of cancers and death. Monoclonal antibodies targeting programmed cell death-ligand 1 (PD-L1), avelumab (Tecentriq®), durvalumab (Imfinzi®), and atezolizumab (Tecentriq®), avelumab (Bavencio®), and durvalumab (Imfinzi®) bind to PD-L1 (Table 14.2), blocking interaction with PD-1 and B7.1 and thus removing the PD-L1 – PD-1-mediated inhibition of the activated antitumor response.

Dinutuximab (Unituxin®) (Table 14.2) binds the tumor-associated carbohydrate antigen, sialic glycosphingolipid (ganglioside), disialoganglioside GD2, a short sialated polysaccharide linked to ceramide through a β-glycosidic linkage and found highly expressed on neuroectoderm-derived cancers such as neuroblastoma, melanoma, brain tumors, osteosarcoma, and Ewing’s sarcoma in children. Administered as passive antibody therapy, dinutuximab should be used in combination with GM-CSF, IL-2, and 13-cis-retinoic acid.

Daratumumab (Darzalex®) (Table 14.2) is targeted to the 48 kDa glycoprotein CD38 (cyclic ADP ribose hydrolase), a surface antigen expressed by multiple myeloma cells and found on many immune cells including CD4+, CD8+, B lymphocytes, and natural killer (NK) cells. The mAb acts by inhibiting the growth of tumor cells expressing CD38, leading to apoptosis by Fc-mediated cross-linking and cell lysis induced
via CDC, ADCC, and ADCP. In April 2020, the CD38-targeted chimeric IgG1κ cytolytic mAb, isatuximab-irfc (Sarcilis®), was approved by the FDA for the treatment of multiple myeloma (Tables 14.2 and 14.4).

Elotuzumab (Empliciti®) (Table 14.2) targets the cell surface glycoprotein receptor CS1 (also known as CD2 subunit 1, SLAMF7, and CD319), a member of the signaling lymphocytic activation molecule (SLAM) receptor family. SLAMF7 is highly expressed on myeloma cells but not on other tissues, including hematopoietic stem cells. Elotuzumab should be given in combination with lenalidomide and dexamethasone. Elotuzumab targets SLAMF7 on myeloma cells and natural killer (NK) cells, facilitating the latter to kill myeloma cells through ADCC. The addition of lenalidomide to the mAb therapy results in enhanced NK cell-mediated killing.

The ADCs, inotuzumab ozogamicin (Besponsa®) and moxetumomab pasudotox-tdfk (Lumoxiti®) (Table 14.2), inhibit B-cell receptor calcium signaling by targeting CD22, a sialic acid binding immunoglobulin-like lectin expressed on many B-cell malignancies. Inotuzumab ozogamicin is a conjugate of the mAb inotuzumab and a cytotoxic calicheamicin derivative. Following internalization and intracellular hydrolytic cleavage of the cytotoxic complex, the released toxin induces double-strand DNA breaks, cell cycle arrest, and apoptotic death. Moxetumomab pasudotox-tdfk is a recombinant immunotoxin fusion protein composed of the Fv fragment of an anti-CD22 monoclonal antibody fused to a 38 kDa fragment of Pseudomonas exotoxin A, PE38. Following binding to CD22 on the cell surface of B cells, internalization of the toxin complex results in ADP-ribosylation of elongation factor 2, inhibition of protein synthesis, and apoptotic cell death.

Gemtuzumab ozogamicin (Mylotarg™) (Table 14.2) is a CD33-directed ADC made up of the mAb gemtuzumab linked to a cytotoxic calicheamicin derivative (Fig. 14.10). Following binding to CD33 on tumor cells, internalization of the cytotoxic complex, and intracellular hydrolytic cleavage, toxin-induced double-strand breaks of DNA leads to cell cycle arrest and apoptotic cell death.

Polatuzumab vedotin-piiq (Polivy®) (Table 14.2) is an ADC targeted to the B cell surface protein CD79b with cytotoxic activity against dividing B cells. After binding to CD79b, the ADC is internalized, and the linked cytotoxic agent monomethyl auristatin E is cleaved by lysosomal proteases, freeing the toxin to bind to microtubules and kill dividing cells by inhibiting cell division and inducing apoptosis.

Olaratumab (Lartruvo®) (Table 14.2) binds platelet-derived growth factor alpha receptor (PDGFR-α), a receptor tyrosine kinase expressed on cells of mesenchymal origin and some tumor and stromal cells, including sarcomas. Signaling through this receptor has a role in cell growth, chemotaxis, and differentiation and can influence cancer cell proliferation, metastasis, and the tumor microenvironment. Olaratumab interacts with PDGFR-α preventing binding to its ligands, ligand-induced receptor activation, and downstream signaling. By disrupting the PDGFR-α signaling pathway, olaratumab exerts antitumor activity against selected sarcoma cell lines.

In April 2020, sacituzumab govitecan-hziy (Trodelvy™), an ADC prepared by conjugating the toxic topoisomerase I inhibitor govitecan (SN-38) to a humanized IgG1κ mAb against trophoblastic cell surface antigen-2 (Trop-2), was approved in the USA for the treatment of metastatic triple negative breast cancer (Tables 14.2 and 14.4).

14.2.2 Range of Side Effects of Monoclonal Antibodies Used for Cancer Therapy

Monoclonal antibodies used for cancer immunotherapy are highly specific for their targets, less prone to drug-drug interactions, and generally better tolerated than small molecule chemotherapeutic drugs. Despite these attributes and their specifically targeted nature and consequent hoped-for safety benefits, their range of adverse effects remains wide with some events immune-mediated and others non-immune or even the result of direct cytotoxic effects (Table 14.4 and Box 14.1). Limitations on the use of mAbs include their size which may limit tissue penetration, their
| Monoclonal antibody<sup>a</sup> | Target<sup>b</sup> | Warnings, precautions, risks, and safety concerns | Other adverse events<sup>d</sup>, serious and common |
|---|---|---|---|
| **Catumaxomab**<sup>e</sup> (Removab<sup>®</sup>) | EpCAM/CD3<sup>f</sup> | Monitor and evaluate for CRS, SIRS, HAMA/HARA, GI hemorrhage, hepatic disorders, abdominal infection, ileus/intestinal perforation, decreased lymphocyte count | **Systemic**: Cytopenias, hepatoxicity, abdominal disorders, pyrexia, chills, nausea, vomiting, infections, immunogenicity, dyspnea  **Cutaneous**: Rash, erythema, allergic dermatitis, hyperhidrosis; pruritus |
| **Blinatumomab**<sup>g</sup> (Blincyto<sup>®</sup>) | CD19/CD3<sup>h</sup> 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 |
| **Ibritumomab tiuxetan**<sup>i</sup> (Zevalin<sup>®</sup>) | CD20<sup>j</sup> | *Boxed warning*: Serious IR, severe cytopenias<sup>k</sup>, 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 |
| **Obinutuzumab**<sup>b</sup> (Gazyva<sup>®</sup>; Gazyvaro<sup>®</sup>) | CD20 | *Boxed warning*: Hepatitis B virus reactivation; PML.  **Other**: IR, TLS, neutropenia, thrombocytopenia, infections, immunization | **Systemic**: Anemia, pyrexia, musculoskeletal disorders, headache, cough |
| **Ofatumumab** (Arzerra<sup>®</sup>) | 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, urticarial, hyperhidrosis |
| **Rituximab** (MabThera<sup>®</sup>; Rituxan<sup>®</sup>) | 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 | **Systemic**: Pulmonary events, renal toxicity, neutropenias, serum sickness, anaphylaxis, fever, lymphopenia, chills, asthenia  **Cutaneous**: Paraneoplastic pemphigus, lichenoid dermatitis, vesiculobullous dermatitis, SJS, TEN |
| **Brentuximab vedotin**<sup>m</sup> (Adcetris<sup>®</sup>) | CD30<sup>n</sup> | *Boxed warning*: PML.  **Other**: Peripheral neuropathy, IR and anaphylaxis, neutropenia, infections, fatal harm, hepatotoxicity, TLS, SJS | **Systemic**: Cytopenias, immunogenicity, URTI, pyrexia, nausea, vomiting, fatigue, cough, anaphylaxis  **Cutaneous**: Rash, pruritus, SJS, alopecia |
| **Alemtuzumab**<sup>b</sup> (Campath<sup>®</sup>; MabCampath<sup>®</sup>) | CD52<sup>o</sup> | *Boxed warning*: Cytopenias, IR, immunosuppression/infections<sup>q</sup>  **Other**: Immunosuppression | **Systemic**: Pulmonary events, immunogenicity, cardiac events, diarrhea, nausea, emesis, insomnia  **Cutaneous**: Rash, urticarial, erythema, pruritus |

(continued)
| Monoclonal antibody\textsuperscript{a} INN and trade names\textsuperscript{b} | Target\textsuperscript{c} | Warnings, precautions, risks, and safety concerns | Other adverse events\textsuperscript{d}, serious and common |
|---|---|---|---|
| Cetuximab (Erbitux\textsuperscript{®}) | EGFR | 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 |
| Panitumumab\textsuperscript{b} (Vectibix\textsuperscript{®}) | EGFR | Boxed warning: Dermatologic toxicity, IR  
Other: Increased toxicity with bevacizumab and chemotherapy, pulmonary toxicities, electrolyte depletion, ocular events | Systemic: Pulmonary events\textsuperscript{f}, pulmonary embolism, GI, fatigue, abdominal pain, hypomagnesemia  
Cutaneous: Rash, dermatitis ‘acneiform’, erythema, exfoliation, paronychia, skin fissures, photosensitivity, xerosis, pruritus |
| Necitumumab (Portrazza\textsuperscript{®}) | EGFR | Boxed warning: Cardiopulmonary arrest, hypo-magnesemia  
Other: Venous, arterial thromboembolic events; dermatologic toxicities; embryo-fetal toxicity; † toxicity, mortality in patients with non-squamous NSCLC; IR | Systemic: Diarrhea; vomiting  
Cutaneous: Exfoliative dermatitis, alopecia, ovarian failure |
| Bevacizumab (Avastin\textsuperscript{®}) | VEGF | 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 fasciitis, taste alteration, lacrimation disorder  
Cutaneous: Exfoliative dermatitis, alopecia, ovarian failure |
| Ramucirumab (Cyramza\textsuperscript{®}) | VEGFR-2 | Boxed warning: Hemorrhage, GI perforation, impaired wound healing  
Other: Arterial thromboembolic events, IR, RPLS, hypertension, deterioration in patients with cirrhosis, proteinuria including nephrotic syndrome, thyroid dysfunction, embryo-fetal risk | Systemic: Hypertension, diarrhea, headache, hyponatremia, neutropenia, epistaxis, stomatitis, immunogenicity\textsuperscript{e} |
| Pertuzumab (Perjeta\textsuperscript{®}) | 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) |
| Trastuzumab (Herceptin\textsuperscript{®}) | HER2 | Boxed warning: Cardiomyopathy\textsuperscript{v}, IR, pulmonary toxicity  
Other: Exacerbation of chemotherapy-induced neutropenia, embryo-fetal toxicity | Systemic: Neutropenia\textsuperscript{v}, anemia, thrombocytopenia, pulmonary events, LVD\textsuperscript{v}, GI, chills, fever, URTI, anaphylaxis/angioedema, headache, cough, stomatitis; mucosal inflammation  
Cutaneous: Rash; nail disorders; pruritus |
| Monoclonal antibody<sup>a</sup> | INN and trade names<sup>b</sup> | Target<sup>c</sup> | Warnings, precautions, risks, and safety concerns | Other adverse events<sup>d</sup>, serious and common |
|-------------------------------|-------------------------------|----------------|-----------------------------------------------|--------------------------------------------------|
| Ado-trastuzumab emtansine<sup>1</sup> (Kadcyla<sup>e</sup>) | HER2 | **Boxed warning:** Hepatotoxicity, cardiac toxicity, embryo-fetal toxicity<br>**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<br>**Cutaneous:** Rash; pruritus |
| Denosumab (Xgeva<sup>e</sup>; Prolia<sup>e</sup>) | RANKL | Hypocalcemia, osteonecrosis of jaw, embryo-fetal toxicity | **Systemic:** Osteomyelitis, hypophosphatemia, dyspnea, fatigue/asthenia, back pain, nausea, extremity pain<br>**Cutaneous:** Rash; pruritus; eczema |
| Ipilimumab (Yervoy<sup>e</sup>) | CTLA-4<sup>f</sup> | **Boxed warning:** Immune-mediated adverse reactions<sup>1</sup> | **Systemic:** Diarrhea, fatigue, colitis<br>**Cutaneous:** Rash; pruritus; dermatitis |
| Siltuximab (Sylvant<sup>e</sup>) | 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<br>**Cutaneous:** Rash; pruritus |
| Nivolumab (Opdivo<sup>e</sup>) | PD-1 | Immune-mediated adverse reactions<sup>s</sup>, embryo-fetal toxicity | **Systemic:** Increased ALT, AST, AP; hyponatremia; hyper- and hypokalemia; hyper- and hypocalcemia; lymphopenia; fatigue; asthenia; musculoskeletal and abdominal pain; dyspnea; cough; GI<br>**Cutaneous:** Rash; pruritus |
| Pembrolizumab (Keytruda<sup>e</sup>) | PD-1 | Immune-mediated adverse reactions<sup>s</sup>, embryo-fetal toxicity | **Systemic:** Fatigue, peripheral edema, chills, pyrexia, renal failure, cellulitis, decreased appetite, dyspnea, arthralgia, nausea, diarrhea, cough<br>**Cutaneous:** Rash; pruritus; vitiligo |
| Cemiplimab-rwlc (Libtayo<sup>e</sup>) | PD-1 | Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, infections, embryo-fetal toxicity | **Systemic:** Diarrhea, fatigue, nausea, constipation, musculoskeletal pain<br>**Cutaneous:** Rash; pruritus |
| Atezolizumab (Tecentriq<sup>e</sup>) | 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<br>**Cutaneous:** Rash; pruritus |
| Avelumab (Bavencio<sup>e</sup>) | 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<br>**Cutaneous:** Rash; pruritus |
| Durvalumab (Imfinzi<sup>e</sup>) | PD-L1 | Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, embryo-fetal toxicity, infections, IR | **Systemic:** Fatigue, musculoskeletal pain, diarrhea, nausea, decreased appetite, peripheral edema, urinary tract infection, pneumonitis, dyspnea, URTI, cough<br>**Cutaneous:** Rash; pruritus |

(continued)
| Monoclonal antibody\(^a\) | Target\(^b\) | Warnings, precautions, risks, and safety concerns | Other adverse events\(^a\), serious and common |
|--------------------------|-------------|-------------------------------------------------|------------------------------------------------|
| Dinutuximab (Unituxin\(^®\)) | GD2 | Boxed warning: Serious IR, neuropathy Other: CLS and hypotension, infection, neurological disorders of eye, BMS, electrolyte abnormalities, AHUS, embryo-fetal toxicity | Systemic: Hypokalemia, pain, fever, hypocalcemia, hypotension, anemia, thrombocytopenia, lymphopenia, neutropenia, increased AST, ALT; GI Cutaneous: Urticaria |
| 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 |
| Elotuzumab (Empliciti\(^®\)) | SLAMF7 | IR, infections, second primary malignancies, hepato-toxicity, interference in monitoring M-protein impacting determination of complete response in patients with IgGk myeloma protein | Systemic: Fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite, pneumonia |
| 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, cytopenas, nausea, fatigue, hemorrhage, pyrexia, infection, headache, febrile neutropenia, increased transaminases, hyperbilirubinemia |
| Moxetumomab pasudotox-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 |
| 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 |
| Polatuzumab vedotin-piiq (Polivy\(^®\)) | CD79b | Peripheral neuropathy, myelosuppression and related reactions, infections, IR, TLS, FML, hepatotoxicity, embryo-fetal toxicity | Systemic: Cytopenia, fatigue, decreased appetite, diarrhea, pyrexia, pneumonia |
| Olaratumab (Lartruvo\(^®\)) | PDGFRA | IR, embryo-fetal toxicity | Systemic: Olaratumab + doxorubicin: Fatigue, musculoskeletal pain, diarrhea, decreased appetite, headache, neuropathy, cytopenas, hyperglycemia, elevated aPTT, hypokalemia, hypophosphatemia Cutaneous: Alopecia |
| Mogamulizumab-kpkc (Poteligeo\(^®\)) | CCR4 | Dermatologic toxicity, IR, infections, autoimmune reactions, HSCT complications | Systemic: IR, diarrhea, fatigue, URTI, musculoskeletal pain Cutaneous: Rash |
Table 14.4 (continued)

From Baldo BA. Safety of biologics therapy. Monoclonal antibodies, cytokines, fusion proteins, hormones, enzymes, coagulation proteins, vaccines, botulinum toxins. Cham, Switzerland: Springer Nature; 2016. Adapted and reproduced with permission from Springer Nature

**Note:** For sacituzumab govitecan-hziy (Trodelvy™) (Table 14.2), the FDA has issued a boxed warning for febrile neutropenia and diarrhea. Other warnings and precautions include hypersensitivity (including anaphylaxis), nausea/vomiting, EFT, and for patients homozygous for UGT1A1 who are at increased risk for neutropenia. For isatuximab-irfc (Sarclisa®) (Table 14.2), the FDA has warnings and precautions for infusion reactions, neutropenia, second primary malignancies, and EFT.

ADCC antibody-dependent cell-mediated cytotoxicity, AHUS atypical hemolytic syndrome, ALT acute alanine transaminase, AML acute myelogenous leukemia, AP alkaline phosphatase, ASAT aspartate transaminase, BMS bone marrow suppression, CHF congestive heart failure, CLS capillary leak syndrome, CNS central nervous system, CRS cytokine release syndrome, CTLA-4 cytotoxic T lymphocyte-associated antigen 4, EFT embryo-fetal toxicity, EGF epidermal growth factor receptor (HER1, ErbB1), EM erythema multiforme, EpCAM epithelial cell adhesion molecule, GD2 disialoganglioside expressed on tumors of neuroectodermal origin, GI gastrointestinal/gastrointestinal symptoms, eg. nausea, diarrhea, vomiting, constipation, etc.; 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, LVD left ventricular dysfunction, MDS myelodysplastic syndrome, 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, PPA palmar-plantar erythrodysesthesia, RANKL receptor activator of nuclear factor kappa-B ligand (CD254), RPS reversible posterior leukoencephalopathy syndrome, SIRS systemic inflammatory response syndrome, SJS Stevens-Johnson syndrome, TLS tumor lysis syndrome, UGT1A1 uridine diphosphate-glucuronosyl transferase 1A1, URTI upper respiratory tract infection, VEGF vascular endothelial growth factor, VEGFR-2 vascular endothelial growth factor receptor 2

1. Nomenclature: mAbs of murine origin are given the suffix, or stem, omab; chimeric antibodies in which the V region is spliced into human C region is given the -ximab stem; humanized antibodies with murine hypervariable region spliced into human antibody have the -zumab stem; and antibodies with complete human sequence are given the -umab stem
2. Approved by FDA or EMA or both
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. Registered by EMA, Health Canada & Ministry of Health, Israel but not FDA. Catumaxomab is a bispecific mouse – rat hybrid (given suffix –axomab) recognizing both EpCAM and CD3
6. EpCAM (CD326) – expressed on epithelial and epithelial-derived neoplasms; CD3 – part of TCR complex on T lymphocytes
7. A BITE (bispecific T cell-engaging) fusion protein
8. CD19, a B cell antigen; CD3, part of the T cell receptor
9. With Yttrium-90 or Indium-111. Tiuxetan is a chelator
10. Expressed on B-lymphocytes where it aids optimum B cell response to T-independent antigens
11. Severe neutropenia, thrombocytopenia, anemia, lymphopenia. Incidences of thrombocytopenia grades III and IV in ibritumomab tiuxetan-treated non-Hodgkin lymphoma patients were 87% and 13%, respectively
12. Glycoengineered to enrich Fc carbohydrate with non-fucosylated sugars and higher binding to FcγRIII with consequent enhanced ADCC
13. Conjugated to cytotoxic monomethyl auristatin E (MMAE)
14. CD30 – a cell membrane protein of the tumor necrosis receptor family. Expressed on activated T and B lymphocytes
15. Withdrawn from the United States and Europe in 2012 to be re-launched for multiple sclerosis
16. CD52 – present on the surface of mature lymphocytes and associated with some lymphomas
17. In particular Pneumocystis jiroveci, CMV, EBV and herpes virus
18. Not indicated for use in combination with chemotherapy due to increased toxicity
19. Should be discontinued in patients developing interstitial lung disease, pneumonitis and lung infiltrates
20. Most common drug-induced reactions following this mAb are skin toxicities
21. Neutralizing antibodies detected in 1 of 33 patients
22. Greatest risk (LVD) when administered with anthracyclines
23. Highest risk with myelosuppressive therapy
24. Called Ado-trastuzumab emtansine in the United States to distinguish it from trastuzumab emtansine and linked to the cytotoxic mertansine (DMI), a tubulin inhibitor. Also known as trastuzumab emtansine and T-DM1
25. Binds CD80/CD86 on antigen-presenting cells
26. Immune-mediated reactions due to T cell activation and proliferation – enterocolitis, hepatitis, dermatitis, neutropathies, endocrinopathies and other immune-mediated reactions including cutaneous and ocular manifestations
27. Immune-mediated pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism, and hyperthyroidism
28. Immune-mediated colitis, hepatitis, nephritis, hypothyroidism and hyperthyroidism
instability, the expression of specifically targeted tumor antigens on normal cells, lack of oral absorption, immunogenicity, and the possibility of hypersensitivity reactions to the proteins. Even so, the relatively non-specific, nondiscriminatory approach of killing rapidly dividing normal, healthy cells by promiscuous binding to off-target sites with consequent cytotoxicity and other wide-ranging side effects often makes treatment regimens with small molecule antineoplastic agents difficult to manage and a less attractive option than mAb-targeted therapies despite their limitations.

### 14.2.2.1 Monoclonal Antibody-Induced Cytopenias

Cytopenias are a well-known side effect of mAb therapy (Box 14.1), but the underlying mechanisms frequently remain unexplored, and types II and III hypersensitivities induced by the antibodies may be underdiagnosed and under-reported. Thrombocytopenia, for example, a well-known adverse event following the use of many small molecule chemotherapeutic drugs, is much more rarely reported during and after mAb treatments. Boxed warnings have been issued for the risk of severe cytopenias with ibritumomab tiuxetan and alemtuzumab, and for severe neutropenia with sacituzumab govitecan-hziy, while general warnings and precautions are set down for obinutuzumab (thrombocytopenia, neutropenia); ofatumumab (cytopenias); brentuximab vedotin (neutropenia); trastuzumab (neutropenia); and ado-trastuzumab emtansine (thrombocytopenia).

Listed among the other warnings/adverse events for the 36 anticancer mAbs are cytopenias for catumaxomab, brentuximab vedotin, and pertuzumab; lymphopenia for elotuzumab; lymphopenia and leukopenia for blinatumomab; neutropenia for rituximab; thrombocytopenia and neutropenia for daratumumab; thrombocytopenia and anemia for trastuzumab; thrombocytopenia, lymphopenia, anemia, and neutropenia for dinutuximab; thrombocytopenia, leukopenia, and neutropenia for inotuzumab ozogamicin; thrombocytopenia and neutropenia for polatuzumab vedotin-piiz; and thrombocytopenia, lymphopenia, and neutropenia for olaratumab (Table 14.4).

### Box 14.1 Non-immune-Mediated Adverse Events to mAbs Used for Cancer Therapy

- Mechanisms of mAb-induced thrombocytopenia, neutropenia, hemolytic anemia, and vasculitis are often not investigated. Some may be immune-mediated (see Box 14.2).
- Mab-induced lung disease: The mechanisms are generally not known; therefore, classification on the basis of pathogenesis is difficult. Some reactions immune-mediated (see Box 14.2).
- Cardiac events occur with at least nine mAbs: trastuzumab; ado-trastuzumab; pertuzumab; bevacizumab; rituximab; cetuximab; alemtuzumab; bevacizumab; inotuzumab ozogamicin.
- Liver events/hepatotoxicity: Catumaxomab, ipilimumab, ado-trastuzumab, inotuzumab ozogamicin, gemtuzumab ozogamicin, polatuzumab vedotin-piiz. Some reactions (e.g., to immune checkpoint inhibitors) are immune-mediated (see Box 14.2).
- Tumor lysis syndrome is well-known after brentuximab vedotin, rituximab, blinatumomab, obinutuzumab, polatuzumab vedotin-piiz.
- Progressive multifocal leukoencephalopathy (PML) is occasionally seen after brentuximab, ofatumumab, obinutuzumab, polatuzumab vedotin-piiz.
- Papulopustular (acneiform) eruptions occur to EGFR-targeted mAbs, e.g., cetuximab, panitumumab, necitumumab.
- Posterior reversible encephalopathy syndrome (PRES; RPLS) may occur e.g., with bevacizumab, ramucirumab.

### 14.2.2.2 Monoclonal Antibody-Induced Types I–IV Hypersensitivities

Immunogenicity is always a safety concern for mAbs, even those that are fully human, since the possibility of generating anti-idiotype antibodies remains (Chap. 13, Sect. 13.1.1). Apart from such recognition of foreign antigens, patient responses to mAbs cover the full range of hypersensitivities...
from type I IgE antibody-mediated immediate reactions such as anaphylaxis, urticaria, and angioedema; to type II drug-induced thrombocytopenia, hemolytic anemia, and agranulocytosis; type III serum sickness and drug-induced vasculitis; a range of type IV cutaneous hypersensitivities mediated by Th1, Th2, and Th17 lymphocytes; and often poorly understood effector mechanisms involving cytotoxic lymphocytes, macrophages, eosinophils, and a number of other cell types (Table 14.4 and Boxes 14.1 and 14.2).

Monoclonal antibodies are proteins, and anaphylaxis mediated by IgE antibodies is the classic example of a type I hypersensitivity. The possibility of an anaphylactic reaction to a mAb is therefore always considered especially for therapies known to be of greatest potential risk, namely, chimeric proteins used for cancer therapy containing mouse and/or rat sequences (catumaxomab, ibritumomab, cetuximab, rituximab, brentuximab, bevacizumab, trastuzumab, pertuzumab, ibritumomab, dinutuximab, gemtuzumab ozogamicin, sacituzumab govitecan-hziy).

- Type I: There is a low incidence of reactions. Chimeric molecules, catumaxomab, ibritumomab, cetuximab, rituximab, and brentuximab carry warnings. Anaphylaxis is reported for cetuximab, rituximab, brentuximab, ibritumomab, trastuzumab, pertuzuzumab, bevacizumab, dinutuximab, gemtuzumab, ozogamicin, sacituzumab govitecan-hziy.
- Type II: There is little or no good evidence for immune thrombocytopenia to an anticancer mAb (c.f. abciximab). Rituximab-induced late-onset neutropenia may be immune-mediated. Autoimmune hemolytic anemia is induced by rituximab and alemtuzumab.
- Type III: Cellular and humoral processes may be involved in some cases of mAb-induced vasculitis. Chimeric mAbs can induce serum sickness (e.g., rituximab).
- Immune-mediated (hypersensitivity) pneumonitis involves both type III and type IV hypersensitivity reactions mediated by immune complexes and Th1 and likely Th17 T cells, respectively. Reactions caused by mAb PD-1 (nivolumab, pembrolizumab, cemiplimab-rwle) and PD-L1 (atezolizumab, avelumab, durvalumab) immune checkpoint inhibitors.
- Precise mechanisms of immune-mediated colitis, hepatitis, nephritis, hypothyroidism, and endocrinopathies induced by mAb PD-1 and PD-L1 checkpoint inhibitors not yet established.
- Type IV: Rare reactions to ibritumomab, brentuximab, pembrolizumab, and especially rituximab (SJS, TEN, lichenoid dermatitis, vesiculobullous dermatitis, and paraneoplastic pemphigus). Dermatitis induced by catumaxomab, bevacizumab, denosumab, ipilimumab, panitumumab. Immune-mediated dermatologic adverse reactions induced by durvalumab and cemiplimab-rwlc may be type IV reactions, but the mechanisms are not yet unequivocally established.

### Boxes 14.2 Hypersensitivity Reactions to mAbs Used for Cancer Therapy

- **Type I:** There is a low incidence of reactions. Chimeric molecules, catumaxomab, ibritumomab, cetuximab, rituximab, and brentuximab carry warnings. Anaphylaxis is reported for cetuximab, rituximab, brentuximab, ibritumomab, trastuzumab, pertuzuzumab, bevacizumab, dinutuximab, gemtuzumab, ozogamicin, sacituzumab govitecan-hziy.
- **Type II:** There is little or no good evidence for immune thrombocytopenia to an anticancer mAb (c.f. abciximab). Rituximab-induced late-onset neutropenia may be immune-mediated. Autoimmune hemolytic anemia is induced by rituximab and alemtuzumab.
- **Type III:** Cellular and humoral processes may be involved in some cases of mAb-induced vasculitis. Chimeric mAbs can induce serum sickness (e.g., rituximab).
- **Type IV:** Rare reactions to ibritumomab, brentuximab, pembrolizumab, and especially rituximab (SJS, TEN, lichenoid dermatitis, vesiculobullous dermatitis, and paraneoplastic pemphigus). Dermatitis induced by catumaxomab, bevacizumab, denosumab, ipilimumab, panitumumab. Immune-mediated dermatologic adverse reactions induced by durvalumab and cemiplimab-rwlc may be type IV reactions, but the mechanisms are not yet unequivocally established.

Apart from abciximab (Chap. 13), targeted to platelet glycoprotein GP IIb/IIIa and used for the prevention of cardiac ischemic complications, there appears to be a dearth of convincing evidence for the involvement of mAbs in type II hypersensitivity reactions. Immune thrombocytopenia is a complex autoimmune disease, the pathogenesis of which remains unclear although both antibody-mediated and T cell-mediated platelet destruction are involved. Thrombocytopenia is a well-known adverse event following rituximab mono- or combination therapy with an incidence of ~1.7%, but a clear demonstration of an immune mechanism is lacking. In one study it was not possible to implicate rituximab-dependent antibodies, and IL-1 and IL-6
were not increased but complement levels were elevated leading investigators to conclude that mAb-induced transient thrombocytopenia might be mediated by complement activation and associated with cytokine release syndrome (CRS). Alemtuzumab and trastuzumab are other mAbs implicated in treatment-related severe thrombocytopenia. Three percent of patients given alemtuzumab developed potentially fatal thrombocytopenia, and 5 of 11 patients with peripheral T cell lymphoproliferative disorders developed lymphopenia, neutropenia, and thrombocytopenia. Rituximab-induced neutropenia is a suspected example of a mAb-induced type II hypersensitivity. It has been implicated in both early and late forms of the condition. Late-onset neutropenia manifests at least 4 weeks after the cessation of therapy; it occurs with a comparatively high incidence (4–23%) and appears to be caused by a different mechanism than early-onset neutropenia. Direct cytotoxicity does not seem to be involved, and autoantibodies may be responsible for the rituximab-induced disease. Rituximab has also been implicated as a cause of severe anemia (incidence 1.1–5.2%), severe autoimmune hemolytic anemia, intravascular hemolysis, rhabdomyolysis, renal failure, bone marrow necrosis, and multiple organ ischemia due to anti-Pr cold agglutinins. At least two mAbs, rituximab and alemtuzumab, have been implicated in the induction of pure red cell aplasia and autoimmune hemolytic anemia (Table 14.4 and Box 14.2).

Hypersensitivity vasculitis and serum sickness-like reactions are examples of type III hypersensitivity responses known to be provoked by mAbs although the latter condition is probably underdiagnosed and underreported. Again, the human-mouse antibody rituximab has most often been the culprit mAb involved, an example of the greater potential of chimeric antibodies to induce the reactions. It has been claimed that rituximab-induced serum sickness-like reactions can occur in up to 20% of treated patients, especially in those with hypergammaglobulinemia and autoimmune diseases, particularly autoimmune thrombocytopenia. Figure 14.12 shows an example of mAb-induced cutaneous vasculitis during treatment with the fully human TNF-targeted adalimumab.

Checkpoint inhibitors ipilimumab that targets CTLA-4, nivolumab, pembrolizumab, and cemiplimab-rwlc that block PD-1, and atezolizumab, avelumab, and durvalumab that block PD-L1, provoke a number of immune-mediated reactions. Perhaps one of the most dangerous and reported reaction is immune-mediated, or hypersensitivity, pneumonitis, a combined type III and IV hypersensitivity reaction in a Th1/Th17 response. Compared to nivolumab, pembrolizumab showed an increase in grade 3–5 pneumonitis, a difference attributed to the small specificity differences in the PD-1 mAb combining sites. Compared with nivolumab or ipilimumab monotherapy, combined therapy with these two mAbs showed significant increases in grades 1–5 and 3–5 pneumonitis. As well as the immune-mediated lung reactions, anti-PD-1 and anti-PD-L1 therapy

Fig. 14.12 Cutaneous vasculitis, a type III hypersensitivity, during adalimumab treatment. (Reproduced from Aubin F, Carbonnel, Wendling D. The complexity of adverse side-effects to biologic agents. J Crohn’s Colitis. 2013;7:257–62, an open access article distributed under a Creative Commons License; reproduced with permission from Elsevier)
may induce immune-mediated colitis, hepatitis, endocrinopathies, nephritis, and thyroid reactions. Presumably, these immune reactions may also have at least a component of a type III hypersensitivity response (Table 14.4 and Box 14.2).

Monoclonal antibody-induced type IV hypersensitivity reactions of the skin include allergic contact dermatitis, psoriasis, maculopapular exanthema, fixed drug eruption, acute generalized exanthematous pustulosis, erythema multiforme, DRESS, and cutaneous bullous toxidermias such as SJS and TEN (Table 14.4 and Box 14.2). The last two of these reactions are rare with most reported cases restricted mainly to ibritumomab tiuxetan, brentuximab vedotin, and rituximab. Lichenoid dermatitis, vesiculobullous dermatitis, and paraneoplastic pemphigus have also occurred in response to rituximab, and a case of lichenoid eruption occurred after obinutuzumab. Other mAb-induced cutaneous manifestations with features seemingly common to a type IV response may be true type IV hypersensitivities, but mechanisms remain to be established, for example, cases of dermatitis induced by catumaxomab, bevacizumab, denosumab, ipilimumab, and panitumumab. In fact, panitumumab carries a black box warning for dermatologic toxicity. Cutaneous acneiform rash reactions that are not genuine hypersensitivities are seen with the EGFR-targeted mAbs cetuximab, panitumumab, and necitumumab (Sect. 14.2.2.5).

14.2.2.3 Monoclonal Antibody-Induced Pulmonary Adverse Events

Classified under the heading drug-induced lung diseases (DILDs), these pulmonary adverse events make up a heterogeneous group of diseases, most still of unknown, or poorly understood, mechanism of action. Although there are a number of classifications, DILDs have been grouped here into four categories: interstitial pneumonitis and fibrosis; acute respiratory distress syndrome (ARDS); bronchiolitis obliterans organizing pneumonia (BOOP); and hypersensitivity pneumonitis. At least 14 of the currently approved mAbs for cancer therapy have been implicated in some form of pulmonary toxicity in

| Box 14.3 Pulmonary Adverse Events Caused by mAbs |
|-----------------------------------------------|
| **Mouse antibodies**                          |
| – Ibritumomab tiuxetan: hypersensitivity bronchospasm |
| **Human-mouse chimeric antibodies**          |
| – Cetuximab: interstitial pneumonitis         |
| – Rituximab: ARDS, BOOP, bronchospasm, diffuse alveolar hemorrhage, hypersensitivity pneumonitis |
| **Humanized antibodies**                     |
| – Alemtuzumab: bronchospasm, diffuse alveolar hemorrhage, pulmonary infection |
| – Bevacizumab: anaphylaxis/bronchospasm, pulmonary hemorrhage from tumor site |
| – Pembrolizumab: immune-mediated pneumonitis, dyspnea |
| – Trastuzumab: ARDS, BOOP, dyspnea, interstitial pneumonitis, pleural effusions, pulmonary infiltrates/ fibrosis/edema |
| – Ado-trastuzumab: interstitial lung disease, pneumonitis, ARDS, dyspnea, pulmonary infiltrates, radiation pneumonitis |
| – Atezolizumab: immune-mediated pneumonitis, dyspnea |
| **Fully human antibodies**                   |
| – Panitumumab: interstitial lung disease, lung infiltrates, pneumonitis, pulmonary fibrosis |
| – Nivolumab: immune-mediated pneumonitis, dyspnea |
| – Cemiplimab-rwlc: immune-mediated pneumonitis |
| – Avelumab: immune-mediated pneumonitis |
| – Durvalumab: immune-mediated pneumonitis, dyspnea |

ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia
treated cancer patients (Box 14.3). As discussed above, immune-mediated or hypersensitivity pneumonitis is now seen as a combined type III and type IV hypersensitivity reaction in a Th1/Th17 response. It has also been suggested that early-onset organizing pneumonia is a hypersensitivity reaction to the mAb, whereas the late-onset condition is either related to mAb toxicity or to immune system restoration. ARDS symptoms appearing within a few hours of infusion may be a manifestation of CRS (Sect. 14.2.2.6) or tumor lysis syndrome (TLS) (Sect. 14.2.2.7) with no relationship to hypersensitivity although ARDS has also been linked to release of proinflammatory cytokines. Of the 36 mAbs currently approved for anticancer therapy (at April 2020), rituximab, trastuzumab, alemtuzumab, and panitumumab provoke the biggest range of pulmonary adverse events.

### 14.2.2.4 Monoclonal Antibody-Induced Cardiac Adverse Events

Cardiac adverse events have occurred with at least 13 of the approved mAbs used for cancer therapy (Table 14.5). Induced events are wide ranging and include decreased left ventricular ejection fraction (LVEF), cardiac arrhythmias, angina, supraventricular arrhythmia in some lymphoma patients, fatal myocardial infarction, heart failure, QT interval prolongation, and cardiopulmonary arrest and/or sudden death. Necitumumab carries an FDA black box warning for cardiopulmonary arrest. Decreases in LVEF are well-known for mAbs and other drugs that block HER2 activity, and this risk is increased in patients given anthracyclines (Chap. 15) or radiotherapy to the chest. Patients administered trastuzumab show a fourfold to sixfold elevation in the incidence of myocardial infarction, and this risk is highest when the mAb is given with an anthracycline.

### 14.2.2.5 Mucocutaneous Reactions to Monoclonal Antibodies Targeted to Epidermal Growth Factor Receptor

These cutaneous reactions are not immune-mediated, that is, they are not genuine hypersensi-

| Table 14.5 | Cardiac adverse events caused by approved monoclonal antibodies used for cancer therapy |
|------------|---------------------------------------------------------------------------------------|
| **Monoclonal antibody** | **Cardiac adverse events** |
| Ibritumomab tiuxetan (Zevalin®) | Cardiac arrest related to infusions |
| Obinutuzumab (Gazyva®, Gazyvaro®) | Worsening of pre-existing cardiac conditions leading to fatal cardiac events |
| Rituximab (MabThera®, Rituxan®) | Cardiac arrhythmias and angina, fatal cardiac failure |
| Brentuximab vedotin (Adcetris®) | Supraventricular arrhythmia in systemic anaplastic large cell lymphoma |
| Necitumumab (Portrazza®) | Cardiopulmonary arrest |
| Alemtuzumab (Campath®, MabCampath®) | Cardiomyopathy, decreased LVEF, cardiac arrhythmias associated with infusions |
| Cetuximab (Erbitux®) | Cardiopulmonary arrest/sudden death |
| Bevacizumab (Avastin®) | CHF: incidence of grade 3 reaction for LVD 1% |
| Ramucirumab (Cyramza®) | Serious, sometimes fatal, myocardial infarction |
| Pertuzumab (Perjeta®) | Cardiomyopathy manifesting as CHF and decreased LVEF |
| Trastuzumab (Herceptin®) | Cardiomyopathy manifesting as CHF and decreased LVEF |
| Ado-trastuzumab emtansine (Kadcyla®) | Decreased LVEF |
| Inotuzumab ozogamicin (Besponsa®) | QT interval prolongation |

From Baldo BA. Safety of biologics therapy. Monoclonal antibodies, cytokines, fusion proteins, hormones, enzymes, coagulation proteins, vaccines, botulinum toxins. Cham, Switzerland: Springer Nature; 2016. Adapted and reproduced with permission from Springer Nature

CHF congestive heart failure, LVD left ventricular dysfunction, LVEF left ventricular ejection fraction

*Can be life threatening. Discontinue infusions. Perform cardiac monitoring after each infusion for patients with arrhythmia/angina

*Incidence is highest when mAb is administered with cardiotoxic agents such as anthracyclines

*In ~14% of previously untreated patients. Most reaction temporarily associated with infusions

*In patients treated with cetuximab and radiation therapy

*Patients receiving trastuzumab alone or in combination therapy show a fourfold to sixfold increase in the incidence of myocardial dysfunction

activities. Skin reactions after mAbs cetuximab and panitumumab often appear as a papulopustular eruption (sometimes less precisely called an acneiform rash), in a large proportion of patients (50–
100%) and in a more severe form than seen with small molecule tyrosine kinase inhibitors such as erlotinib, gefitinib, and lapatinib (refer Sect. 14.1.1.3 and Fig. 14.4). The skin lesions occurring after the mAbs consist of erythematous follicular papules that may evolve into pustules. The acneiform rash usually occurs a few days after administration of the mAb and reaches a maximum after 2–3 weeks. Eruptions tend to be confined to seborrheic regions of the face (Fig. 14.13), scalp, neck, shoulders, and upper trunk (Figs. 14.14, 14.15, and 14.16a–c). These areas normally maintain their integrity via EGFR expressed in the epidermis, sebaceous glands, and hair follicles, but in the presence of inhibitors of EGFR, the epithelial barrier may be weakened allowing bacterial access.
Fig. 14.16 Examples of dermatologic side effects of papulopustular (acneiform) rash, mucositis, stomatitis, rhagades, xerosis, and nail changes during treatment with EGFR-targeted monoclonal antibodies such as cetuximab and panitumumab. (a–c) Papulopustular rash; (d, e) radiation dermatitis enhancement of papulopustular rash; (f, g) mucositis; (h) fingertip fissures; (i) paronychia. (Reproduced from Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011;19:1079–95. Reprinted with permission from Springer Science + Business Media)
and ultimately the development of the characteristic rash. EGFR inhibition together with radiotherapy may lead to radiation dermatitis enhancement, giving rise to wet or dry desquamation, necrosis, or cutaneous ulceration (Fig. 14.16d, e). Other adverse effects induced by mAbs targeted to EGFR include mucositis (Fig. 14.16f, g), xerosis, fissures (Fig. 14.16h), paronychia (Fig. 14.16i) including periungual granulation type (Fig. 14.17), palmar-plantar rash, hair changes, hyperkeratosis, nail pyrogenic granuloma, and skin hyperpigmentation.

14.2.2.6 Infusion Reactions and Cytokine Release Syndrome

The FDA has issued boxed warnings for the possibility of serious or even fatal infusion reactions to ibritumomab vedotin, rituximab, alemtuzumab, cetuximab, panitumumab, trastuzumab, and dinutuximab and a general warning for the risk of infusion reactions during or following treatment with obinutuzumab, ofatumumab, brentuximab vedotin, bevacizumab, ramucirumab, pertuzumab, ado-trastuzumab emtansine,
Infusion reactions provoked by mAbs usually begin within hours of the initial infusion. Reactions are typically mild to moderate manifesting as “flu”-like symptoms of fever, chills, rigor, headache, nausea, asthenia, pruritus, and rash. In a small number of patients, severe, life-threatening symptoms common to type I IgE antibody-mediated anaphylaxis, in particular, hypotension, bronchospasm, cardiac arrest, and urticaria, may occur, usually during the first or second infusion. The similarity of the signs and symptoms can make it difficult to distinguish an infusion reaction from a true allergic hypersensitivity although IgE-mediated reactions generally have a faster and more severe onset, usually within minutes. Severe reactions have been reported for all, or almost all, the mAbs although some show a much higher incidence with the chimeric rituximab and humanized trastuzumab antibodies being the leading offenders. The incidence of reactions for cetuximab, another human-mouse chimera, is ~15–20% (grade 3–4, 1%); for trastuzumab, first infusion ~40% (grade 3–4, <1%); and for rituximab, first infusion ~77% (grade 3–4, 10%). Approximately 80% of fatal infusion reactions to rituximab occurred after the first infusion and 30% and 14% of patients still reacted after the fourth and eighth infusions, respectively. Even though trastuzumab is a humanized mAb, it induces a relatively high incidence of infusion reactions, but bevacizumab, another humanized antibody, shows a reaction incidence of only <3% (grade 3–4, 0.2%) which is similar to the fully humanized panitumumab (3%, grade 3–4, ~1%). Elotuzumab, recently approved for the treatment of multiple myeloma, provokes infusion reactions in a large proportion of patients and needs to be given with premedication. The mechanisms of mAb-induced infusion reactions are not yet fully understood. Cytokines, especially TNF and interleukins such as IL-6, may be involved since the symptoms they produce are similar in infusion and type I allergic reactions. An important finding was the observation that the severity of infusion reactions is related to the number of circulating lymphocytes. For example, a severe reaction is thought to require a high lymphocyte count. In the early years following the release of rituximab, the first mAb approved specifically for cancer therapy in 1997, a relationship between CRS in patients and high lymphocyte counts was observed after treatment with the mAb. Patients with lymphocyte counts greater than 50 × 10^6/L experienced a severe cytokine-release syndrome shown by peaks in release of TNF and IL-6 90 min after infusion and accompanied by fever, chills, nausea, vomiting, hypotension, dyspnea, an increase in liver enzymes and prolongation of the prothrombin time. When used to treat B cell cancers, the frequency and severity of first-dose reactions to rituximab were shown to be dependent on the initial number of circulating tumor cells—patients with counts exceeding 50 × 10^6/L experienced more adverse reactions than patients with lesser numbers of peripheral tumor cells. CRS may be seen after use of mAbs such as rituximab to treat malignant immune cells. It is thought that the systemic inflammatory response produced together with a high fever is a consequence of antibody binding to, and activating, the cells. The distinguishing features in the literature between CRS and severe infusion reactions are often not clear, and in many reported cases, the two designations may be interchangeable.

14.2.2.7 Tumor Lysis Syndrome

Depending on the anticancer agent used and the tumor load, within 48–72 h of starting therapy, large numbers of malignant cells may be destroyed in a short time resulting in hyperkalemia, hypercalcemia, hyperphosphatemia, and hyperuricemia. Especially in patients with high tumor load, this can produce profound ionic imbalances in potassium, calcium phosphate, and uric acid and progress to acute renal failure, cardiac arrhythmias, seizures, and death. Known as tumor lysis syndrome (TLS) and, unlike CRS, the response is easy to distinguish from type I immediate hypersensitivity reactions. TLS usually occurs in patients with leukemias and high-grade lymphomas and is rarely seen in association with solid tumors. The syndrome is well-known to occur with the use of the CD20-targeted mAbs and brentuximab vedotin targeted to CD30, but the reaction elicited by rituximab appears to be somewhat atypical and remains to be further characterized. The FDA has issued a TLS boxed warning for
rituximab and warnings and precautions for obinutuzumab, brentuximab vedotin, blinatumomab, and polatuzumab vedotin-piiq (Table 14.4).

**14.2.2.8 Capillary Leak Syndrome**
Capillary leak syndrome (CLS), also known as systemic capillary leak syndrome, vascular leak syndrome, or Clarkson’s disease, manifests as an increase in body weight, malaise, weakness, and sometimes abdominal pain, myalgia, pyrexia, vomiting, and diarrhea. Symptoms are variable and causes not well understood. An example of the condition may be seen following infusion of interleukin (IL)-2 for metastatic cancer. Within 24 h there is an increase in vascular permeability accompanied by extravasation of fluids and proteins resulting in peripheral and interstitial edema, pleural and pericardial effusions, ascites, and, in severe form, pulmonary and cardiovascular failure. Complications such as renal failure, stroke, ischemia, deep vein thrombosis, and rhabdomyolysis may occur. Erythematous cutaneous eruptions that often accompany the syndrome may be induced by cytokine activation of endothelial cells, and it has been suggested that these cells may have a role in the events underlying the syndrome. Monoclonal antibodies implicated in CLS include bevacizumab and dinutuximab.

**14.2.2.9 Systemic Inflammatory Response Syndrome**
Systemic inflammatory response syndrome (SIRS) is a serious systemic inflammatory disorder related to sepsis with the potential to cause organ dysfunction and failure. It may be caused by an infection or variety of noninfectious stimuli such as ischemia, trauma, pancreatitis, hemorrhage, adrenal insufficiency, anaphylaxis, or therapy, including treatments with biologic agents. SIRS may be diagnosed on the basis of two or more manifestations related to body temperature, heart rate, tachypnea, and white blood cell count. SIRS without infection may involve renal failure, deep vein thrombosis, disseminated intravascular coagulation, gastrointestinal bleeding, anemia, and hyperglycemia. In the early events in SIRS following trauma, infection, or other relevant stimuli, an inflammatory cascade is activated producing a multitude of cytokines, in particular, the proinflammatory cytokines IL-1, TNF, IL-6, IL-8, and IFN gamma. Infections stimulate the release of more TNF which in turn leads to more IL-6 and IL-8 and a higher rate of fever than is seen with trauma-induced SIRS. SIRS has been reported following infusion of catumaxomab and eculizumab.

**14.2.2.10 Progressive Multifocal Leukoencephalopathy**
The polyomavirus JC virus which persists asymptptomatically in about one third of the population causes progressive multifocal leukoencephalopathy (PML) in severely immunodeficient individuals such as transplant and AIDS patients. PML is a progressive, usually fatal, disease resembling multiple sclerosis in which the myelin sheath of nerve cells is destroyed affecting nerve transmission. Although rare, the disease is occasionally seen after administration of some mAbs directed to B cells, in particular, rituximab, obinutuzumab, and brentuximab vedotin, and there are currently FDA boxed warnings for potentially fatal PML in patients treated with these mAbs and a warning for ofatumumab and polatuzumab vedotin-piiq (Table 14.4). In 2009, 57 cases of PML following rituximab therapy in HIV-negative patients were reported. A 2010 report of the WHO Collaborating Centre for International Drug Monitoring Adverse Event Data Bank revealed that rituximab was responsible for 114 of 182 cases of PML.

**14.3 Summary**

- Specific targeting of tumor cells without inflicting collateral damage on normal healthy cells has been, and remains, a long-standing aim in cancer therapy. In what has been the mainstay of therapy, the administration of small cytotoxic molecules used with, or without, radiation therapy to kill rapidly dividing cells, often adversely affects normal, healthy cells such as mucosal lining cells and those in the bone marrow and hair follicles.
- Here, targeted drugs have been divided into the natural or synthetic “small” molecules (i.e., generally MW ≤ 1 kDa; often called “chemotherapy” drugs) and the biologics.
- Effective targeting of tumor cells without accompanying toxicity has started to be realized with the introduction of signal transduction therapies and mAbs.
- Signal transduction involves the utilization of biochemically induced signals generated by a range of large and small molecules such as growth factors, neurotransmitters, hormones, cytokines, chemokines, and ATP, to produce a wide variety of cell responses like cell division, metabolic changes, gene expression, and cell death.
- The first signaling proteins to be utilized as targets for a new generation of unique anticancer drugs were protein kinases. Kinases transfer a γ-phosphate group (PO₃²⁻) from adenosine triphosphate to the hydroxyl group of tyrosine on signal transduction molecules (proteins), thus maintaining cellular functions.
- Overexpression, dysregulation, and mutations of protein kinases involve them in the pathogenesis of many diseases including an association with oncogenesis.
- At March 2019, the US FDA had approved 48 small molecule protein kinase inhibitors.
- The Philadelphia translocation t(9;22) (q34;q11) or Philadelphia chromosome is a chromosomal defect resulting in gene fusion of the BCR and ABL genes. The resultant fusion gene is the BCR-ABL oncogene. The Philadelphia chromosome is a cytogenetic abnormality seen in 95% of chronic myeloid leukemia patients and 15–30% of adults with acute lymphoblastic leukemia.
- The drug imatinib mesylate which inhibits both the ABL and BCR-ABL tyrosine kinases has been successful in treating chronic myeloid leukemia.
- In addition to imatinib, some inhibitors of receptor tyrosine kinases targeting epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptors (VEGFR), and platelet-derived growth factor receptors (PDGFR) have been found to have antitumor and/or other activities.
- For most of the tyrosine kinase inhibitors targeting the EGFR, papulopustular rash, hand-foot skin reaction, pigmentary changes, xerosis, pruritus, and mouth, hair, scalp and nail abnormalities are the primary adverse events.
- Imatinib is generally well tolerated especially when compared to most cytotoxic chemotherapies. Patients receiving standard-dose imatinib therapy in the chronic phase of chronic myeloid leukemia experience neutropenia in 35–45% of cases, thrombocytopenia in 20%, and anemia in 10% of cases.
- Although most cutaneous reactions to imatinib are mild and dose dependent, severe reactions such as SJS, exfoliative dermatitis, TEN, AGEP, DRESS, and lichenoid eruptions have been reported.
- Gefitinib and erlotinib are EGFR inhibitors, inhibiting the receptor’s tyrosine kinase domain by binding to the ATP-binding site of the enzyme. EGFR is overexpressed by the cells of some cancers such as lung and breast leading to uncontrolled cell proliferation.
- The most frequent adverse reactions to gefitinib are diarrhea and skin reactions. The main adverse responses to erlotinib include rash, diarrhea, anorexia, ocular effects, and stomatitis. The FDA has referred to rare serious gastrointestinal, skin, and ocular disorders in some patients taking erlotinib.
- As with other tyrosine kinase inhibitors, papulopustular rash, hand-foot skin reaction, and pigmentary changes are commonly seen with gefitinib and erlotinib.
- Inhibition of the EGFR in skin often produces xerosis, skin fissures, nail alterations, paronychia, periungual ulcers, and pruritus.
- Bortezomib, an N-protected dipeptide that contains a boron atom, inhibits proteasomes by binding via the boron atom to the catalytic site of the 26S proteasome with high affinity. This ultimately leads to the killing of multiple myeloma cells.
- Gastrointestinal symptoms, thrombocytopenia, peripheral neuropathy, and neuropathic pain are the most common side effects of bortezomib. Adverse cutaneous reactions to the drug are numerous – rash is frequently reported in more than 10% of patients.
- Cutaneous adverse drug reactions to bortezomib include Sweet’s syndrome, ulceration, leukocytoclastic vasculitis, morbilliform exan-
thema, folliculitis-like rash, erythematous nodules and plaques, and perivascular dermatitis.

- Carfilzomib, a tetrapeptide epoxyketone, is structurally and mechanistically different to bortezomib.

- Adverse reactions to carfilzomib include pulmonary hypertension, dyspnea, cardiac toxicities, cytopenias, infusion reactions, venous thrombosis, hemorrhage, tumor lysis syndrome, hepatotoxicity, posterior reversible encephalopathy syndrome, acute renal failure, rash, and urticaria.

- Like bortezomib, ixazomib (MLN9708) is also a peptide boronate, but it is orally active with a shorter half-life and shows greater tissue penetration. FDA warnings and precautions for the drug relate to thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy, hepatotoxicity, and cutaneous reactions.

- Other promising proteosome inhibitors are the γ-lactam-β-lactone bicyclic marizomib and orally active oprozomib which shows similarities to carfilzomib and bortezomib.

- Serine/threonine mTOR kinase belongs to the phosphoinositide 3-kinase (PIK3)-related family. mTOR inhibitors (e.g., everolimus), are associated with a considerable number of adverse events including interstitial lung disease, mucositis, hyperglycemia, new-onset diabetes mellitus, hyperlipidemia with increased levels of cholesterol and triglycerides, and reproduction effects.

- Histone deacetylase inhibitors (HDACIs) lead to differentiation, cell-cycle arrest and inhibition of migration, invasion, and angiogenesis in many different cancer cells.

- Myelosuppression involving thrombocytopenia, leukopenia, and anemia induced by romidepsin, vorinostat, belinostat, and panobinostat HDACIs is a frequent and often severe adverse event sometimes leading to serious hemorrhage and infection. Cardiac effects may occur, especially with QTc prolongation induced by vorinostat, and panobinostat has an FDA Boxed Warning for diarrhea.

- Expression of the PML/RARA oncprotein is diagnostic of promyelocytic leukemia (PML) and is downregulated in response to all-trans retinoic acid (tRA; ATRA; tretinoin). Approved for PML cases resistant to tRA, arsenic trioxide targets the PML moiety of PML/RARA protein.

- Retinoic acid syndrome is a potentially fatal side effect of acute PML. The syndrome occurs in about one quarter of acute promyelocytic leukemia patients treated with tRA and/or arsenic trioxide. Symptoms include fever, hypotension, weight gain, dyspnea with pulmonary infiltrates, pleuroperticardial effusion, and renal failure. The syndrome is called differentiation syndrome since it occurs in patients previously treated with arsenic trioxide but not in patients treated with tRA for other disorders.

- The synthetic retinoic X receptor (RXR) agonist bexarotene, an oral retinoid therapy, is approved for the treatment of cutaneous T cell lymphoma. Side effects include hypothyroidism, hypertriglyceridemia, and hypercholesterolemia.

- Hormone therapy for some cancers such as breast and prostate can be as potent and effective as many other cancer treatments. Symptoms induced by the administered hormone or analog may cause nausea, muscle and joint pain, hair loss, blood clots, and an increased risk of some cancers, for example, endometrial cancer and cancer of the uterus. Side effects in males include tiredness, hot flashes, nausea, loss of sex drive, impotence, and breast tenderness.

- At April 2020, of the currently approved 88 mAbs, 36 or 41% are indicated for the treatment of human cancers covering hematologic, solid tumor, and cutaneous malignancies.

- In achieving the wide and diverse coverage of a large variety of tumors, a range of different targets and mechanisms of action have been sought. Twenty-three different targets have been utilized so far.

- Some targets are complementary to more than one mAb: CD20 is targeted by 4 mAbs, EGFR by 3, HER2 by 3, PD-L1 by 3, PD-1 by 2, D38 by 2, and CD22 by 2.

- Mechanisms employing mAb-targeted therapies are predominately direct cytotoxic action against cancer cells, an effect on signaling
pathways, or immune modulatory effects leading to the indirect destruction of cancer cells.

- A direct cytotoxic action can be achieved by using an antibody-drug conjugate (ADC), whereby cell killing is effected by an attached bioactive payload of a potentially lethal toxin, drug, cytokine, or radionuclide. Ado-trastuzumab emtansine, brentuximab vedotin, ibrutinomab tiuxetan, inotuzumab ozogamicin, moxetumomab pasudotox-tdfk, gemtuzumab ozogamicin, polatuzumab vedotin-piiq, and sacituzumab govitecan-hziv are 8 currently approved ADCs.

- Examples of cell-destructive immune modulatory effects include antibody-dependent cell cytotoxicity (ADCC) and modulation of immune checkpoints by the targeting of inhibitory pathways regulating signaling between T cells and antigen-presenting cells. Monoclonal antibody checkpoint inhibitors are ipilimumab, nivolumab, pembrolizumab, cemiplimab-rwlc, atezolizumab, avelumab, and durvalumab.

- Cytopenias are a well-known side effect of mAbs therapy, but the underlying mechanisms frequently remain unexplored, and types II and III hypersensitivities induced by the antibodies may be underdiagnosed and underreported. Boxed warnings have been issued for the risk of severe cytopenias with ibrutinomab tiuxetan and alemtuzumab, while general warnings and precautions are set down for obinutuzumab, ofatumumab, pembrolizumab, cemiplimab-rwlc, atezolizumab, avelumab, and durvalumab.

- Apart from abciximab, targeted to platelet glycoprotein GP IIb/IIIa and not used to treat cancer, there appears to be a dearth of convincing evidence for the involvement of anti-cancer mAbs in type II hypersensitivity reactions. Rituximab-induced neutropenia is a suspected example of a mAb-induced type II hypersensitivity.

- With some mAbs, type III hypersensitivity serum sickness-like reactions are reported in up to 20% of treated patients. Cases of mAb-induced cutaneous vasculitis during treatment also occur, for example, with adalimumab.

- The checkpoint inhibitors provoke a number of immune-mediated reactions. Perhaps the most dangerous is immune-mediated, or hypersensitivity, pneumonitis, a combined type III and type IV hypersensitivity reaction. Anti-PD-1 and anti-PD-L1 therapy may induce immune-mediated colitis, hepatitis, endocrinopathies, nephritis, and thyroid reactions.

- Monoclonal antibody-induced type IV hypersensitivity reactions of the skin include allergic contact dermatitis, psoriasis, maculopapular exanthema, fixed drug eruption, acute generalized exanthematous pustulosis, erythema multiforme, DRESS, and cutaneous bullous toxidermias such as SJS and TEN. Panitumumab carries a black box warning for dermatologic toxicity. Cutaneous acneiform rash reactions that are not genuine hypersensitivities are seen with the EGFR-targeted mAbs cetuximab, panitumumab, and necitumumab.

- At least 14 of the currently approved mAbs for cancer therapy have been implicated in some form of pulmonary toxicity in treated cancer patients, but rituximab, trastuzumab, alemtuzumab, and panitumumab provoke the biggest range of pulmonary adverse events.

- Cardiac adverse events have occurred with at least 13 of the approved mAbs used for cancer therapy. Necitumumab carries an FDA black box warning for cardiopulmonary arrest. Decreases in LVEF are well-known for mAbs that block HER2 activity. The risk is increased in patients given anthracyclines or radiotherapy.

- Skin reactions after cetuximab and panitumumab often appear as a papulopustular eruption usually confined to seborrheic regions of the face, scalp, neck, shoulders, and upper trunk. Other adverse effects induced by mAbs targeted to EGFR include mucositis, xerosis, fissures, paronychia, palmar-plantar rash, hair changes, hyperkeratosis, nail pyrogenic granuloma, and skin hyperpigmentation.

- Infusion reactions provoked by mAbs usually begin within hours of the initial infusion.
Reactions typically manifest as “flu”-like symptoms. In a small number of patients, severe, life-threatening symptoms common to type I IgE antibody-mediated anaphylaxis are seen. The similarity of the symptoms can sometimes make it difficult to distinguish an infusion reaction from a true allergic hypersensitivity.

- Cytokines may be involved in infusion reactions since the symptoms they produce (called cytokine-release syndrome (CRS)) resemble those seen in type I allergic reactions. The severity of such reactions is related to the number of circulating lymphocytes. The distinguishing features between CRS and severe infusion reactions are often not clear.
- Depending on the anticancer agent used and the tumor load, large numbers of malignant cells may be destroyed in a short time resulting in hyperkalemia, hypercalcemia, hyperphosphatemia, and hyperuricemia. Known as tumor lysis syndrome (TLS) and, unlike CRS, the response is easy to distinguish from type I immediate hypersensitivity reactions. The FDA has issued a TLS boxed warning for rituximab and warnings and precautions for obinutuzumab, brentuximab vedotin, blinatumomab, and polatuzumab vedotin-piiq.
- Capillary leak syndrome, also known as vascular leak syndrome, manifests as an increase in body weight, malaise, and weakness. Symptoms are variable and causes not well understood. Within 24 h there is an increase in vascular permeability, extravasation of fluids, and proteins resulting in peripheral and interstitial edema, pleural and pericardial effusions, ascites, and, in severe form, pulmonary and cardiovascular failure. Complications such as renal failure, stroke, ischemia, deep vein thrombosis, and rhabdomyolysis may occur. Endothelial cells and cytokine release may have a role in the events underlying the syndrome. The mAbs bevacizumab and dinutuximab have been implicated.
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- Caused by the polyomavirus JC virus which persists asymptotically in about one third of the population, progressive multifocal leukoencephalopathy (PML) is a progressive, usually fatal, disease resembling multiple sclerosis in which the myelin sheath of nerve cells is destroyed affecting nerve transmission. The disease is occasionally seen after administration of some mAbs directed to B cells, in particular, rituximab, obinutuzumab, and brentuximab vedotin.

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