CHAPTER

1

Drug classification for the treatment of hematologic malignancies

Svitlana A. Husieva[a], *Olena Ya. Antonyuk*[b], *and Valeriia Husieva*[c]

[a]Ukrainian Military Medical Academy, Kyiv, Ukraine [b]Hematology Clinic of the National Military Medical Clinic Center "Main Military Clinical Hospital", Major of the Medical Service, Kyiv, Ukraine [c]Institute of Molecular Physiology and Genetics, Centre of Biosciences, Slovak Academy of Sciences, Bratislava, Slovakia

Abstract

The authors used the international classification of medications used in modern hematologic practice. The first attempt at using chemotherapy began with the introduction of deoxyribonucleic acid (DNA) alkylating drugs into clinical practice, along with antimetabolites and antitubulin agents, the activity of which was caused by mitotic band disruption and/or altered DNA replication. Despite the definite success achieved by DNA-interacting agents, they have typical myelotoxic dose-dependent effects that limit the possibility of treatment for many hematologic malignancies (HMs). An important event in onco-hematology is the development and use of targeted drugs, such as highly specific small molecules and monoclonal antibodies (mAbs) that inhibit molecular targets involved in the growth and spread of malignant cells, as antitumor agents in clinical practice. An important development in hematology for the treatment of HMs was the introduction of mAbs into clinical practice. Following the successful use of anti-CD20 (rituximab) therapy, various modifications, including the currently approved immunotoxin and one bispecific mAb, have been developed to improve the therapeutic efficacy of mAbs. The Food and Drug Administration approved the world's first genetically modified chimeric antigen receptor T therapy in the past decade. Chimeric antigen receptor T-cells are significantly different from other anticancer drugs due to their ability to proliferate and expand. They can persist in the patient's blood for months or even years and, for this reason, are called "live drugs." Chimeric antigen receptor T-cells are the most promising type of anticancer therapy, especially for patients with relapsed or refractory HMs who do not respond to standard therapy. New medications are still being developed due to the need to reduce adverse effects and improve the management of HMs.

Abbreviations

ABVD chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine
ADCC antibody-dependent cell-mediated cytotoxicity

Copyright © 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

ADCP	antibody-dependent cellular phagocytosis
AEs	adverse events
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
AZA	azacitidine
BCMA	B-cell mature antigen
BEN	bendamustine
bsAb	bispecific antibody
BTK	Bruton's tyrosine kinase
BTZ	bortezomib
CAR-T	chimeric antigen receptor-T
CFZ	carfilzomib
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CR	complete remission
CRh	partial hematologic recovery
CRi	incomplete hematologic recovery
CTCL	cutaneous T-cell lymphoma
DEX	dexamethasone
DLBCL	diffuse large B-cell lymphoma
DOX	doxorubicin
EMA	the European Medicines Agency
FDA	Food and Drug Administration
FL	follicular lymphoma
IFN	interferon
IL	interleukin
IMiDs	immunomodulatory drugs
HCT	hematopoietic cell transplantation
HDACis	pan-histone deacetylase inhibitors
HL	Hodgkin lymphoma
HM	hematologic malignancy
LPD	lymphoproliferative disorder
mAbs	monoclonal antibodies
MCL	mantle cell lymphoma
MDR	multidrug resistance
MDS	myelodysplastic syndrome
MM	multiple myeloma
MOPP	chemotherapy with chloromethine, vincristine, procarbazine, and prednisolone
mOS	median overall survival
mPFS	median progression-free survival
MZL	marginal zone B-cell lymphoma
ORR	overall response rate
OS	overall survival
PD-1	programmed death-1
PFS	progression-free survival
Ph+	Philadelphia chromosome-positive
PMF	primary myelofibrosis
PTCL	peripheral T-cell lymphoma
NHL	non-Hodgkin lymphoma
NK	natural killer cells
R	rituximab
RR	relapsed/refractory
sCR	stringent complete response
SMI	small-molecule inhibitor

STC stem cell transplantation
TKs tyrosine kinases
TKI tyrosine kinase inhibitor
TNF tumor necrosis factor
VCR vincristine
VEGF vascular endothelial growth factor
VEN venetoclax
VGPR very good partial response

Conflict of interest

The authors declare the absence of conflicts of interest.

Introduction

Chemotherapy is an effective treatment method for patients with hematologic malignancies (HMs), a group of diseases affecting blood, marrow, and lymphatic nodules. These diseases are classified into two types: lymphoid and myeloid [1]. Despite the undoubted success in the treatment of these diseases, some patients have a high risk of death. This risk is due to the large number of disease subtypes, high heterogeneity, primary refractoriness, and progression with early or multiple relapses. This category of patients seems to be the most difficult in terms of achieving an antitumor effect, since some tumor cells may be resistant to cytostatic drugs even before the start of therapy.

Different forms of multidrug resistance (MDR) have been proposed, each corresponding to different approaches to overcome MDR: substituting the current chemotherapy regimen with a more potent regimen, employing high-dose chemotherapy coupled with hematopoietic stem cell transplantation (SCT), utilizing noncytostatic therapeutic drugs, and employing other methods that actively influence the apoptosis of tumor cells. Drugs used to treat HMs can be divided into two groups according to their mechanism of action: deoxyribonucleic acid (DNA)-interacting agents and molecularly targeted agents, such as highly specific small molecules and monoclonal antibodies (mAbs) [2,3].

This chapter provides a brief overview of the drugs adopted by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in recent decades for the treatment of patients with HMs.

DNA-interacting agents are the oldest group of anticancer agents and can be divided into alkylating agents, cross-linking agents, intercalating agents, DNA topoisomerase inhibitors, and DNA-cleaving agents. The first alkylating agent approved by the FDA in 1949 was chloromethamine (mechlorethamine). This drug is used to treat lymphoma and leukemia. Folic acid antagonists (antifolates) became the next class of drugs for the treatment of HMs [3]. In 1948, Farber [4] reported the use of aminopterin (a derivative of folic acid) to treat children with acute leukemia. Subsequently, methotrexate (ametopterin), which has a better ratio of therapeutic efficacy to toxicity, was introduced into clinical practice for the treatment of solid and hematologic neoplasia. Later, mercaptopurine was discovered as the first structural analog of purine.

Thus folate, purine, and pyrimidine antagonists constitute one of the oldest classes of anticancer drugs, that is, antimetabolites. Natural plant alkaloids with antitubulin activity (vinca alkaloids) have become other useful agents in the treatment of HMs. Other natural

products include cytotoxic antibiotics such as bleomycin and doxorubicin (DOX). Bleomycin was the first approved DNA-cleaving agent. This drug is used to treat malignant lymphomas [5]. DOX was approved by the FDA in 1974 and has shown antitumor activity in the treatment of various HMs through multiple mechanisms, including intercalation into DNA and inhibition of topoisomerase II activity [6]. Four years later (1978), the FDA approved cisplatin, which inhibits cell division by cross-linking purine bases, preferentially guanines. Cisplatin was subsequently tested against a wide range of cancers and exhibited potent antitumor activity. Imatinib, the first small-molecule inhibitor (SMI) of several tyrosine protein kinases, is indicated primarily for the treatment of patients with chronic myeloid leukemia (CML) [3].

An important step in the development of onco-hematologic treatment is the introduction of targeted therapy with effective SMIs or with specific mAbs after humanization. An important development in hematology for treating HMs has been the introduction of mAbs into clinical practice. The first mAb approved by the FDA in 1997 for the treatment of relapsed or refractory B-cell lymphoma, poorly differentiated lymphoma, or follicular non-Hodgkin lymphoma (NHL) was rituximab (R) (anti-CD20) [7].

Finally, the FDA and EMA approved the first therapy using genetically modified T-cells, known as chimeric antigen receptor T (CAR-T) therapy. Cellular therapies, including CAR-T cells, have the advantage of remaining in the body for long periods of time, allowing them to proliferate and expand. This property has earned them the nickname "living drugs" because they can remain in a patient's bloodstream for months or even years. CAR-T cells represent a promising form of antitumor therapy, particularly for patients with relapsed or refractory HMs who do not respond to standard treatments [8–10]. According to focused research, their application in the treatment of solid tumors could be expected. Chemotherapy is one of the most important methods for treating onco-hematologic diseases. Various chemotherapeutic agents, including alkylating agents, antimetabolites, antitumor antibiotics, antimitogenic drugs, and topoisomerase inhibitors, are used in modern hematology.

Chemotherapeutic drugs

Alkylating agents

The first drugs that began to be used to treat tumors were alkylating agents [11]. Alkylating agents cause damage to DNA and RNA through alkylation of the guanine backbone at the nitrogen atom at position 7. As a result, cross-links and DNA breaks are formed, the replication process is disrupted, mutations occur, and cells die [12].

This process leads to a disruption of the DNA structure and the inability of malignant cells to undergo mitosis. This process, in turn, triggers the apoptosis mechanism in damaged cells. The cytostatic effect of alkylating agents occurs regardless of the phase of the cell cycle. Several alkylating agents have been developed. They are chlorethinamine derivatives, aziridine derivatives, disulfonic acid esters, nitrosourea derivatives, triazines, platinum complexes, and several more recently developed groups. The first alkylating agent approved by the FDA was nitrogen mustard **mechlorethamine (*chlormethine*)** [3]. Currently, chloroethyl amine derivatives have a broad spectrum of action and are used to treat chronic lymphoproliferative disorders (LPDs).

Alkylating agents have been developed whose antitumor effects require their transformation into active metabolites in cells. In tumor cells, the concentration and activity of the necessary enzymes that "transform" the inactive prodrug into its active form are usually significantly higher than those in healthy tissues. This property substantially expands the antitumor action of these drugs on different types of tumors compared with the spectrum of action of "nonspecific" alkylating drugs, such as **mechlorethamine** and **chlorambucil**. This mechanism is precisely the principle of action of alkylating medications from the group of **chloroethylamine derivatives** (the so-called "phosphoramide mustard"): **cyclophosphamide**, **ifosfamide,** etc. **Cyclophosphamide** undergoes biological transformation by enzymes such as phosphatases in malignant cells. These drugs are metabolized in the liver by cytochrome P450 [13]. The intermediates phosphoramide mustard and acrolein are cytotoxic. A typical complication of this group of cytostatics is hemorrhagic cystitis leading to fibrosis of the bladder.

Several alkylating agents have been specially synthesized so that the active alkylating group (in most cases, a bis-β-chloroethylamine group) is combined with one or another body metabolite, the need for which has increased in cancer cells [13]. Thus **melphalan**, which is widely used in LPD and multiple myeloma (MM) [14], was synthesized. Agents in which an alkylating group is combined with a hormonally active substance to selectively act on the DNA of cells expressing specific hormone receptors have been synthesized.

Dialkylating alkylating agents can simultaneously react with two different 7-N-guanine nucleotide residues of the DNA molecule they attack [15]. If the attacked 7-N-guanine bases are on different strands of double-stranded DNA, a cross-link forms between the two DNA strands. This cross-linking leads to the impossibility of unfolding the DNA molecule and dividing the helix into two strands. As a result, the cell, deprived of the ability to divide, starts the process of apoptosis. If two 7-N-guanine residues with which the alkylating agent molecule reacts are located on the same DNA strand, "intrastrand binding" of DNA occurs, which disrupts the spatial structure of DNA and its function [16]. A classic example of an alkylating agent is **busulfan**; the main indication for its use is CML [13]. *Monoalkylating agents* can react with one molecule only with one 7-N atom of one guanine residue. Unlike dialkylation, neither intrastrand binding nor monoalkylation can prevent double-stranded DNA from unfolding and separating. However, both prevent enzymes vital for the division process from gaining access to DNA. This effect inhibits or suppresses tumor growth and/or stimulates apoptosis [15]. Monoalkylating drugs include **Leukeran** [16].

Nitrosourea derivatives include **carmustine** and **lomustine.** The mechanism of action of **carmustine** is the action of active metabolites on tumor cells through alkylation, resulting in the formation of breaks and cross-linking of the DNA of malignant cells, which leads to the arrest of mitosis and possibly DNA replication. In combination with prednisone, **carmustin**e is used for Hodgkin lymphoma (HL) and NHL [16].

Platinum complex compounds are sometimes classified as a separate group, but their mechanism of action is the same as that of other representative alkylating agents. In 1965, Rosenberg et al. discovered that cisplatin, a platinum coordination complex, inhibited cell division [17]. **Cisplatin** was introduced into trials against a wide range of tumor types, where it showed antitumor activity by cross-linking DNA. The drug was approved by the FDA in 1978 and has since been in use as a first-line treatment for patients with various forms of HMs. **A representative triazine** is **dacarbazine**, and its antitumor effect is due to the active

metabolite 5-aminoimidazole-4-carboxamide, which forms methyl carbon ions that bind nucleophiles in the DNA molecule**. Dacarbazine** is used to treat patients with advanced-stage HL who are considered incurable. The introduction of poly-chemotherapy according to the MOPP regimen [chloromethine, vincristine (VCR), procarbazine, and prednisolone] [18] into medical practice led to favorable treatment results in approximately 50% of patients with late-stage HL.

The dose-limiting toxicity of all representative alkylating agents is the inhibition of hematopoiesis, which is often persistent. The use of these drugs can have mutagenic and teratogenic effects. The development of secondary leukemia is possible. The most common undesirable effects are nausea, vomiting, and sometimes alopecia and dry skin [11].

Antimetabolites

As a result of the work on folic acid antagonists conducted by S. Farber, antifolates were developed. One of these drugs is **aminopterin** (4-aminofolic acid), which is used for the treatment of children with acute leukemia [4]. Then, **mercaptopurine** and **fluorouraci**l were developed as the first structural analogs of purines and pyrimidines. **Mercaptopurine** was synthesized by Elion et al. in 1952 [19] and was first approved by the FDA in 1953 [20], while **fluorouracil** has been used in practice since 1962. These drugs are widely used for the treatment of HMs, such as acute leukemia [4]. **Mercaptopurine** was commercially available only as 50 mg tablets until 2014, when the FDA approved a new liquid formula, **mercaptopurine (PURIXAN)** [21]. **PURIXAN** is a 20 mg/mL oral suspension indicated for treating patients with acute lymphoblastic leukemia (ALL) as part of a combined treatment. This drug causes a delay in DNA synthesis without disrupting the synthesis of RNA. Researchers believe that the selective (selective) antimetabolic (opposite to the action of metabolites—natural metabolic products in the body) effect is associated with a disruption of the enzymatic conversion of ribonucleotides into deoxyribonucleotides. Additionally, hydroxyurea may delay the incorporation of thymidine into DNA.

Bendamustine (**BEN**) was first considered a synthetic alkylating agent for use in patients with refractory and relapsed HL. Recently, it has been characterized by the terminological oxymoron "new old" drug [22]. **BEN** is a drug that combines the properties of an alkylating agent and an antimetabolite [23]. **BEN** is widely used to treat chronic lymphocytic leukemia (CLL) [24–28], NHL [29–31] and MM [32,33]. In the United States, the drug was approved in March 2008 as a first-line treatment for patients with CLL and for the treatment of NHL. The **BEN** molecule consists of three structural elements: a mechlorethamine group, a benzimidazole ring, and butyric acid. Mechlorethamine (mustargen) has alkylating properties similar to those of cyclophosphamide and chlorambucil. The benzimidazole ring, which replaces the benzene ring as in the chlorambucil molecule, has antimetabolic activity identical to that of the purine analogs. Finally, the hydroxylated butyric acid chain provides water solubility [23]. The mechanism of action of **BEN** is not completely clear [34]. Molecular studies have revealed the differences between **BEN** and traditional alkylating agents and their multifunctional effects on tumor cells [35].

For less than two decades, BEN has been confirmed to be a highly effective treatment for CLL and indolent lymphomas [36]. As a bifunctional anticancer drug with alkylating activity and additional antimetabolic properties [37], **BEN** has pronounced antiproliferative and proapoptotic effects on quiescent and dividing malignant cells, regardless of the status of

the p53 gene. In this case, the cells die due to the arrest of the cell division cycle at the control point G2/M and mitotic catastrophe [34].

The drug initiates "classical" p53-dependent apoptosis. Nevertheless, its unique feature is more pronounced and faster formation of an intracellular proapoptotic signal, irreparable DNA damage, and inhibition of several mitotic checkpoints, ultimately leading to mitotic catastrophe. Along with the robust activation of the "classical" cascade of programmed cell death, including alternative cell death through mitotic catastrophe, parallel induction may explain the high effectiveness of **BEN** in treating patients with refractory courses of various types of lymphomas [25]. The leading role of this powerful proapoptotic drug is the presence of additional antimetabolic agents with a purine-like effect. The effect of **BEN** on intracellular signal transduction cascades at the molecular level leads to necrosis and p53-dependent and p53-independent apoptosis in target cells through DNA alkylation [26]. In vitro evidence that **BEN** and **R** exhibit synergistic effects [27] allowed the introduction of this regimen into clinical practice as a "rescue" therapy. In addition, this immuno-chemotherapy regimen has shown to be a highly effective anticancer therapy for patients with progression of HL after high-dose chemotherapy with autoSCT and for patients with continuously relapsing disease [28]. **BEN** is combined with **etoposide**, **cytarabine**, and **melphalan** (**BeEAM** scheme) as a conditioning regimen in patients with refractory/recurrent (RR) NHL. **BEN** has been successfully used as part of chemotherapy regimens such as **BR** (**BEN + R**) [38], **R-BAC** (**R + BEN + cytarabin**e), **VBR (R + BEN + bortezomib**), and others for the treatment of chronic LPD.

Natural alkaloids with antitubulin activity

Natural alkaloids with antitubulin activity have received good clinical evaluations and were approved by the FDA in 1963 as a therapy for various HMs. R. L. Noble isolated the first two vinca alkaloids, **vinblastine** and **VCR**, which bind to tubulin proteins and thus inhibit their polymerization in microtubules [39].

Changes in microtubule structure cause the breakdown of the mitotic spindle and the accumulation of chromosomes, leading to the activation of apoptotic pathways and cell death (Fig. 1). A new VCR formulation for the treatment of adults with rare leukemias (pH-negative ALL) is vincristine sulfate encapsulated in sphingomyelin and cholesterol-based nanoparticles (vincristine sulfate liposome injection; MARQIBO). **Vincristine sulfate liposome injection** comprises a unique slow-release liposomal system suitable for **VCR** delivery and dose enhancement. The liposomal carrier prolongs the circulation time of the drug, optimizes delivery to target tissues, and increases the therapeutic index [40].

Cytotoxic antibiotics

Other natural products include **cytotoxic antibiotics** such as **bleomycin** and **DOX**. **Bleomycin** was the first DNA cleavage agent registered in 1973 [5] for treating NHL, and **DOX** was first approved by the FDA in 1974 [40]. The drug showed antitumor activity through several mechanisms, including intercalation into DNA and inhibition of topoisomerase II activity. **DOX** entered clinical practice as part of the ABVD regimen (DOX, bleomycin, vinblastine, and dacarbazine) in 1975 [41]. This treatment option was recommended for patients who experienced HL relapse after first-line MOPP therapy. The choice of drugs was determined

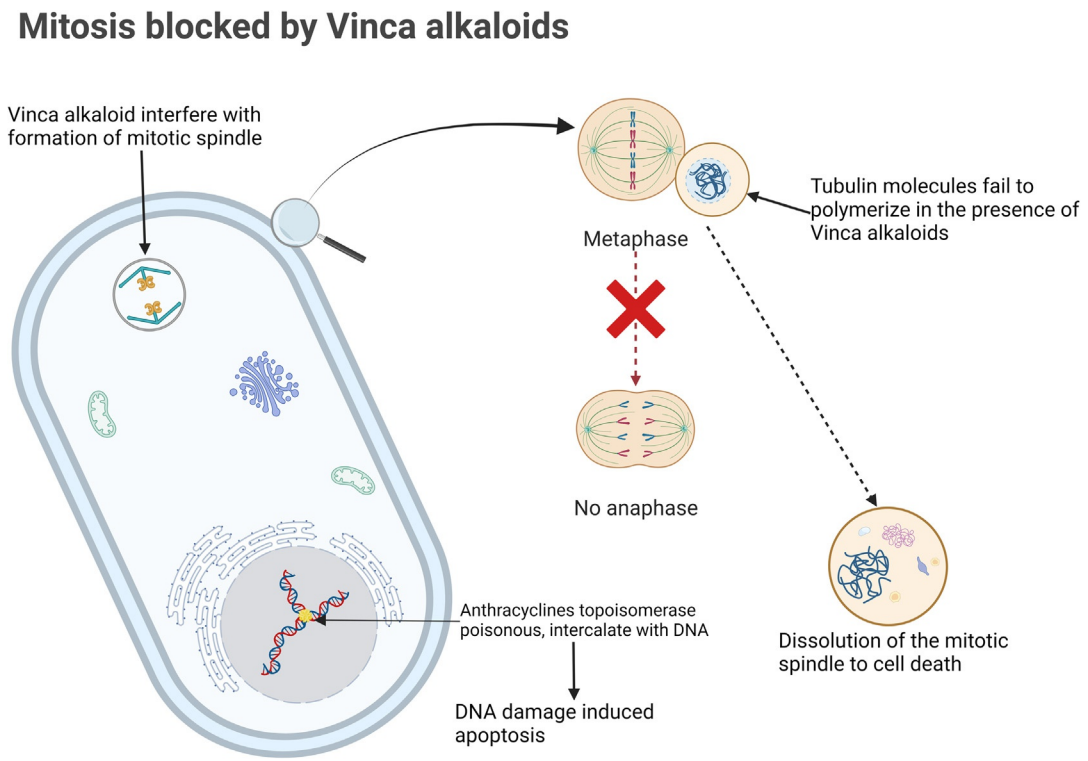


FIG. 1 The schematic representation of the mitosis blocked by Vinca alkaloid. The vinca alkaloid's cytotoxicity is due to its synergy with tubulin and disruption of microtubule activity. This primarily happens in the microtubules that comprise the mitotic spindles, resulting in a halt in the metaphase phase of the cell cycle.

because **vinblastine**, a natural alkaloid with antitubulin activity, has shown high efficacy as a monotherapy for several malignant neoplasms and is not cross-resistant to other cytostatics. **DOX** and bleomycin are known to be effective antitumor drugs. These agents produce a positive response to treatment in approximately 50% of patients, and dacarbazine was added to the regimen as an effective drug in monotherapy and in synergistic therapy with **DOX** [41–43]. An analysis of treatment results using three courses of ABVD or MOPP followed by radiation therapy revealed the advantage of the ABVD regimen over the MOPP regimen: survival and freedom from progression for ABVD were 81% versus 63% for MOPP [44,45]. Subsequent multicenter studies showed that the effectiveness of the MOPP and ABVD regimens and their combination is approximately 80%–90%. At the same time, the rates of freedom from treatment failure and overall survival (OS) at the 5-year follow-up were only 65%–70% and 75%–85%, respectively [45,46]. The hybrid MOPP/ABV regimen (chlormethine, VCR, procarbazine, prednisone, DOX, bleomycin, and vinblastine) was compared with the alternating MOPP/ABVD regimen and two sequential courses of MOPP and ABVD. The efficacy of the ABVD regimen is similar to that of the MOPP/ABV regimen. Nevertheless, at the same time, it is less toxic [42,47,48]. The Stanford V regimen (DOX, vinblastine, chlormethine, bleomycin, VCR, etoposide, and prednisolone) was created according to a regimen with reduced toxicity. The

5-year event-free survival rate in this centralized training group was 89%, and the OS rate was 96% at a median follow-up of 5.4 years [49]. DOX has been widely used to treat HMs [50].

Fixed-dose combination drugs

Almost 40 years later, **fixed-dose combination drugs**, which are combinations of two or more active agents and are a promising strategy for antitumor therapy, have been synthesized and approved by the FDA as anticancer agents since all their ingredients act on the target malignant cell simultaneously through different mechanisms. Disruption of the cell cycle in different phases leads to better suppression of malignant cells.

VYXEOS is the first FDA-approved liposomal encapsulation formulation. It consists of **cytarabine** and **daunorubicin** at a molar ratio of 5:1, which are enclosed in liposomes. After the liposome is destroyed during the internalization of the drug into the target cells, **cytarabine** and **daunorubicine** enter the cell. **Cytarabine**, a pyrimidine nucleoside analog approved in 1969, is incorporated into DNA and inhibits DNA synthesis in the S phase of the cell cycle, followed by apoptosis [51,52]. **Daunorubicine,** an anthracycline antibiotic approved for medical use in 1979, inhibits DNA **synthesis** by intercalating and blocking topoisomerase II activity [53]. Both drugs work synergistically to induce the death of leukemic cells. **VYXEOS** produced a clinically significant improvement in OS compared with conventional chemotherapy in scheme "**7 + 3**" (**cytarabine and daunorubicine)** in adults with different forms of acute myeloid leukemia (AML) [54,55]. CLTR0310-301, a multicenter, randomized, phase III trial of liposomal VYXEOS injection compared with a standard "7 + 3" regimen in patients aged 60–75 years with untreated high-risk AML showed a statistically significant difference in OS between the two groups. OS was more than double at 5 years of treatment with VYXEOS (18%) versus "7 + 3" (8%). The median overall survival (mOS) was 9.56 months in the VYXEOS group compared with 5.95 months for standard chemotherapy, reducing the risk of death by 31% [54,55]. While cancer therapy might increase survival time, it can also lead to major adverse events (AEs) that negatively impact patients' quality of life. The most common side effects were hypersensitivity, including rash, febrile neutropenia, edema, diarrhea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, and decreased appetite [56].

Small-molecule anticancer drugs

Tyrosine kinase inhibitors

The next agents for treating HMs are inhibitors of various kinases. **Tyrosine kinases (TKs)** are enzymes that selectively phosphorylate the hydroxyl groups of tyrosine residues in various proteins using ATP and are involved in regulating growth, differentiation, proliferation, migration, cell metabolism, and apoptosis. **Imatinib** was the first SMI to be selective for various protein TKs. It was synthesized by Buchdunger in 1996 and approved by the FDA in 2001. The indications for usage are newly diagnosed adult and pediatric patients with Philadelphia chromosome-positive (Ph+), BCR-ABL fused gene-positive CML (Ph+cCML) in the chronic phase; patients with Ph+ CML in the blast crisis, accelerated phase, or chronic phase after the failure of interferon-alpha therapy; adult patients with RR Ph+ or Ph+ ALL, pediatric

patients with newly diagnosed Ph+ ALL in combination with chemotherapy; and adult patients with hypereosinophilic syndrome and chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH evidence of CHIC2 allele deletion) [57–62]. The main AEs of **imatinib** that require medical attention are bleeding problems; bloating or swelling of the face, hands, lower legs, and feet; chest pain; chills; cough; decreased urination; painful or difficult urination; fever; pale skin; rapid weight gain; weight loss; shortness of breath or trouble breathing on exertion; convulsions (seizures); muscle pain or cramps; nausea and vomiting; chest tightness; wheezing; bone pain; loose stools; constipation; headache; joint pain; and night sweats [63].

Recently, the FDA and EMA have approved four new drugs known as TK inhibitors (TKIs). These drugs include agents that target the nonreceptor Bruton TK (BTK) or nonreceptor sarcoma and Abelson kinases. **Ibrutinib** [64,65], **acalabrutinib** [66], and **zanubrutinib** were developed as second-line therapies for treating mantle cell lymphoma (MCL) [67].

The mechanism of action of these drugs is the irreversible inhibition of BTK activity. This inhibition results in the blockade of B-cell antigen receptor signaling [i.e., nuclear factor of activated T-cell pathway, nuclear factor kappa light chain enhancer of activated B-cells (NF-κB) pathway, and mitogen-activated protein kinase pathway]. As a result of these processes, the proliferation and survival of malignant B-cells are impaired [67–69]. The overall response rate (ORR) for the use of a TKI (ibrutinib) was 62% (CR—14%) [70]. The most common AEs leading to treatment interruption or discontinuation in ibrutinib-treated patients with CLL are atrial fibrillation, infections, and cytopenias, as well as joint/bone pain, muscle cramps, and hypertension [71].

To date, **ibrutinib** has been used as a therapy for patients with Waldenström macroglobulinemia [72] and CLL with a deletion of chromosome 17 (17p deletion) [71]. In 2019, the FDA approved **ibrutinib** in combination with **obinutuzumab**, an anti-CD20 mAb, as the first regimen for patients with previously untreated CLL [73]. **Acalabrutinib** is a second-generation, highly selective, potent, covalent BTK inhibitor that exhibits minimal off-target activity in in vitro assays, providing the potential to improve tolerability over the first-in-class BTK inhibitor ibrutinib [66,74]. The FDA approved acalabrutinib for treating RR MCL and CLL in the US in 2017 and 2019, respectively. **Acalabrutinib** is also undergoing trials for other B-cell malignancies, both as a monotherapy and in combination therapy [75–80].

Bosutinib is a dual inhibitor of nonreceptor sarcoma and Abelson kinases [81]. It is approved for the treatment of patients with Ph+ CML who are resistant or intolerant to prior therapy [82,83]. Preclinical and clinical data on the use of **bosutinib** in both hematologic diseases (CML or ALL) and solid tumors indicate the clinical effectiveness of this drug [82–87]. **Bosutinib** has a distinct side effect profile with very few cardiovascular and thromboembolic events compared with other TKIs. Common side effects are gastrointestinal symptoms (frequent diarrhea in more than 80% of patients) [86].

Multikinase inhibitors

Resistance to TKIs has necessitated the development of new mutation-resistant inhibitors, such as **ponatinib, midostaurin, and gilteritinib** [88]. **Ponatinib** is a multitarget inhibitor with high affinity and optimized binding to the active site of the BCR-ABL kinase domain, which may contain T315. This mutation is the main cause of inhibition of drug access to the ATP-binding site of the enzyme, which leads to resistance to first- and second-generation

TKIs [89,90]. **Ponatinib** is effective at inhibiting native and mutant BCR-ABL and is used in patients with Ph+ leukemia who are resistant or intolerant to all other TKIs [89,91–93]. The drug is also indicated for Ph+ ALL [94].

Midostaurin and gilteritinib are FDA-approved agents for treating patients with newly diagnosed FLT3-mutated AML. Midostaurin is a type III receptor TKI that inhibits FLT3 and other receptor TKs, including platelet-derived growth factor receptors, cyclin-dependent kinase 1, src, c-kit, and vascular endothelial growth factor [95–97]. In combination with all-trans retinoic acid, **midostaurin** shows antitumor activity against AML with wild-type FLT3 mutations both in vitro and in vivo. These results may provide new therapeutic strategies for some patients with AML without FLT3 mutations and indicate a new target for midostaurin [98]. **Midostaurin** has been approved by the FDA and EMA for treating AML with FLT3 mutations in combination with intensive induction and consolidation therapy, as well as for treating systemic mastocytosis with an associated HM [99,100]. **Midostaurin** in combination with standard chemotherapy effectively improved the OS of patients with FLT3-mutated AML, with a median of 57 months and an mOS of 74.7 months versus 26 months for the placebo group ($P = .007$), indicating a 23% reduction in the risk of death after treatment with midostaurin. Compared with the placebo**, midostaurin** significantly improved the median progression-free survival (mPFS): the mPFS was 8 months for **midostaurin** compared with 3.6 months for the placebo ($P = .003$) [100]. The results of the UNIFY trial showed that the clinical effect of **midostaurin** on AML is manifested mainly in patients with FLT3 mutations [101–104]. The most common adverse events (AEs) associated with midostaurin that led to discontinuation were infections (7.8%) and gastrointestinal disorders (4.5%) [97].

The mechanism of action of **gilteritinib** involves binding to the active conformation of FLT3 at the ATP-binding site, which leads to a decrease in the proliferation of malignant cells that overexpress the mutant protein [105,106]. **Gilteritinib** is an oral, potent FLT3 inhibitor active against FLT3-ITD and FLT3-TKD mutations. **Gilteritinib** became the first and only FDA-approved targeted drug that can be used as monotherapy to treat RR AML with FLT3 mutations [107,108]. In the randomized phase III ADMIRAL trial comparing gilteritinib [106] with salvage therapy in patients with RR FLT3-mutated AML, gilteritinib improved OS (mOS of 9.3 months vs. 5.6 months with chemotherapy; $P < .001$). In addition, the use of gilteritinib in this study suppressed transfusion dependency.

Gilteritinib combined with venetoclax (VEN), a BCL-2 inhibitor, enhances BCL-2 dependency and reduces BCL-xL and MCL-1 expression [109–111]. In a phase Ib clinical trial of **gilteritinib plus VEN** in patients with RR FLT3-mutated AML, the combination achieved modified composite complete remission, defined as complete remission (CR) with incomplete hematologic recovery (CRi), a morphological leukemia-free state rate of 75% and an mOS of 10.0 months [112]. These results compare favorably with those of **gilteritinib** monotherapy in the ADMIRAL study—for which the modified composite CR rate was 54% [109]—although patients in the **gilteritinib plus VEN** study were more heavily pretreated.

The standard of care for patients with newly diagnosed AML who are unfit for intensive chemotherapy is a combination of azacitidine (AZA) plus VEN [113,114]. However, FLT3 mutations are a common mechanism of resistance to this regimen. Adding **gilteritinib,** an oral FLT3 inhibitor, to **AZA** and **VEN** improved outcomes in patients with FLT3-mutated AML [106]. The CR/CRi rate was 96% (CR, 90%; CRi, 6%). Sixty-five percent of the evaluated patients with the FLT3-ITD mutant achieved measurable residual disease [115].

Mutations that activate the intracellular JAK kinase and signal transducer and activator of transcription pathways (STAT) (JAK2, V617F, and JAK2 exon 12) have been identified in patients with chronic myeloproliferative disorders. Two drugs have been registered for the treatment of primary myelofibrosis (PMF), namely, **ruxolitinib and fedratinib** [116]. Ruxolitinib is a JAK inhibitor that selectively inhibits the JAK1 and JAK2 protein kinases. The application of **ruxolitinib** (a JAK1/2 inhibitor) results in improved blood counts, spleen size, and quality of life in patients with PMF [117–121]. It is an oral medication approved by the FDA for the treatment of high-risk myelofibrosis, patients with polycythemia vera who are intolerant or resistant to hydroxyurea, and patients with steroid-refractory acute graft-versus-host disease [116–122].

Fedratinib, an alternative-approved JAK inhibitor, is potent and selective for JAK2, regardless of its mutational status [123]. Fedratinib, an oral JAK2 inhibitor, is approved for patients with PMF and platelet counts $\geq 50 \times 10^9$/L, based on outcomes from the phase III placebo-controlled JAKARTA trial in JAK-inhibitor-naive myelofibrosis and the phase II, single-arm JAKARTA2 trial in patients previously treated with ruxolitinib [120]. Compared with **ruxolitinib, fedratinib** causes a more significant reduction in spleen size and disease-related symptoms [120–124].

The most common nonhematologic AEs included ecchymosis, headache, dizziness, abdominal pain, fatigue, and diarrhea. The most common hematologic AEs observed with ruxolitinib during the trials included anemia and thrombocytopenia [120].

Phosphatidylinositol 3-kinase inhibitors

Phosphatidylinositol 3-kinases are a family of lipid kinases that phosphorylate phosphoinositides at the 3-hydroxyl group of the inositol ring. Dysregulation of the phosphatidylinositol 3-kinase pathway, particularly aberrant activation, is one of the most commonly observed alterations in HMs and is an important target for selective anticancer therapy [121]. Three phosphatidylinositol 3-kinase inhibitors have been approved since 2011: idelalisib, copanlisib, and duvelisib [125–127]. These drugs directly reduce the proliferation and survival of malignant B-cell leukemia and lymphoma cells. As a result, the FDA has approved these drugs for the treatment of various types of leukemia and lymphoma [127–131]. Idelalisib is a potent SMI of phosphoinositide 3-kinases [132]. A phase I study of idelalisib monotherapy in patients with RR CLL showed an ORR of 72% and an mPFS of 15.8 months [125]. A randomized, double-blind, placebo-controlled phase III study in patients with previously treated, high-risk CLL with the del17p mutation, TP53, or no immunoglobulin heavy chain hypermutation was stopped early due to the high efficacy of idelalisib in combination with R. The median progression-free survival (PFS) in the idelalisib and placebo groups at 24 weeks was 93% and 46%, respectively ($P < .001$), and the OS at 12 months was 92% and 80%, respectively ($P = .02$) [130].

A phase II study examining the role of **idelalisib** in combination with **R** in treatment-naive CLL patients reported an ORR of 96.9%. CLL patients with del17p/TP53 mutations also had similar ORRs. The median duration of response and mPFS were not reached at the time of analysis, with mPFS rates of 92.9% at 24 months and 82% at 36 months [131]. Based on the results of these studies, the researchers concluded that **idelalisib** is a highly effective, new targeted therapy for treating patients with NHL and CLL [131], as it induces high long-term

response rates with favorable mPFS, PFS, and mOS. Combinations of **idelalisib** with **BEN + R (BR)** chemotherapy in the RR CLL population are safe, producing both mPFS and mOS benefits. Combined targeted therapy including **idelalisib** is crucial for treating CLL/NHL [131,133–136].

Copanlisib showed efficacy and safety as a monotherapy in patients with RR NHL who had received at least two anti-CD20 mAb-containing therapies and who were progression-free and treatment-free for at least 12 months or at least 6 months for patients unwilling or unfit to receive chemotherapy [137]. The combination of **copanlisib** with **R** significantly improved the mPFS compared with placebo plus **R**, with an mPFS of 21.5 months versus 13.8 months ($P < .0001$) [138,139]. The most common grade 3–4 AEs were hyperglycemia at 56% in the **copanlisib** plus **R** group versus 8% in the placebo plus rituximab group and hypertension at 40% versus 9%, respectively [139]. The high efficiency of copanlisib in treating chronic LPDs in combination with other drugs has been noted [140,141].

Duvelisib, a first-in-class dual phosphatidylinositol 3-kinase inhibitor, inhibits phosphatidylinositol 3-kinase activity, resulting in decreased differentiation and migration of various components of the tumor microenvironment, such as T helper cells and M2 tumor-associated macrophages [142,143]. **Duvelisib** was effective in treating CLL, follicular lymphoma (FL), and marginal zone B-cell lymphoma (MZL): the ORR of patients with CLL, FL, and MZL was 67.9%, 42.2%, and 38.9%, respectively, and the mPFR was 9.5 months [64,144,145]. Common AEs of any grade were diarrhea (48.8%), nausea (29.5%), neutropenia (28.7%), fatigue (27.9%), and cough (27.1%).

Enzyme inhibitors

Histone deacetylase inhibitors

Since 2011, two histone deacetylase inhibitors have been approved for the treatment of HMs. These agents include **belinostat (**for patients with RR peripheral T-cell lymphoma (PTCL)) and **panobinostat** (for patients with recurrent MM), who have received at least two prior treatment regimens, including **bortezomib (BTZ) and immunomodulators** [146–149].

Histone deacetylase (HDAC) inhibitors have shown efficacy in treating PTCL, as well as other hematologic and solid malignancies [150,151]. HDAC inhibitors lower the apoptotic threshold of malignant cells by downregulating antiapoptotic proteins, upregulating proapoptotic proteins, inhibiting DNA repair, and inducing DNA damage [152]. In patients with RR PTCL, the ORR was 26% after **belinostat** monotherapy at a dosage of 1000 mg/m^2/day administered as an intravenous infusion for 30 min on days 1–5 of a 21-day cycle [150], including a CR rate of 11% and a PR frequency of 15%. The median time to respond was 5.6 weeks (range 4.3–50.4 weeks), with a mean duration of response of approximately 8.3 months. The BELIEF study analyzed patients with variable platelet counts [146]. In patients with platelet counts $\geq$100,000/μL, the ORR was 28%, including 11% of patients who achieved a CR. The researchers concluded that even patients with a poor bone marrow reserve and low platelet counts tolerated and benefited from belinostat treatment. Another interesting finding of the BELIEF trial was the response rate in patients with angioimmunoblastic T-cell lymphoma; among 22 patients with angioimmunoblastic T-cell lymphoma, the ORR was 46%.

The BELIEF study included an analysis of ORR rates stratified by different RR PTCL subtypes.

Despite the magnitude of this response, this trial still included a small number of patients, and the study could not describe differences in response rates between different subtypes. However, the results of the BELIEF study suggest that **belinostat** may target some discrete biological factors in angioimmunoblastic T-cell lymphoma that are not targeted by other HDAC inhibitors. A study [151] supported the conclusion that this class of drugs produces ORRs in the 25%–30% range, with a very favorable safety profile. **Belinostat** has been shown to be safe as an ambulatory intravenous infusion for more than 30 min. Common AEs included nausea, fatigue, pyrexia, anemia, and vomiting. The most common serious AEs (≥5%) were pneumonia (5%), pyrexia, infection, anemia, increased creatinine levels, thrombocytopenia (13%), neutropenia (13%), and anemia (10%) (6%) [151]. HDAC inhibitors synergize with various drugs and can be combined with targeted therapy and traditional cytotoxic agents [147–157]. Thus **belinostat**, a new-generation HDAC inhibitor, has shown promising activity in patients with heavily treated PTCL and has a very favorable safety profile with minimal grade 3 and 4 toxicities. It is exceptionally well tolerated in patients with thrombocytopenia.

Panobinostat monotherapy in patients with RR MM resulted in limited clinical activity, with 2/38 patients achieving a partial and minor response [153]. At the same time, after a course of therapy using the "BTZ **+ panobinostat**" regimen, 26.3% of patients achieved PR [154]. In the Panorama clinical trial ("**panobinostat-BTZ-dexamethasone (DEX)**" scheme), CR was diagnosed in 34.5% of patients, with an mPFS of 5.4 months [155]. The combination of **panobinostat** with **carfilzomib (CFZ)** was further studied in another trial [156]: 57% of patients achieved CR with an mPFS of 8 months and an mOS of 23 months. Positive results from clinical studies were obtained using other combinations: BTZ or thalidomide-panobinostat, lenalidomide and panobinostat [157], BTZ, thalidomide, DEX-panobinostat [158], **CFZ**-panobinostat [159,160].

Isocitrate dehydrogenase inhibitors

Isocitrate dehydrogenases play essential roles in many cellular processes, including modulation of the response to glucose by regulating insulin secretion, glutamine metabolism or synthesis, and lipid metabolism. In addition, enzymes exhibit antioxidant activity associated with the regulation of the redox status of cells, which protects against lipid peroxidation and oxidative DNA damage [161]. Isocitrate dehydrogenase mutations are found in many solid tumors, as well as in AML [162,163]. Since 2011, first-in-class mutant isocitrate dehydrogenase inhibitors, such as **enasidenid and ivosidenib,** have been approved by the FDA for the treatment of RR AML. Both induce terminal differentiation of bone marrow leukemic blast cells [162,163]. **Ivosidenib** is safe and well tolerated as maintenance therapy following allogeneic SCT. The 2-year mPFS was 81%, and the 2-year OS was 88% [164]. Studies have documented the effectiveness of ivosidenib as a monotherapy for RR AML [164–166] and in combination with AZA [167–169].

Enhancer ofzZeste homolog 2 inhibitor

Tazemetostat is a first-in-class, potent, and highly selective inhibitor of enhancer of zeste homolog 2 (a histone lysine methyltransferase). Its mechanism of action is to block enhancer

of zeste homolog 2 activity and lysine trimethylation, which leads to tumor regression [170]. During clinical development, **tazemetostat** showed favorable safety and response profiles in patients with lymphomas [171–173]. **Tazemetostat** showed antitumor activity as a monotherapy in patients with RR FL who received ≥2 prior lines of therapy. In clinical studies of patients with RR FL, **tazemetostat** in combination with **lenalidomide** and **R** generated an objective response rate of 73%–78% and an mPFS of 36–39 months [174].

DNA and RNA methyltransferases inhibitor

DNA and RNA methyltransferases are enzymes that catalyze DNA and RNA methylation, respectively. DNA methyltransferases play important roles in epigenetic gene regulation, including transcriptional silencing and transcriptional activation, while RNA methyltransferases are involved in RNA stability, splicing, and epigenetic mechanisms [175,176]. **AZA** is a cytidine nucleoside analog that is phosphorylated in the cell to its active form, that is, AZA triphosphate, and is included in DNA and RNA [177]. **AZA** further reduces DNA and RNA methylation through noncompetitive inhibition of DNA methyltransferases and RNA methyltransferases. The resulting DNA hypomethylation leads to the activation and expression of genes that regulate tumor suppressor functions and cellular differentiation. Decreased RNA methylation leads to decreased RNA stability and decreased protein synthesis. **AZA** also exhibits direct cytotoxicity to abnormal hematopoietic bone marrow cells [177].

AZA was approved by the EMA for the treatment of patients with malignancies caused by defective differentiation in the myeloid branch of hematopoiesis who are not suitable for SCT. The EMA has recommended the use of AZA for patients with myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia, AML with 20%–30% blasts, and multilineage dysplasia, and for adult patients aged 65 years or older with AML with >30% blasts in the bone marrow [178]. In the USA, Vidaza was also approved by the FDA for the treatment of patients with MDS and chronic myelomonocytic leukemia [179].

The AZA-001 trial showed that compared with conventional care regimens, **AZA** significantly prolonged the mOS (24.5 vs. 15.0 months; $P = .0001$) [180]. In the study by Yamauchi et al. [181], the 1-year OS rate of all MDS patients was 60.5%. The prognosis was slightly poorer than the 1-year OS in the AZA-001 trial (approximately 70%). One study [181] included patients with treatment-related MDS (58.6%). Additionally, **AZA** was administered for a median of four cycles in the study by Yamauchi but for six cycles in the AZA-001 trial. These differences may cause a shorter mOS and poorer prognosis [181]. More patients with very poor risk karyotypes tended to be included in the treatment-related MDS group, but no significant differences in 1-year OS or PFS were observed between the treatment-related MDS group and the de novo MDS group. The immunomodulatory effect of AZA on dysplastic hematopoiesis in MDS patients was manifested by significant increases in effector and naive T lymphocytes [167].

Good results of **AZA** treatment have been obtained in patients with MPZ in the phase of transformation to MDS or AML [168], as well as when using **AZA** with **VEN** in patients with AML [168] and AZA in combination with enasidenib [167,169] and ivosidenib [168].

Compared with conventional/supportive care, AZA significantly prolongs OS [182]. Based on these data, hypomethylating agent therapies are now the standard of care for the management of higher-risk MDS [183,184].

After 16 years, a new oral formulation of film-coated tablets was approved as a first-line treatment for AML (**ONUREG**). **ONUREG** is the first drug approved by the FDA for maintenance therapy [184]. Oral **AZA (ONUREG)** is approved for the treatment of adult patients with AML in first CR or CR/CRi following intensive induction chemotherapy who are ineligible for SCT [185]. A many clinical trials for AML, MDS, and other HMs have assessed hypomethylating agents used alone or in combination with other drugs in frontline, maintenance, and peri-transplant settings (QUAZAR AML-001, HOVON 97 AML, UK NCRI AML16, and QoLESS-AZA-AMLE) [186–189]. In the QUAZAR AML-001 trial, compared with the placebo, oral AZA significantly improved OS, with an increase in OS of 9.9 months (24.7 months versus 14.8 months, $P < .001$). The median time to relapse was also better for oral AZA, and the incidences of TEAEs were similar for the two arms [190]. The most frequent grade 3–4 AEs associated with oral AZA therapy were hematologic and gastrointestinal disorders. Nevertheless, implementing effective management of AEs may optimize the survival benefits of oral AZA AML therapy to maintain remission [191].

In 2006, decitabine was approved as an intravenous drug because it is broken down by cytidine deaminase in the gastrointestinal tract and liver [192]. **INQOVI** is a fixed-dose combination of **decitabine** and **cedazuridine. INQOVI** is intended for oral administration of **decitabine** through the inhibition of cytidine deaminase activity by cedazuridine [185].

The mechanism of action of **decitabine**, a deoxycytidine analog, involves its incorporation into replicating DNA and inactivation of DNA methyltransferases. Subsequent DNA hypomethylation leads to the death of malignant cells through several mechanisms [193]. **INQOVI** is indicated for the treatment of adult patients with newly diagnosed and secondary MDS, a group of bone marrow diseases that change the production of functional blood cells (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts and chronic myelomonocytic leukemia [194]).

Smoothed receptor antagonists

Deregulation of **smoothed receptor activity** is common in human malignant cells and is of great biomedical importance for the development of **new anticancer agents**. Smoothed receptor activity can be modulated by SMIs, several of which are currently FDA-approved anticancer drugs, including **glasdegib, vismodegib, and sonidegib. Glasdegib** potently inhibits the Hedgehog signaling pathway and has clinical activity in elderly patients with newly diagnosed AML [195]. In a randomized study [196], **glasdegib combined** with low-dose **cytarabine** (LDAC) significantly increased the OS of patients with AML compared with **cytarabine** alone. After 20 months of observation, the **probabilities** of survival in the glasdegib + cytarabine and cytarabine groups **were** 28.2% and 7.9%, respectively. Compared with **patients treated with cytarabine, patients treated with glasdegib + cytarabine** had a significantly longer mean **duration** without symptoms of disease progression or toxicity. These results indicate that when chemotherapy, that is**, cytarabine, is used**, a statistically significant increase in OS occurs [196,197]. **Glasdegib** is a next-generation smoothed receptor activity inhibitor and does not share the same binding site as **vismodegib** and **sonidegib** [198]. Therefore it is not susceptible to MDR evolution, mainly acquired mutations in smooth receptor activity receptors. **Vismodegib and sonidegib** are antineoplastic agents used for the

treatment of locally advanced recurrent basal cell carcinoma following surgery and radiation therapy or in cases where surgery or radiation therapy is not appropriate [199,200].

However, **vismodegib** and **sonidegib** are being intensively investigated in ongoing clinical trials as therapies for HMs, such as PMF, CML, and MDS. The most common adverse effects include muscle spasm (72%), fatigue (40%), alopecia (64%), dysgeusia (55%), and weight loss (45%). Additionally, elevated creatine phosphokinase levels and azotemia may occur [201].

Various protein inhibitors

Over the past 10 years, significant progress has been achieved in the development of SMIs as anticancer agents targeting various types of proteins, including BCL-2 (B-cell leukemia/lymphoma-2), XPO1 (exportin-1), proteolytic subunits of the proteasome and the tubulin protein. BCL-2 family proteins are key regulators of the mitochondrial apoptotic pathway. They control cell death by forming pores within the mitochondrial outer membrane, which leads to the release of proteins (cytochrome C) from the intermembrane space with subsequent activation of the initiating caspase, executive caspase 3/7, and apoptosis cascade.

B-cell leukemia/lymphoma-2 protein inhibitors

Since impaired apoptosis plays a crucial role in cancer resistance to therapy, pharmacological inhibition of antiapoptotic proteins, especially BCL2, is an attractive way to induce clonal cell death. Blockade of antiapoptotic proteins leading to the release of proapoptotic proteins can restart the process of apoptosis in malignant cells. **VEN** is a first-in-class, highly selective BCL-2 inhibitor. VEN (ABT-199, GDC-0199, Venclexta) is a unique, small, and highly selective orally bioavailable molecule that has been explicitly designed to target the BH3 domain of BCL2 [202]. **VEN** can displace proapoptotic proteins associated with BCL2. Thus free proteins activate apoptotic effectors (BAX and BAK) or inhibit other antiapoptotic members (MCL-1). Thus VEN triggers and restores apoptosis in tumor cells by releasing proapoptotic proteins from BCL2 [203] (Fig. 2).

The drug received its first approval as monotherapy in patients with RR CLL with 17p deletion who received at least one prior therapy. ORR was achieved in 79% of patients, and CR was achieved in 20% of patients. The most common serious AEs (grade 3–4) were neutropenia, febrile neutropenia, pneumonia, upper respiratory tract infection, and immune thrombocytopenia [204]. **VEN** monotherapy in patients with RR CLL with del17p contributed to an ORR of 79% and a CR of 8%. The 1-year PFS and OS were 72% and 87%, respectively [205]. Another study evaluated the efficacy of **VEN** monotherapy in patients who experienced relapse after treatment with B-cell receptor inhibitors (idelalisib or ibrutinib). In the group of patients who received ibrutinib for a median of 17 months, 70% responded to **VEN**, and 2% achieved CR. In the group of patients who previously received **idelalisib** for 8 months, a PR was obtained after treatment with **VEN**. The one-year PFS and OS were 72% and 90%, respectively. Hematologic toxicity (neutropenia, anemia, and thrombocytopenia), febrile neutropenia, and pneumonia were the most common grade 3–4 AEs [205].

Positive results of treatment with VEN have been achieved in patients with MCL and MM, especially in patients with the chromosomal translocation t(11, 14), even in the

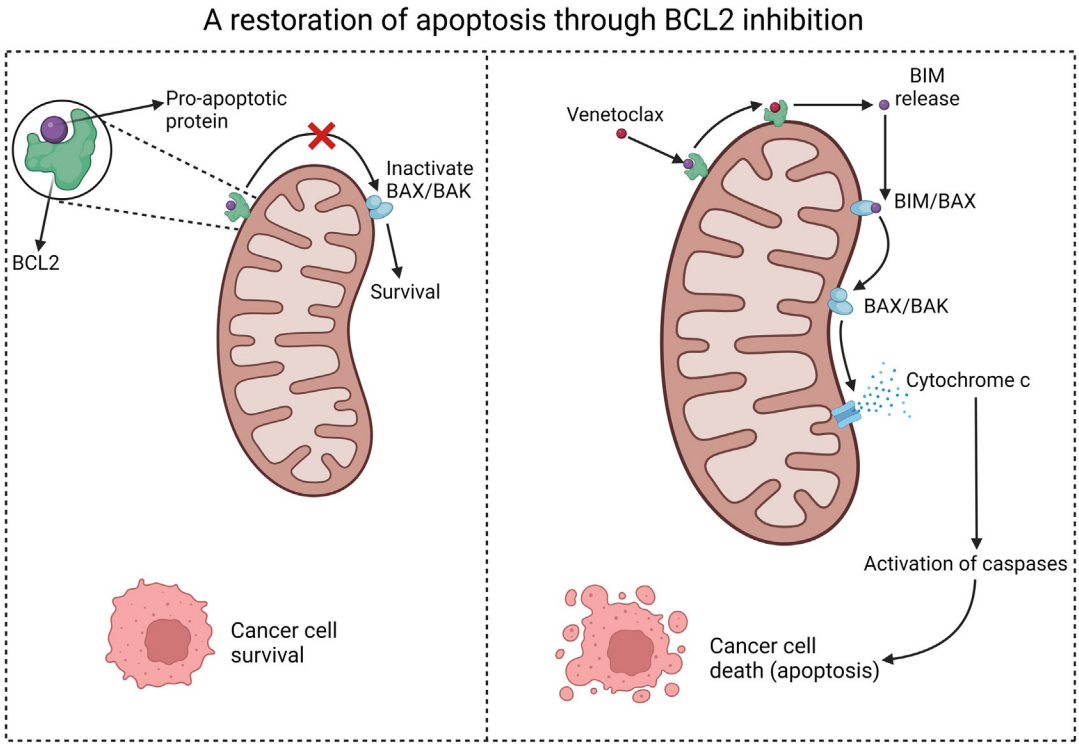


FIG. 2 The schematic representation of restoration of apoptosis BCL2 inhibition. Venetoclax is a selective BCL2 inhibitor that releases proapoptotic proteins upon binding, hence inducing apoptosis.

presence of high-risk deletions (del17p) [206–210], in elderly patients with AML in whom inhibition of BCL2 contributed to a significant increase in the effectiveness of low doses of cytarabine or hypomethylating agents [211–213], and in patients with Waldenström macroglobulinemia [214]. The results of clinical trials revealed that **VEN**, in combination with **R** (a phase I study of RR CLL), was feasible in 86% of patients, with 51% achieving CR. The 2-year estimated PFS and OS were 82% and 89%, respectively. Toxicity appeared to be similar to that of **VEN** in monotherapy [215,216]. Good results were obtained from using **VEN** with **ibrutinib** [217]. In June 2018, the indications were expanded to include **R** as a combination therapy for CLL, and in May 2019, **R** in combination with **obinutuzumab** was used for previously untreated patients with CLL. Encouraging results were obtained in patients who did not respond to treatment and in RR CLL patients who received obinutuzumab, ibrutinib, or VEN [218–220]. Eichhorst et al. [221] determined the effectiveness of four treatment regimens: fludarabine-cyclophosphamide-R, BEN-R, VEN-obinutuzumab and VEN-obinutuzumab-ibrutinib. After month 15, the percentage of patients with undetectable MRD was significantly greater in the **VEN-obinutuzumab** group (86.5%) and the **VEN-obinutuzumab-ibrutinib** group (92.2%) than in the chemo-immunotherapy group (52.0%). However, this percentage was not significantly higher in the VEN-R group (57.0%). Based on the data obtained, the authors [221] concluded

that VEN-obinutuzumab with or without ibrutinib is superior as a first-line treatment for fit patients with CLL.

Finally, in October 2020, the FDA approved the combination of **VEN** with **AZA**, **decitabine,** or **cytarabine** for patients with AML. Clinical studies have confirmed the effectiveness of these combinations in patients with HMs. When the combination of **AZA** and VEN was used, the mOS was 14.7 in the **VEN-AZA** group and 9.6 months in the control group, respectively ($P < .001$). The incidence of CR was higher with **VEN-AZA** than with the control regimen (36.7% vs. 17.9%) [222]. The combination of **AZA**, **VEN,** and **gilteritinib** resulted in high rates of CR/CRi, deep FLT3 molecular responses, and improved survival in patients with newly diagnosed FLT3-mutated AML; the CR/CRi rate was 96% (CR—90%; Cri—6%). Sixty-five percent of the evaluated patients achieved FLT3-ITD measurable residual disease within four cycles. With a median follow-up of 19.3 months, the mRFS and OS were not reached, and the 18-month RFS and OS rates were 71% and 72%, respectively. The most common grade 3 or higher nonhematologic AEs were infection (62%) and febrile neutropenia (38%) [115].

The high effectiveness of **VEN** in the treatment of HMs makes it possible to consider the appearance of this drug as a new wave in onco-hematology [223].

Exportin-1 inhibitors

Exportin-1 is a karyopherin that exports a range of cargo proteins and several classes of RNAs from the nucleus to the cytosol. This transporter is involved in the trafficking of tumor suppressor proteins (such as p53, p21, and IκB) between the nucleus and cytosol. As Exportin-1 is expressed in most malignant cells, it represents a promising target for anticancer therapy. Selinexor is a first-in-class selective inhibitor of nuclear export that ultimately induces cell cycle arrest and apoptosis [224] and is responsible for the translocation of approximately 220 nuclear proteins into the cytoplasm through nuclear pores [225]. **Selinexor** has shown synergistic activity in combination with **DEX** [226], **BTZ** [227], and **CFZ** [228]. The combination of **selinexor and DEX** (STORM trial) contributed to an ORR in 26% of MM patients, with an mOS of 15.6 months [228].

Selinexor received its first approval in combination with **DEX** for the treatment of adults with RR diffuse large B-cell lymphoma (DLBCL), and in 2020, **selinexor** was also approved for the treatment of adults with RR DLBCL who had previously attempted at least two lines of systemic therapy [229]. In December 2020, the indications were expanded to XVd therapy**, which includes selinexor** in combination with **BTZ** and **DEX**, for the treatment of adult patients with MM after at least one prior therapy [229,230]. The high efficacy of this combination was confirmed in the BOSTON study [231]: the ORR of 76%, very good partial response (VGPR) of 45%, and stringent complete response (sCR)/CR of 17% were significantly higher than those of Vd therapy (62%, 32%, and 11%, respectively), with mPFS values of 13.9 versus 9.5 months, respectively. Additional selinexor-based triplet regimens, including **selinexor** plus (1) an immunomodulatory drug and **DEX** [232,233] and (2) **daratumumab-DEX** [234], have shown high efficacy (ORR of 54%–69% and ≥VGPR of 23%–34%) and outcomes (mPFS of 8.9–12.5 months). The SELIBORDARA trial evaluated a selinexor-based quadruplet regimen including XVd therapy combined with daratumumab, resulting in an ORR of 82% and an sCR/CR rate of 24% [235]. Good responses were also observed in patients with t(11;14) MM treated with selinexor-VEN, with or without **CFZ**. [236]. Selinexor received its

first approval in combination with DEX for the treatment of adults with RR DLBCL, and in 2020, selinexor was also approved for the treatment of adults with RR DLBCL who had previously attempted at least two lines of systemic therapy. In December 2020, the indications were expanded to include **selinexor** in combination with **BTZ** and **DEX** for treating adult patients with MM after at least one prior therapy [237].

Proteasome inhibitors

The discovery of the role of the ubiquitin-proteasome pathway in the development of malignant tumors provided the key to solving the problem of blocking the action of NFκB (Nuclear factor kappa-light-chain-enhancer of activated B-cells). Proteasomes represent potential targets for new anticancer drugs [238] since the ubiquitin-mediated degradation system is central to the regulation of the cell cycle, apoptosis, and angiogenesis. The researchers' theoretical premises led to the synthesis of a drug based on a dipeptylboronic acid backbone that has the ability to inhibit proteasomal degradation by attacking the proteolytic β5 subunit of the 20S proteasome [238,239]. This drug is called PS-341 or BTZ [240].

In the complex and multistage process of apoptosis, the activation of the transcription NFκB factor plays a unique role. The main effects of NFκB on the cell nucleus are the enhancement of malignant cell growth (activation of the transcription of growth factors, cell adhesion, and angiogenesis), inhibition of apoptosis (production of BCL-2), and activation of the MDR gene. The mechanisms underlying each of these effects are mediated by their own complex set of factors released under the influence of NFκB on the cell nucleus [241]. The I|B inhibitor belongs to a class of regulatory short-lived intracellular proteins that are destroyed after ubiquitin (an intracellular protein) binds to them. The addition of ubiquitin indicates that the protein is subject to degradation in the proteasome (the so-called "kiss of death"). The interaction of proteasomes with the NFκB-I|B complex leads to the release and proteolysis of the inhibitor, and liberated [241].

In the mid-1990s, Adams [238] suggested that the proteasome is responsible for eliminating damaged or harmful proteins in the cell and beneficial proteins, which initially prevent complex diseases such as cancer [242]. Experimental studies have suggested a close connection between proteasome dysfunction and cancer progression [243]. This pathophysiological association has helped researchers develop an entirely new class of anticancer drugs called proteasome inhibitors, such as **BTZ** [244]. **BTZ** binds to proteasomes and inhibits intracellular ubiquitinated protein degradation. Moreover, this process is associated with the interruption of the interaction of malignant cells with stromal cells, which leads to the restoration of impaired regulation of TRAIL (*tumor necrosis factor-related apoptosis-inducing ligand*) and DR5 receptor (*drug resistance 5*) [245]; consequently, apoptosis progression in tumor cells could occur. **BTZ** potentially limits chymotrypsin-like proteasomal activation by reversibly interacting with the β5 subunit of the 20S proteasome, leading to complete inhibition of proteasomal activity followed by the accumulation of polyubiquitinated proteins in cells [245].

In 2003, the FDA approved **BTZ** for the treatment of RR MM [238]. In 2005, the FDA fully approved **BTZ** for use as a second-line MM therapy and as a first-line therapy for patients with newly diagnosed MM after only 3 years [246]. In 2006, **BTZ** was approved for treating RR MCL, and in 2014, it was approved for treating previously untreated MCL and DLBCL [247]. Currently, **BTZ** is being studied for the treatment of various blood cancers and solid tumors [248,249].

BTZ monotherapy prolonged the mOS and restricted the mean survival time by 33.9 and 42.9 months, respectively, compared with lower rates in chemotherapy-only patients (27.9 and 38.4 months, respectively) [250]. Currently, combination therapy with **BTZ**, **lenalidomide**, and **DEX** is the first-line regimen for RR MM, as well as newly diagnosed MM [250], achieving higher ORR, PFS, and OS rates (98%, 85%, and 95%, respectively). Six 28-day cycles of **BTZ-lenalidomide-DEX** therapy resulted in an ORR of 100% and a CR in 43.8% of patients [250]. At the same time, PFS and OS after 2.5 years were 66.6% and 77.3%, respectively, without hematologic or nonhematologic AEs of grade 3 or 4 [251].

Two proteasome inhibitors, namely**, carfilzomib** (2012) and **ixazomib** (2015), have been approved by the FDA for the treatment of patients with RR MM. **CFZ and ixazomib citrate** (a second-generation proteasome inhibitor) are highly effective in combination with **DEX** and an immunomodulatory drug (**lenalidomide**) in patients with MM who have received at least one previous therapy [252,253]. **Ixazomib citrate** is the first orally administered second-generation proteasome inhibitor that contains a citrate-protected boric acid moiety. The drug is hydrolyzed under physiological conditions (in the gastrointestinal tract and plasma) to its biologically active metabolite, that is, **ixazomib**.

The mechanism of action of **CFZ** and **ixazomib** is the formation of irreversible and reversible adducts, respectively, with the 20S unit of the 26S proteasome, mainly at the chymotrypsin-like β5 subunit [254]. At higher concentrations, both drugs exert additional inhibitory effects on caspase-like sites (β1) and trypsin-like (β2) subunits of the 20S proteasomal core [255]. Due to the inhibition of protein degradation by the proteasome, these drugs increase the levels of ubiquitinated proteins, which leads to the activation of the extensive protein stress response, cell cycle arrest, and apoptosis. Programmed cell death induced by **CFZ** is associated with the activation of caspase pathways and c-Jun-N-terminal kinase, as well as depolarization of the mitochondrial membrane and release of cytochrome C [255]. The antimyeloma effect induced by **ixazomib** is mainly due to blocking the NF-κB pathway, which reduces the release of cytokines secreted by bone marrow cells that are important for the proliferation of myeloma cells [255]. This drug also causes activation of caspase pathways, overexpression of the tumor suppressor gene miR33b, and decreased angiogenesis by blocking the expression of VEGFR-2 and platelet endothelial cell adhesion molecule. In addition, ixazomib administration leads to the upregulation of signaling pathways such as p53-p21, p53-NOXA-PUMA, and E2F [254].

CFZ is used as monotherapy or in combination with other drugs [253,256,257]. Compared with BTZ, CFZ has been shown to have a tolerable safety profile**,** with a significant reduction in neuropathy but a greater incidence of cardiotoxicity [256,257]. However, the ORR ranges between 80% and 100% [257]. Achievement of MRD negativity, as measured by multiparameter flow cytometry, ranged between 60% and 95% [257]. **Ixazomib**, the first oral PI, has been approved in combination with lenalidomide and **DEX** (Rd) for the treatment of patients with MM who have received at least one prior therapy [258]. **Ixazomib** exhibits antimyeloma activity as a single agent in patients refractory to BTZ. When combined with alkylating agents and immuno-modulatory drugs (IMiDs), **ixazomib** resulted in adverse MRD effects on a significant proportion of patients [254]. **Compared with the placebo, ixazomib-lenalidomide-DEX** significantly improved PFS (median 20.6 versus 14.7 months) [259]. The oral route of administration of **ixazomib** at a fixed dose allows its long-term use while maintaining optimal quality of life for patients.

Protein translation inhibitors

Disruption of protein translation mechanisms in tumor diseases prompted researchers to use protein synthesis inhibitors as a promising group of antitumor drugs. **Omacetaxine mepesuccinate** is the first cephalotaxine analog approved by the FDA for the treatment of CML that is resistant or intolerant to two or more TKIs [260–262]. The application of this drug additionally leads to the degradation of the Philadelphia gene product (i.e., BCR-ABL fusion protein) by inhibiting heat shock protein 90 function in a dose-dependent manner. In addition, in vitro studies have shown that the apoptotic activity of **omacetaxine mepesuccinate** is associated with the activation of caspase-9, -8, and -3 and poly(ADP-ribose) polymerase [261,262].

Immunomodulators

IMiDs are a group of compounds that are structural and functional analogs of **thalidomide** and exhibit immunomodulatory, antiangiogenic, and antiinflammatory properties.

IMiDs are currently under investigation and have shown efficacy against various HMs, including MM, AML, CLL, NHL, and PMF [263,264]. The ORR of patients with RR MM treated with the single agent thalidomide ranged from 32% to 48% [265]. The addition of BTZ to thalidomide and DEX induction treatment also improved the CR rate. Lenalidomide, an IMiD, is well-established and approved for the treatment of MM and 5q-MDS [266]. Its mode of action includes immune modulation and antiangiogenic, antiinflammatory, and antiproliferative effects [267]. Consequently, when lenalidomide was combined with R in patients with DLBCL, the ORR was 50.8%, with a CR rate of 27.7%. After a median follow-up of 24 months, the mPFS was 14 months, and the 2-year duration of response was 64% [264]. **Pomalidomide** (a third-generation immunomodulatory drug), the newest IMiD, was approved in February 2013 for the treatment of patients with RR MM whose disease progressed after previous lines of therapy, including **lenalidomid**e and **BTZ** [268]. In May 2020, the indications for **pomalidomide** treatment were expanded to patients with AIDS-associated Kaposi's sarcoma refractory to highly active antiretroviral therapy or patients with HIV-negative Kaposi's sarcoma. The mechanism of action of pomalidomide involves various molecular and cellular elements in the bone marrow microenvironment, cytokine production, immunomodulation, and direct antimyeloma activity**. Pomalidomide** decreases the levels of various proinflammatory cytokines, including TNF-α, IL-1β, and IL-6. In addition, the antiinflammatory effect of the drug is associated with the inhibition of COX-2 (cyclooxygenase-2) and the production of prostaglandins by monocytes. Immunomodulatory mechanisms include enhanced T-cell proliferation, which leads to increased production of IL-2 and IFN-γ, in addition to enhanced NK cell activity and antibody-dependent cell-mediated cytotoxicity (ADCC) toward myeloma cells [267]. Clinical trials have shown that **pomalidomide** has the most potent immunomodulatory effect [269]. **Pomalidomide** has been observed to be effective in IMiD- and BTZ-refractory patients [270]. Clinical trials have shown that pomalidomide in combination with low doses of DEX reduces the PFS and OS of patients with RR MM [271,272]. The median PFS and OS for all patients were 3.6 months and 7.7 months, respectively. For patients who achieved a ≥PR, the mPFS and mOS were 10.6 months and 16.3 months, respectively [272]. Myelosuppression is associated with dose-limiting toxicity

for both lenalidomide and pomalidomide. Peripheral neuropathies are generally less severe than those caused by thalidomide. The incidence of venous thromboembolism is approximately 78% [273,274].

Macromolecule anticancer drugs

Monoclonal antibodies

An essential event in oncohematology was developing and using mAbs as antitumor agents in clinical practice. mAbs represent a clonal version of a specified antibody that can bind to antigens found on the surface of cancer cells. mAb activity induces malignant cell death through various mechanisms, affects the tumor microenvironment, and inhibits angiogenesis. mAbs consist of two heavy and two light chains, which form three functional protein domains: two identical fragments for antigen binding (Fab regions) and a permanent or crystallizable fragment (Fc region). Depending on the type of Fab region, mAbs are divided into four classes: murine, chimeric, humanized, and human [275,276]. IgG mAbs are the most commonly used for tumor immunotherapy. These proteins are classified as IgG1, IgG2, IgG3, or IgG4. mAbs approved by the FDA for the treatment of HMs target CD19, CD20, CD38, signaling lymphocyte activation molecule family member 7 (SLAMF7), and programmed death receptor-1 (PD-1).

Anti-CD19 monoclonal antibody

Anti-CD19-mAbs—Tafasitamab-cxix is an Fc-modified humanized mAb that binds to the CD19 antigen on the surface of B lymphocytes. The drug induces the lysis of tumor B-cells through ADCC/antibody-dependent cellular phagocytosis (ADCP). This drug is used in combination with **lenalidomide** as a treatment for adult patients with RR DLBCL who cannot undergo autoSKT [277]. The final analysis of the phase II L-MIND study revealed an objective response rate of 57.5% and a complete response rate of 41.3%. With a median follow-up of 45.6 months, the mPFS was 11.6 months, while the mOS was 33.5 months. Interestingly, patients who received only one frontline treatment exhibited a greater incidence of objective response (67.5%; 52.5% CR) than those who received two or more frontlines (47.5%; 30% CR), although the median subgroup value was not reached in either subgroup. This analysis indicated the efficacy of the combination of tafasitamab and lenalidomide [277].

Anti-CD20 monoclonal antibodies

Anti-CD20 mAb is the first FDA-approved mAb for the treatment of HMs. The drug was first registered in 1997 for the treatment of RR B-cell disease, poorly differentiated disease or FL. The CD20 cluster of differentiation molecule consists of multiple transmembrane domains and is expressed exclusively by B-cells. The interaction of CD20 with antigen-presenting cells leads to the regulation of transmembrane Ca^{2+} transport and cell cycle progression during B-cell activation and proliferation [278]. Anti-CD20 mAbs bind to various epitopes on CD20, resulting in the inhibition of B-cell progression to the S/G2+M stage of the cell cycle [278]. It is used to treat many LPDs, including NHL and CLL. Depending on the mechanisms that cause the death of malignant B-cells, two types of anti-CD20 mAbs exist.

Type I antibodies against CD20, such as **R or** its analogs **rituximab-abbc**, **rituximab-pvvr,** or **rituximab-arrx**, redistribute CD20 molecules into large insoluble lipid microdomains (lipid rafts) and induce complement-dependent cytotoxicity.

R reduced peripheral B-cell counts by approximately 90% within 3 days in patients with RR indolent NHL. Lymphocyte levels remained depressed for 6 months and recovered by 9–12 months after the administration of four doses of 375 mg/m^2 **R** once weekly. The clinical response rates were 46% and 48% in patients with RR NHL [279]. The response rate to **R** was higher in patients with FL than in patients with CLL (56% or 60% versus 13% or 15%). In total, 85%–94% of patients experienced AEs during clinical studies; 90% of patients experienced mild or moderate AEs. The most common AE was a transient set of flu-like symptoms during the first infusion in approximately 50%–87% of patients, which usually resolved entirely within <3 h [279].

Rituximab-abbs has received approval for the treatment of NHL as a single agent or in combination with chemotherapy [280], while **rituximab-pvvr** and **rituximab-arrx** are approved as single agents or in combination with first-line chemotherapy for the treatment of patients with NHL and CLL [281–283].

Type II antibodies (**obinutuzumab**) induce less accumulation of CD20 in lipid rafts and initiate weak complement-dependent cytotoxic activity. **Obinutuzumab** exhibits an enhanced ability to bind and recruit effector cells, thereby inducing ADCC through glycoengineering of the Fc region [92]. **Obinutuzumab** is approved in combination with **chlorambucil** as a treatment for CLL and in combination with **BEN** as a treatment for FL. **Obinutuzumab** was approved by the FDA in November 2013 for use in combination with chlorambucil for the treatment of patients with previously untreated CLL [284,285].

Obinutuzumab is a mAb that targets the CD20 antigen expressed on the surface of pre-B- and mature B-lymphocytes. Upon binding to CD20, **obinutuzumab** mediates B-cell lysis through (1) the engagement of immune effector cells, (2) direct activation of intracellular death signaling pathways, and/or (3) activation of the complement cascade [286]. The immune effector cell mechanisms include ADCC and ADCP [287].

The first study was conducted to determine the effectiveness and safety of **obinutuzumab** in patients with previously untreated CD20 CLL. Patients received control therapy with **chlorambucil** (Group 1), **obinutuzumab plus chlorambucil** (Group 2), or **R plus chlorambucil** (Group 3). The results showed that the mPFS of the **obinutuzumab plus chlorambucil** group was 23.0 months and that in the **chlorambucil** monotherapy group was 11.1 months (median follow-up time 14.2 months) [284]. The most common adverse reactions (incidence ≥10%) were infusion reactions, neutropenia, thrombocytopenia, anemia, fever, cough, and musculoskeletal disorders. Further clinical studies confirmed the effectiveness of **obinutuzumab** [288–290].

Anti-CD38 monoclonal antibodies

Anti-CD38 mAbs represent a promising therapy for MM because CD38 is expressed at high levels in a variety of malignant plasma cells**. Daratumumab** and **isatuximab** kill MM tumor cells through Fc-dependent immune effector mechanisms, that is, complement-dependent cytotoxicity, ADCC/ADCP, and apoptosis. Both drugs also exhibit indirect antitumor activity against CD38 regulatory T-cells, thereby restoring immune effector functions against MM, while **isatuximab** does not reduce CD38 levels. **Daratumumab** is approved

as a monotherapy and in combination with various chemotherapy modalities for the treatment of both newly diagnosed and RR MM patients. **Isatuximab**, in combination with **pomalidomide** and **DEX**, is approved for the treatment of adult patients with MM who have received at least two prior therapies. **Isatuximab** in combination with **CFZ** and **DEX** is registered for the treatment of adult patients with RR MM who have received one to three previous lines of therapy.

On November 16, 2015, the FDA approved the first mAb, **daratumumab,** for the treatment of patients with MM who received at least 3 previous lines of therapy, including a proteasome inhibitor and an IMiD, or for the treatment of patients whose disease is double refractory to proteasome inhibitors and IMiDs [291,292]. The efficacy and safety of **daratumumab** in MM were documented in the SIRIUS (MMY2002) and the GEN501 early-phase, open-label clinical trials evaluating the use of the single agent **daratumumab** in patients with RR MM [293–295]. The ORR was 29%–36%, which included a 3% stringent CR, 9% VGPR, and 17% partial response. The median time to disease progression was 3.7 months, and the mOS was not reached. The most common (≥20%) AEs (all grades) reported by the 156 patients who received **daratumumab** were infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%). None of these nonhematologic AEs were life-threatening (grade 4).

DARZALEX FASPRO is a new subcutaneous formulation of **daratumumab** that was codeveloped with recombinant human hyaluronidase. The drug is administered in significantly less time (i.e., 3–5 min) than the intravenous infusion hours required to administer **DARZALEX**. Hyaluronidase increases the permeability of subcutaneous tissue. At the administered doses, hyaluronidase in **DARZALEX FASPRO** acts locally, and its effects are reversible. The drug was approved as a monotherapy and in combination with four chemotherapy regimens for MM, including for newly diagnosed patients not eligible for transplantation, as well as patients with RR disease [296,297].

Isatuximab is an anti-CD38 mAb approved for use in the treatment of adults with MM; it is used in combination with **pomalidomide** and **DEX for patients** with RR MM who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor. **Isatuximab**, in combination with **pomalidomide** and **DEX**, is approved for the treatment of adult patients with MM who have received at least two prior therapies. **Isatuximab** in combination with **CFZ** and **DEX** is registered for the treatment of adult patients with RR MM who have received one to three previous lines of therapy. **Isatuximab** induces direct apoptosis of plasma cells through caspase-dependent apoptotic and lysosomal-mediated pathways [298]. **Anti-SLAMF7** mAbs—Signaling lymphocyte activation family member molecule 7 (SLAMF7) is a transmembrane receptor that is expressed on hematopoietic cells such as NK, B cells; dendritic cells; and monocytes. The receptor modulates the function of immune cells via immunoreceptor tyrosine switch motifs that mediate an interaction with Ewing's sarcoma-associated transcript 2. SLAMF7 has both activating and inhibitory functions in NK cells, induces the proliferation and production of autocrine cytokines in B-cells, and inhibits the production of proinflammatory cytokines by activated monocytes. **Elotuzumab** is a humanized IgG1 mAb that binds to SLAMF7 on MM tumor cells and NK cells and exerts antimyeloma effects by directly activating NK cells and NK-mediated ADCC, preventing MM cell adhesion to bone marrow stromal cells, which can impair growth and MM cell survival [299]. **Elotuzumab** has received FDA approval in combination with **lenalidomide** and **DEX** or

pomalidomide and **DEX** for the treatment of adult patients with RR MM who have previously received therapy [299]. **Elotuzumab** with **pomalidomide** and **DEX** has indicated to have a superior clinical benefit over **pomalidomide** and **DEX** with a manageable toxicity profile, leading to its approval for the treatment of patients with RR MM [300]. **Elotuzumab-Pd** is a safe and possible therapeutic choice for patients with RR MM who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

Anti-PD-1 monoclonal antibody

Anti-PD-1 mAbs. PD-1 (programmed death-1) ligands are overexpressed in MM, lymphomas, and various types of leukemia, which leads to inhibition of the T-cell immune response in these diseases. Blocking the PD-1/PD-L1 signaling pathway with mAbs restores the effectiveness of tumor-specific T-cells, allowing them to recognize and target malignant cells [301,302]. **Nivolumab and pembrolizumab** are the first two FDA-approved mAbs that target PD-1 [303]. These drugs selectively interfere with the interaction between PD-1 and PD-L1 and lead to the release of T-cells from pathological immunosuppression [39,301].

Nivolumab has received accelerated approval for adult patients with RR classic HL after autologous SCT and treatment with **brentuximab vedotin** [338]. **Pembrolizumab** is registered as monotherapy for the treatment of pediatric and adult patients with RR classical HL [302].

Anti-CCR4 monoclonal antibody

Anti-CCR4 mAbs. CCR4 (chemokine receptor 4) is overexpressed in several subtypes of cutaneous T-cell lymphoma, including mycosis fungoides and Sezary syndrome [304]. **Mogamulizumab-kpkc** is a first-in-class defucosylated, humanized mAb against CCR4 that is used to treat adult patients with RR mycosis fungoides and Sezary syndrome who have received at least one prior systemic therapy [305]. By selectively binding to CCR4, **mogamulizumab-kpkc** marks T-cells for ADCC exhaustion and kills target malignant cells [306,307].

Bispecific antibodies

The use of **bispecific antibodies as antitumor agents** significantly increases the selectivity and effectiveness of therapy for various diseases, including HMs. Bispecific antibodies vary in structure, size, and production methods [308]. **Blinatumomab** is a first-in-class bispecific T-cell Ab that has been approved by the FDA for MRD-positive or RR B-cell ALL patients.

The drug binds to CD19 and CD3, which are expressed on the surface of malignant B-cells and endogenous T-cells. A cytolytic synapse is formed between B-cells and T-cells, resulting in the activation of cytotoxic T-cells, which leads to the induction of apoptosis and lysis of CD19+ B-cells by perforin and granzymes released from cytotoxic T-cell granules [309]. Various clinical trials have investigated the effect of blinatumomab on MRD+ B-cell ALL patients [310].

Antibody-drug conjugates

Antibody-drug conjugates have been developed to reduce off-target toxicity and improve the efficacy of cytotoxic drugs in patients by limiting their exposure to normal tissues [311].

Antibody-drug conjugates are complexes consisting of an antibody, a cytotoxic agent, known as the payload, and a chemical linker. The antibody fragment provides selective delivery of the payload to target tumor cells by directly binding to a specific cancer-associated antigen. After internalization of the antibody-drug **conjugate**-antigen complex into the tumor cell, the antibody-drug conjugates are degraded in the lysosome due to cleavage of the linker, which allows the effective release of the "payload" to induce the death of the target cell [311]. By the end of 2020, four antibody-drug conjugates had received FDA approval, including CD22, CD30, CD79b, and BCMA.

Anti-CD22 antibody-drug conjugate

CD22 is a transmembrane sialoglycoprotein expressed on mature B-cells. The expression of CD22 antigens is generally limited by the line. It is not lost with tumor transformation and is absent in normal hematopoietic stem cells, which makes them ideal targets for HM therapy. **Inotuzumab ozogamicin** is a conjugate of an anti-CD22 antibody (IgG4) and the low-molecular-weight substance calicheamicin, a toxic product isolated from *Micromonospora echinospora* subsp. [312,313]. Calecheamicin is connected to antibodies through an acetophenone-butanoic acid bifunctional linker. The linker forms an amide bond with the lysine residues of the mAb and a hydrazone bond with the *N*-acetyl-calecheamicin DMG. Hydrolysis of the hydrazone functional group allows the release of the cytotoxic component into the acidic environment of the lysosomes of malignant cells. The calecheamicin derivative is then activated by the reduction of the disulfide bond in the presence of intracellular glutathione, a cytoplasmic thiol cofactor. Calecheamicin exhibits a different mechanism of action than other tubulin-binding classes of cytotoxic agents: after a certain rearrangement of the calecheamicin fragment, which is reduced by cellular thiols, hydrogen atoms are released from the phosphodiester bonds of double-stranded DNA and rupture. This process results in cell cycle arrest between gap phase II and mitosis (G2/M) and apoptotic cell death. By binding to the minor groove of DNA and causing double-stranded DNA breaks, regardless of cell cycle progression, calecheamicin induces apoptosis even in rapidly dividing cells [313]. **Inotuzumab ozogamicin** was approved by the FDA in 2017 for treating adults with RR B-cell precursor ALL [312]. In the USA, a phase III trial evaluating inotuzumab ozogamicin in combination with frontline chemotherapy in adults with newly diagnosed B-cell ALL was recently initiated, and inotuzumab ozogamicin was evaluated in a phase II trial in pediatric CD22-positive B-cell ALL patients. Inotuzumab ozogamicin combination therapies are also being evaluated in the phase I/II or II setting for ALL and CML and in the phase I setting for Burkitt's lymphoma [312,314].

Anti-CD30 and anti-CD79b antibody-drug conjugates

CD30 is a transmembrane glycoprotein member of the TNF receptor superfamily expressed on B- or T-lymphocytes in classical HL and anaplastic large cell lymphoma. CD30 induces biological effects on cell growth and survival through the activation of the NF-κB pathway. CD79b, a component of B-cell receptors, is expressed on mature and tumor B-cells. CD79b plays a key role in B-cell receptor signaling [313]. **Brentuximab vedotin and polatuzumab vedotin** are mixtures of two mAbs directed against CD30 and CD79b, respectively. Both antibodies are conjugated with monomethyl auristatin E, a potent antimitotic

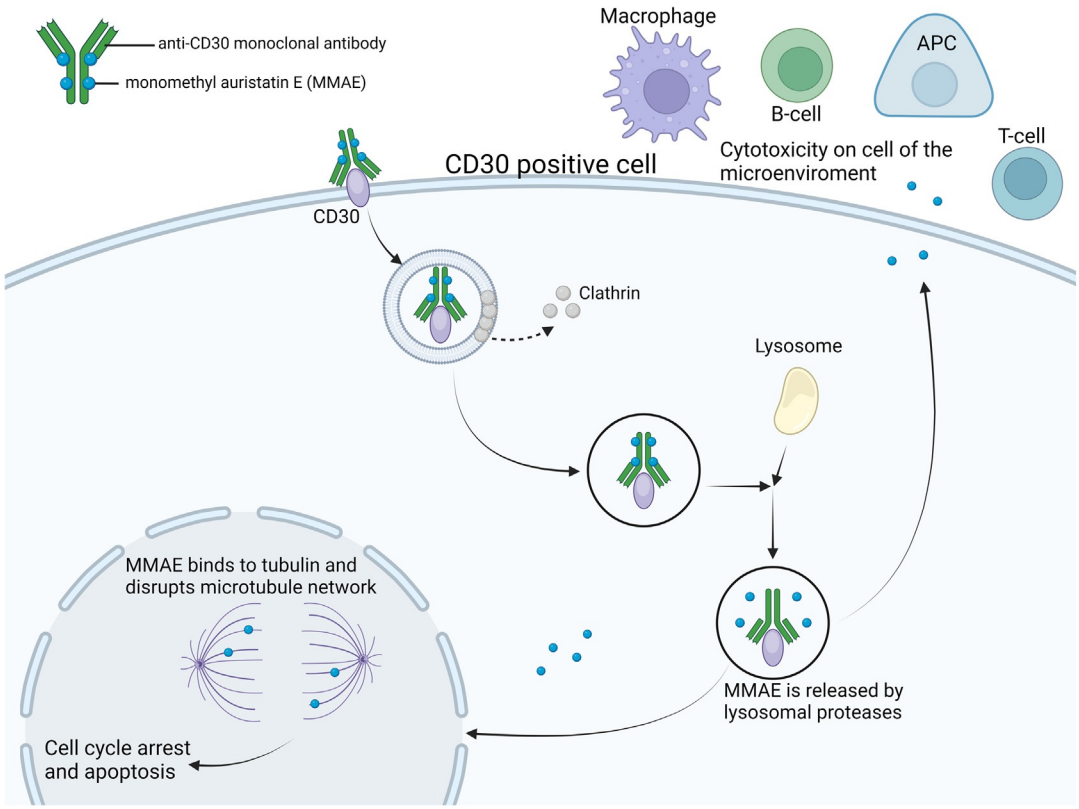


FIG. 3 The schematic representation of the action of Brentuximab vedotin. Brentuximab vedotin is intended to be stable in the bloodstream while releasing MMAE once absorbed into CD30-expressing tumor cells. MMAE binds to tubulin, disrupting the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.

agent. After the internalization of these conjugates into malignant cells, the linker is selectively cleaved by lysosomal enzymes, and monomethyl auristatin E is released (Fig. 3). The antimitotic agent then binds to tubulin and blocks polymerization, which leads to the arrest in G2/M phase of the cell cycle and the induction of cell apoptosis. Both drugs induce tumor cell death via ADCP. **Brentuximab vedotin** alone is used as a therapy in patients after failure of previous combination chemotherapy regimens [315]. This drug is also approved for the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma and mycosis fungoides after the failure of previous systemic therapy. In addition, combination chemotherapy with this drug is a first-line treatment for adult patients with stage III or IV classical HL who have not previously received treatment [316].

Clinical trials have shown that a regimen including **brentuximab vedotin** with **BEN** is a promising treatment for patients with high-risk HL. Polatuzumab vedotin is combined with BEN and R to treat adults with RR DLBCL who have previously received two other treatments [317]. **Brentuximab vedotin,** in combination with **DOX**, **vinblastine**, and **dacarbazine**, is increasingly being used for the treatment of stage III/IV classical HL. The 2-year PFS of

patients with advanced-stage classical HL was 82.7%, and the OS was 97.4%. Peripheral neuropathy was reported by 80% of patients at the time of treatment. Patients who received brentuximab vedotin for peripheral neuropathy did not have a lower PFS rate.

Anti-BCMA antibody-drug conjugate

BCMA is a transmembrane glycoprotein belonging to the TNF receptor family 17. Overexpression of this receptor was detected on both standard and plasma cells in MM. BCMA plays an essential role in the survival of bone marrow plasma cells [318,319]. Belantamab mafodotin-blmf is a first-in-class anti-BCMA drug indicated for the treatment of MM. The drug contains an IgG1 Ab covalently bound to the cytotoxic microtubule inhibitor monomethyl auristatin F. The antibody fragment delivers monomethyl auristatin F to cells expressing BCMA. Following the internalization of the conjugate and release of monomethyl auristatin F, the cytotoxic agent disrupts microtubule formation by inhibiting tubulin polymerization. This inhibition subsequently causes cell cycle arrest in G2/M phase and apoptosis. In addition, belantamab mafodotin-blmf induces tumor cell lysis through ADCC and ADCP. The drug received FDA approval as monotherapy for adults with RR MM after at least four prior treatments [319]. **Belantamab mafodotin (belamaf**) is a novel antibody–drug conjugate targeting B-cell maturation antigen that has shown antimyeloma activity in patients with RR MM [320,321].

A study was conducted to determine the effectiveness of **belantamab mafodotin** as monotherapy in patients with RR MM [321,322]. The results showed that the ORR was 41.8% ($\geq$CR 13.5%, VGPR 9%, PR 17.3%, minor response 2%). The mPFS was 3.61 months and 14.47 months for patients who achieved at least a minor response, respectively ($P < .001$). The median OS in both patients with a minor response and the entire cohort was 23.35 and 11.05 months, respectively. The most frequent AEs were corneal events (87.9%; grade $\geq$3, 33.7%), with thrombocytopenia and infections occurring in 15.4% and 15% of patients, respectively [322]. Good results have also been reported when Belamaf is used in combination therapy [323].

Recombinant immunotoxins

The production of recombinant immunotoxins, a complex of a molecule containing the Fv fragment of a mAb and a protein toxin produced by bacteria, fungi, or plants, has led to the generation of highly cytotoxic molecules that induce apoptotic cell death by inhibiting protein synthesis. Immunotoxins have antitumor activity against various HMs [324]. **Moxetumomab pasudotox** is FDA-approved for the treatment of adult patients with RR hairy cell leukemia after at least two prior systemic therapies [325]. **Moxetumomab pasudotox** consists of an Fv fragment of the anti-CD22 mAb genetically fused to a fragment of *Pseudomonas aeruginosa* exotoxin A. The Fv portion of this drug binds to CD22 and thus delivers the toxin fragment directly to target cells. After binding, the recombinant immunotoxin-CD22 complex is internalized into the cell, where it induces apoptosis [325]. The drug was approved by the FDA in September 2018 to treat patients with hairy cell leukemia who have received at least two lines of standard treatment. [324]. Studies have been conducted on the effectiveness of this drug in patients with RR hairy cell leukemia [326]. CR was achieved in 30% of patients, ORR was achieved in 75%, and MDR negativity was achieved in 85% of patients [327].

Enzymes

Enzymes that target the metabolism of amino acids such as asparagine, arginine, and methionine are currently used as antitumor agents, causing some tumor cells to become auxotrophic. Amino acid deprivation leads to the inhibition and disruption of tumor growth [328,329]. Asparaginase **from** *Erwinia chrysanthemi* (a gram-negative bacterium) is a therapeutically applicable enzyme (L-asparaginase). This drug is immunologically different from L-asparaginase derived from *Escherichia coli* and has increased enzymatic activity. The advantage of this enzyme/drug combination is the absence of side effects such as the development of hypersensitivity, pancreatitis, and hyperglycemia associated with previously approved L-asparaginase therapy from other sources [328]. **Calaspargase pegol-mknl** (*E. coli*-derived enzyme) is also a specific, long-acting enzyme targeting L-asparagine [329]. The asparaginase from *E. chrysanthemi* was approved for the treatment of patients with ALL who had to stop treatment with commonly used *E. coli*-derived asparaginase due to patient hypersensitivity [328]. In contrast, calaspargase pegol-mknl was approved for treating pediatric and young adult patients with ALL [329]. Both drugs are used as components of a multiagent chemotherapy regimen. Their mechanism of action involves the hydrolysis of L-asparagine to aspartic acid and ammonia, which depletes the levels of L-asparagine required for protein metabolism, growth, and survival. Subsequently, L-asparagine deprivation in leukemic cells induces cell death.

CAR-T cells

CAR-T-cell therapy is a new and promising method for treating various HMs [325]**.** In CAR-T therapy, T-cells isolated from a patient's blood are engineered with genetic recombinant receptors known as chimeric antigen receptors. The chimeric antigen receptor is a chimeric protein composed of three parts: an antibody-derived extracellular domain, a transmembrane domain, and an intracellular T-cell signaling domain. The extracellular domain targets specific tumor-associated antigens on neoplastically transformed cells, while the intracellular domain enhances T-cell proliferation and differentiation, as well as their cytotoxicity against cancer cells.

Four generations of chimeric antigen receptor proteins that differ in the structure of their intracellular signaling domain have been developed. CAR-T cells lead to the death of tumor cells through the secretion of cytotoxic granules containing granzymes and perforin and the release of cytokines (IFN and TNF) [330]. CAR-T cells mediate antigen recognition independent of the major histocompatibility complex. For this reason, the immune response during CAR-T-cell therapy may become uncontrolled and cause some toxic side effects [331]. **Tisagenlecleucel**, **axicabtagene ciloleucel**, and **brexucabtagene autoleucel** are second-generation CD19-targeted CAR-T cells. **Tisagenlecleucel** is the first gene therapy consisting of autologous T-cells modified by lentiviral transduction to express a chimeric antigen receptor consisting of a murine single-chain antibody fragment, a transmembrane domain, and CD3ζ (intracellular signaling domain) fused to a costimulatory domain (4-1BB) [331]. It acts by binding to cells expressing CD19 and then initiating T-cell activation through the CD3 ζ component.

Currently, **tisagenlecleucel** is registered for two different indications for RR B-cell ALL and certain types of RR B-large cell lymphomas, including DLBCL, high-grade B-cell

lymphoma, and DLBCL arising from FL, for which other treatment methods are ineffective [331,332]. The pivotal ELIANA clinical trial was conducted in pediatric and young adult patients with RR ALL. The results showed that the ORR of patients who achieved CR plus CR/CRi was 82%. The most recent analysis of this study reported that the 5-year relapse-free survival of patients who initially achieved a CR or CRi after tisagenlecleucel administration was 49% [332]. The impressive overall efficacy in this patient population was also confirmed in a real-world setting [333]. For adults, a phase I trial of 53 patients with relapsed B-ALL showed that a different CAR-T-cell therapy resulted in a CR rate of 83% and a mOS of 12.9 months. However, 26% of patients developed severe cytokine release syndrome, and 44% developed grade 2 or higher neurotoxic effects [333].

Axicabtagene ciloleucel and **brexucabtagene autoleucel** are autologous T-cells expressing a chimeric antigen receptor that contains a murine single chain variable fragment, a transmembrane domain, and CD3ζ integrated with CD28 [334]. **Axicabtagene ciloleucel** is an autologous anti-CD19 chimeric antigen receptor T-cell therapy approved for RR FL. The results of the phase II, multicenter, single-arm ZUMA-5 study of **axicabtagene ciloleucel** for patients with RR indolent NHL, including FL and MZL showed that the ORR was 92% (CR—74%). S. S. Neelapu et al. [335] reported long-term outcomes from the ZUMA-5 trial. Eligible patients with RR indolent NHL underwent leukapheresis after receiving ≥two lines of therapy, followed by lymphodepletion chemotherapy and axis-cell infusion (2×10^6 CAR-T cells/kg). After a median follow-up of 41.7 months in FL patients and 31.8 months in MZL patients, the ORR was comparable to that of the primary analysis (FL, 94%; MZL, 77%). The mPFS was 40.2 months for FL patients and was not reached for MZL patients. The median OS was not reached for patients with either disease type. Patients experiencing grade ≥3 AEs of interest after the prior analyses were considered recently treated patients. After 3 years of follow-up in ZUMA-5, **axicabtagene ciloleucel** exhibited continued durable responses, with very few relapses beyond 2 years, and manageable safety in patients with RR indolent NHL [336]. **Brexucabtagene autoleucel** is an autologous CD19-directed CAR-T-cell approved for RR MCL. The results of the single-arm phase II ZUMA-2 trial showed the best ORR and CR of 91% and 68%, respectively. Wang et al. [337] reported the clinical outcomes of patients treated with **brexucabtagene autoleucel** in the standard-of-care setting for approved indications. The best ORR and CR rates were 90% and 82%, respectively. At a median follow-up of 14.3 months after infusion, the 6- and 12-month PFS estimates were 69% and 59%, respectively. The nonrelapse mortality rate was 9.1% at 1 year, primarily because of infections. Grade 3 or higher cytokine release syndrome and neurotoxicity occurred in 8% and 32% of patients, respectively. According to the univariate analysis, a high-risk simplified MCL international prognostic index, high Ki-67 expression, TP53 aberration, complex karyotype, and blastoid/pleomorphic variant were associated with shorter PFS after Brexit-cell infusion. Patients with recent bendamustine exposure (within 24 months before leukapheresis) had shorter PFS and OS after leukapheresis according to the intention-to-treat univariable analysis [337]. In summary, **brexucabtagene autoleucel** represents an effective treatment option for adult patients with DLBCL and RR MCL [336].

These drugs are administered to the patient after conditioning with lymphodepleting chemotherapy. The mechanism of action of these drugs includes binding to tumor cells expressing CD19, followed by the activation of signaling pathways through the CD28 and CD3ζ domains, which leads to the activation and proliferation of T-cells and the secretion of inflammatory cytokines and chemokines, the actions of which are aimed at the effective

eradication of malignant cells. Although **tisagenlecleucel**, **axicabtagene ciloleucel**, and **brexucabtagene autoleucel** have potent anticancer effects, they may cause severe adverse reactions, including cytokine release syndrome and neurological toxicity.

Conclusions

Modern trends in the early diagnosis and clarification of the pathogenesis of HMs have allowed us to reconsider therapeutic approaches for HM management. Chemotherapy is an effective method for treating patients with HMs. The first attempt at chemotherapy usage began with the introduction of agents that alkylate DNA, antimetabolites, and antitubulin agents into clinical practice, the activity of which was caused by disruption of both the mitotic band and/or DNA replication. Despite the definite success achieved through the use of DNA-interacting agents, they have typical myelotoxic dose-dependent effects that limit the possibility of treating many forms of HMs. Clinicians are seeking to replace chemotherapy programs with more effective treatments using high-dose chemotherapy followed by SCT or the use of less toxic therapeutic drugs in modern treatment options that actively increase the apoptosis of malignant cells. Nevertheless, MDR mechanisms that can still protect cells against apoptosis exist; therefore MDR remains an actual problem in HM therapy.

An important advancement in onco-hematology has been the development and clinical implementation of targeted drugs as antitumor agents. These drugs include highly specific small molecules and mAbs that inhibit molecular targets involved in the growth and spread of malignant cells. Significant results in overcoming drug resistance have been achieved over the past two decades. Fifty-two new drugs have been registered for the treatment of various HMs. Most such medications are small-molecule drugs, and 23 are macromolecules. Accordingly, drugs containing antitumor-active compounds such as *E. chrysanthemi* asparaginase, mercaptopurine, vincristine sulfate, decitabine, AZA, and a combination of cytarabine and daunorubicin at fixed doses have been registered. The new oral forms of these drugs improve the dosage, reduce side effects, and could improve treatment efficacy and quality of life for patients.

In recent years, eight small-molecule medications have been characterized by new mechanisms of action, such as inhibiting different intracellular proteins and signaling pathways (ibrutinib, idelalisib, dulvalisib, enasidenib, ivosidenib, tazemetostat, VEN, and selinexor). Preparations containing a fixed dose of a combination of two active antitumor ingredients have been synthesized and approved for use in clinical practice. Medications belonging to the category of macromolecules, such as antibodies, enzymes, and cell therapies such as CAR-T cells, are starting to be utilized. An important development in hematology for the treatment of lymphoproliferative diseases was the introduction of mAbs into clinical practice. Following the successful use of anti-CD20 (R), various modifications, including the currently approved immunotoxin and one bispecific mAb, have been developed to improve the therapeutic efficacy of mAbs.

The FDA approved the world's first genetically modified CAR-T therapy in the past decade. As of the end of 2020, three CAR-T therapies (i.e., KYMRIAH, YESCARTA, and TECARTUS) [8–10] were used to treat certain types of leukemia and lymphoma. Cell therapy, including CAR-T-cell therapy, has the advantage of allowing cells to proliferate and expand

for longer periods of time. Therefore they can persist in the patient's blood for months or even years and, for this reason, are called "live drugs." CAR-T cells seem to be a highly promising type of antitumor therapy, especially for patients with RR HMs who have not responded to standard therapy and after targeted treatment of solid tumors.

Thus over the past 20 years, large-scale innovations in treating HMs have been introduced into clinical practice. Due to the expansion of the therapeutic arsenal and the inclusion of many new classes of drugs in therapy, according to the National Cancer Institute, the 5-year relative survival rate for some nosological forms of HM has increased from 34.5% in 2000 to almost 60% today [338].

Acknowledgments

Valeriia Husieva is funded by the EU NextGenerationEU through the Recovery and Resilience Plan for Slovakia under project No. 09I03-03-V02-00020.

References

[1] Huang L, Huang J, Huang J, Xue H, Liang Z, Wu J, Chen C. Nanomedicine—a promising therapy for hematological malignancies. Biomater Sci 2020;8:2376–93.
[2] Nussbaumer S, Bonnabry P, Veuthey JL, Fleury-Souverain S. Analysis of anticancer drugs: a review. Talanta 2011;85(5):2265–89.
[3] Sochacka-Ćwikła A, Mączyński M, Regiec A. FDA—approved drugs for hematological malignancies—the last decade review. Cancer 2022;14(1):1–87.
[4] Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolf JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (Aminopterin). N Engl J Med 1948;238:787–93.
[5] Watson RA, De La Peña H, Tsakok MT, Joseph J, Stoneham S, Shamash J, Joffe J, Mazhar D, Traill Z, Ho L-P, Brand S, Protheroe AS. Development of a best-practice clinical guideline for the use of bleomycin in the treatment of germ cell tumours in the UK. Br J Cancer 2018;119:1044–51.
[6] Doxorubicin Hydrochloride NDA #050467. Drugs@FDA: FDA-approved drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050467. [Accessed 25 August 2021].
[7] Grillo-López AJ, White CA, Dallaire BK, Varns CL, Shen CD, Wei A, Leonard JE, McClure A, Weaver R, Cairelli S, Rosenberg J. Rituximab: the first monoclonal antibody approved for the treatment of lymphoma. Curr Pharm Biotechnol 2000;1:1–9.
[8] YESCARTA (Axicabtagene Ciloleucel). Prescribing information. Available from: https://www.fda.gov/media/108377 /download [Accessed 23 October 2021].
[9] TECARTUS (Brexucabtagene Autoleucel). Prescribing information. Available from: https://www.fda.gov/media/140409/download. [Accessed 23 October 2021].
[10] KYMRIAH (Tisagenlecleucel). Prescribing information. Available from: https://www.fda.gov/media/107296/download. [Accessed 21 October 2021].
[11] Devita Jr VT, Lawrence T, Rosenberg SA, editors. Cancer: principles & practice of oncology: annual advances in oncology. 3rd ed. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Lippincott Williams & Wilkins; 2012.
[12] Hartmann M, Zimmer C. Investigation of cross-link formation in DNA by the alkylating cytostatic IMET 3106, 3393 and 3943. Biochim Biophys Acta 1972;287:386–9.
[13] Kufe DW, Pollock RE, Wiechselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E, editors. Holland-Frei cancer medicine. 6th ed. BC Decker: Hamilton (ON); 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12354/.
[14] Byaraktar UD, Bashir Q, Qazilbash M, Champlin RE, Ciurea SO. Fifty years of MELPHALAN use in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2015;19(3):344–56.

[15] Kumar R, Tutlani A. Alkylating agent used in mutation breeding. Just Agric 2023;3(11):366–73.
[16] Weber GF. DNA damaging drugs. Mol Ther Cancer 2014;9–112.
[17] Rosenberg B, Vancamp L, Krigas T. Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. Nature 1965;205:698–9.
[18] DeVita Jr VT, Simon RM, Hubbard SM, Young RC, Berard CW, Moxley 3rd JH, Frei 3rd E, Carbone PP, Canellos GP. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP treated patients at the National Cancer Institute. Ann Intern Med 1972;92(5):587–95.
[19] Elion GB, Burgi E, Hitchings GH. Studies on condensed pyrimidine systems. IX. The synthesis of some 6-substituted purines. J Am Chem Soc 1952;74:411–4.
[20] Purinethol NDA #009053. Drugs@FDA: FDA-approved drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=009053. [Accessed 24 August 2021].
[21] PURIXAN (Mercaptopurine). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205919s000lbl.pdf. [Accessed 27 September 2021].
[22] Kalaycio M. Bendamustine: a new look at an old drug. Cancer 2009;115:473–9.
[23] Gandhi V. Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. Semin Oncol 2002;29:4–11.
[24] Cheson BD, Wendtner C-M, Pieper A, Dreyling M, Friedberg J, Hoelzer D, Moreau P, Gribben J, Knop S, Montillo M, Rummel M. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. Clin Lymphoma Myeloma Leuk 2010;10(1):21–7.
[25] Friedberg JW, Cohen P, Chen L, Robinson KS, Forero-Torres A, La Casce AS, Fayad LE, Bessudo AS, Camacho ES, Williams ME, van der Jagt RH, Oliver JW, Cheson BD. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicentere, single-agent study. J Clin Oncol 2008;26(2):204–10.
[26] Furukawa Y, Hiraoka N, Wada T, Kikuchi J, Kano Y. Mechanisms of action and clinical effectiveness of the newly approved anti-cancer drug bendamustine. Nihon Yakurigaku Zasshi (Folia Pharmacol Jpn) 2011;138(1):26–32.
[27] Rummel MJ, Chow KU, Hoelzer D, Mitrou PS, Weidmann E. In vitro studies with bendamustine: enhanced activity in combination with rituximab. Semin Oncol 2002;29(4 Suppl 13):12–4.
[28] Corazzelli G, Angrilli F, D'Arco A, Ferrara F, Musto P, Guarini A, Cox MC, Stelitano C, Storti S, Iannitto E, Falorio S, Califano C, Amore A, Arcamone M, De Filippi R, Pinto A. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. Br J Haematol 2013;160(2):207–15.
[29] Herold M, Schulze A, Niederwieser D, Franke A, Fricke HJ, Richter P, Freund M, Ismer B, Dachselt K, Boewer C, Schirmer V, Weniger J, Pasold R, Winkelmann C, Klinkenstein C, Schulze M, Arzberger H, Bremer K, Hahnfeld S, Schwarzer A, Müller C, Chr M. Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO# 19). J Cancer Res Clin Oncol 2006;132:105–12.
[30] Koenigsmann M, Knauf W, Herold M, Pasold R, Müller G, Eschenburg H, Chr K, Lakner V, Assmann M, Jentsch-Ullrich K, Mohren M, Bartsch R, Franke A. Fludarabine and bendamustine in refractory and relapsed indolent lymphoma—a multicenter phase I/II trial of the East German Society of Hematology and Oncology (OSHO). Leuk Lymphoma 2004;45:1821–7.
[31] Rummel MJ, Al-Batran SE, Kim S-Z, Welslau M, Hecker R, Kofahl-Krause D, Josten K-M, Dürk H, Rost A, Neise M, von Grünhagen U, Chow U, K, Hansmann M-L, Hoelzer D, Mitrou PS. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23:3383–9.
[32] Knop S, Straka C, Haen M, Schwedes R, Hebart H, Einsele H. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. Haematologica 2005;90:1287–8.
[33] Pönisch W, Mitrou PS, Merkle K, Herold M, Assmann M, Wilhelm G, Dachselt K, Richter P, Schirmer V, Schulze A, Subert R, Harksel B, Grobe N, Stelzer E, Schulze M, Bittrich A, Freund M, Pasold R, Friedrich T, Helbig W, Niederwieser D. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone—a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). J Cancer Res Clin Oncol 2006;132:205–12.
[34] Cheson BD, Leoni L. Bendamustine: mechanism of action and clinical data. Clin Advanc Hematol Oncol 2011;9(8 Suppl 19):1–12.

[35] Leoni LM, Bailey B, Reifert J, Bendall HH, Zeller RW, Corbeil J, Elliott G, Niemeyer CC. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agent. Clin Cancer Res 2008;14:309–17.
[36] Bergmann MA, Goebeler ME, Herold M, Emmerich B, Wilhelm M, Ruelfs C, Boening L, Hallek MJ. Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. Haematologica 2005;90:1357–64.
[37] Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. J Clin Oncol 2009;27(9):1492–501.
[38] Fischer K, Stilgenbauer S, Schweighofer CD, Bottcher S, Staib P, Kiehl M, Eckat MJ, Kranz G, Goede V, Elter T, Buhler A, Winker D, Kneba M, Dohner H, Eichhnorst BF, Hallek M, Wendtner C-M. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the German CLL Study Group (GCLLSG). Blood 2007;110:913A.
[39] Noble RL. The discovery of the vinca alkaloids—chemotherapeutic agents against cancer. Biochem Cell Biol 1990;68:1344–51.
[40] Silverman JA, Deitcher SR. Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. Cancer Chemother Pharmacol 2013;71:555–64.
[41] Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 1975;36 (1):252–9.
[42] Jones SE, Haut A, Weick JK, Wilson HE, Grozea P, Fabian CJ, McKelvey E, Byrne Jr GE, Hartsock R, Dixon DO, Coltman Jr CA. Comparison of adriamycin-containing chemotherapy (MOP-BAP) with MOPP-bleomycin in the management of advanced Hodgkin's disease. A Southwest Oncology Group Study. Cancer 1983;51 (8):1339–47.
[43] Viviani S, Bonadonna G, Santoro A, Bonfante V, Zanini M, Devizzi L, Soncini F, Valagussa P. Alternating versus hybrid MOPP and ABVD combinations in advanced Hodgkin's disease: tenyear results. J Clin Oncol 1996;14 (5):1421–30.
[44] Glick JH, Young ML, Harrington D, Schilsky RL, Beck T, Neiman R, Fisher RI, Peterson BA, Oken MM. MOPP/ABV hybrid chemotherapy for advanced Hodgkin's disease significantly improves failure-free and overall survival: the 8-year results of the intergroup trial. J Clin Oncol 1998;16(1):19–26.
[45] Duggan DB, Petroni GR, Johnson JL, Glick JH, Fisher RI, Connors JM, Canellos GP, Peterson BA. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 2003;21(4):607–14.
[46] Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, Green MR, Gottlieb A, Peterson BA. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327(21):1478–84.
[47] Behar RA, Horning SJ, Hoppe RT. Hodgkin's disease with bulky mediastinal involvement: effective management with combined modality therapy. Int J Radiat Oncol Biol Phys 1993;25(5):771–6.
[48] Gobbi PG, Levis A, Chisesi T, Broglia C, Vitolo U, Stelitano C, Pavone V, Cavanna L, Santini G, Merli F, Liberati M, Baldini L, Deliliers L, Angelucci E, Bordonaro R, Federico M, Intergruppo Italiano Linfomi. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 2005;23(36):9198–207.
[49] Horning SJ, Hoppe RT, Mason J, Brown BW, Hancock SL, Baer D, Rosenberg SA. Stanford-Kaiser Permanente G1 study for clinical stage I to IIA Hodgkin's disease: subtotal lymphoid irradiation versus vinblastine, methotrexate, and bleomycin chemotherapy and regional irradiation. J Clin Oncol 1997;15(5):1736–44.
[50] Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, Altman RB. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet Genom 2011;21:440–6.
[51] Brittain HG, editor. Profiles of drug substances, excipients and related methodology, Vol. 34. Cambridge, MA, USA: Academic Press; 2009.
[52] Cytarabine NDA #016793. Drugs@FDA: FDA-approved drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016793. [Accessed 29 September 2021].
[53] Dowd F, Johnson B, Mariotti A, editors. Pharmacology and therapeutics for dentistry. 7th ed. Maryland, MI, USA: Mosby; 2017.
[54] Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, Stuart RK, Strickland SA, Hogge D, Solomon SR, Stone RM, Bixby DL, Kolitz JE, Schiller GJ, Wieduwilt MJ, Ryan DH, Hoering A, Banerjee K, Chiarella M, Louie AC, Medeiros BC. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional

cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol 2018;36:2684–92.
[55] Tzogani K, Penttilä K, Lapveteläinen T, Hemmings R, Koenig J, Freire J, Marcia S, Cole S, Coppola P, Flores B, Barbachano Y, Roige SD, Pignatti F. EMA review of daunorubicin and cytarabine encapsulated in liposomes (Vyxeos, CPX-351) for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukemia or acute myeloid leukemia with myelodysplasia-related changes. Oncologist 2020;25:e1414–20.
[56] Cortes JE, Lin TL, Uy GL, Ryan RJ, Faderl S, Lancet J. Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) analysis of CPX-351 versus 7 in older adults with newly diagnosed high-risk/secondary AML. J Hematol Oncol 2021;14(1):110.
[57] Waller CF. Imatinib mesylate. Recent Results Cancer Res 2018;212:1–27.
[58] Kantarjian HM, O'Brien S, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, Shan J, Faderl S, Garcia-Manero G, Thomas DA, Resta D, Talpaz M. Results of imatinib mesylate (STI571) therapy in patients (pts) with chronic myelogenous leukemia (CML) in relapse after allogeneic stem cell transplantation (Allo SCT). Blood 2001;98:137a.
[59] Arico M, Valsecchi MG, Camitta B, Schrappe M, Chessells J, Baruchel A, Gaynon P, Silverman L, Janka-Schaub G, Kamps W, Pui CH, Masera G. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 2000;342:998–1006.
[60] Talpaz M, Silver RT, Druker B, Goldman JM, Gambacorti-Passerini C, Guilhot F, Schiffer CA, Fischer T, Deininger MWN, Lennard AL, Hochhaus A, Ottmann OG, Gratwohl A, Baccarani M, Stone R, Tura S, Mahon F-X, Fernandes-Reese S, Gathmann I, Capdeville R, Kantarjian HM, Sawyers C. Gleevec (formerly STI571): an active drug in patients with Ph+ chronic myeloid leukemia in accelerated phase—updated results of a phase II study. Blood 2001;98:845a.
[61] Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, Schiffer CA, Talpaz M, Guilhot F, Deininger MWN, Fisher T, O'Brien SG, Stone RM, Gambacorti-Passerini CB, Russell NH, Reiffers JJ, Shea TC, Chapuis B, Coutre S, Tura S, Morra E, Larson RA, Saven A, Chr P, Gratwohl A, Mandelli F, Ben-Am M, Gathmann I, Capdeville R, Paquette RL, Druker BJ. Gleevec/Glivec (imatinib mesylate, STI-571) in patients with chronic myeloid leukemia (CML) in myeloid blast crisis: updated results of a phase II study. Blood 2001;98:845a.
[62] Cohen MH, Williams G, Johnson JR, Duan J, Gobburu J, Rahman A, Benson K, Leighton J, Kim SK, Wood R, Rothmann M, Chen G, U MK, Staten AM, Pazdur R. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clin Cancer Res 2002;8:935–42.
[63] Burton C, Azzi A, Kerridge I. Adverse events after imatinib mesylate therapy. N Engl J Med 2002;346:713.
[64] Davids MS, Fisher DC, Tyekucheva S, McDonough M, Hanna J, Lee B, Francoeur K, Montegaard J, Odejide O, Armand P, Arnason J, Brown JR. A phase 1b/2 study of duvelisib in combination with FCR (DFCR) for frontline therapy for younger CLL patients. Leukemia 2021;35(4):1064–72.
[65] Berglof A, Hamasy A, Meinke S, Palma M, Krstic A, Mansson R, Kimby E, Osterborg A, Smith CI. Targets for Ibrutinib beyond B cell malignancies. Scand J Immunol 2015;82(3):208–17.
[66] Sun C, Nierman P, Kendall EK, Cheung J, Gulrajani M, Herman SEM, Pleyer C, Ahn IE, Stetler-Stevenson M, Yuan CM, Maric I, Gaglione EM, Harris HM, Pittaluga S, Wang MH, Patel P, Farooqui MZH, Izumi R, Hamdy A, Covey T, Wiestner A. Clinical and biological implications of target occupancy in CLL treated with the BTK inhibitor acalabrutinib. Blood 2020;136(1):93–105.
[67] Hillmen P, Eichhorst B, Brown JR, Lamanna N, O'Brien SM, Tam CS, Qiu L, Kazmierczak M, Zhou K, Šimkovič M, Mayer J, Gilespie-Twardy A, Shadman M, Ferrajoli A, Ganly PS, Weinkove R, Grosiki S, Mital A, Robak T, Österborg A, Yimer HA, Salmi T, Ji M, Yecies J, Idoine A, Wu K, Huang J, Jurczak W. Zanubrutinib versus Ibrutinib in relapsed/refractory chronic lymphocytic leukemia and Small lymphocytic lymphoma: interim analysis of a randomized phase III trial. J Clin Oncol 2022;41:1035–45.
[68] Dreyling M, Tam CS, Wang M, Smith SD, Ladetto M, Huang H, Novotny W, Co M, Romano A, Holmgren E, Huang J, Le Gouill S. A phase III study of zanubrutinib plus rituximab versus bendamustine plus rituximab in transplant-ineligible, untreated mantle cell lymphoma. Fut Oncol (Lond, Engl) 2021;17(3):255–62.
[69] Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, Šimkovič M, Shadman M, Österborg A, Laurenti L, Walker P, Opat S, Chan H, Ciepluch H, Greil R, Tani M, Trněný M, Brander DM, Flinn IW, Grosicki S, Verner E, Tedeschi A, Li J, Tian T, Zhou L, Marimpietri C, Paik JC, Cohen A, Huang J, Robak T, Hillmen P. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase III trial. Lancet Oncol 2022;23(8):1031–43.

[70] Mato AR, Nabhan C, Barr PM, Ujjani CS, Hill BT, Lamanna N, Skarbnik AP, Howlett Chr PJJ, Sehgal AR, Strelec LE, Vandegrift A, Fitzpatrick DF, Bachow SH, Kaur G, Svoboda J, Nasta SD, Porter D, Landsburg DJ, Schuster SJ, Cheson BD, Kiselev P, Evens AM. Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. Blood 2016;128(18):2199–205.
[71] Barr PM, Owen C, Robak T, Tedeschi A, Bairey O, Burger JA, Hillmen P, Coutre SE, Dearden C, Grosicki S, McCarthy H, Li J-Y, Offner F, Moreno C, Zhou C, Hsu E, Szoke A, Kipps TJ, Ghia P. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv 2022;6(11):3440–50.
[72] Buske C, Tedeschi A, Trotman J, García-Sanz R, MacDonald D, Leblond V, Mahe B, Herbaux C, Matous JV, Tam CS, Heffner LT, Varettoni M, Palomba ML, Shustik C, Kastritis E, Treon SP, Ping J, Hauns B, Arango-Hisijara I, Dimopoulos MA. Ibrutinib plus rituximab versus placebo plus rituximab for Waldenström's Macroglobulinemia: final analysis from the randomized phase III iNNOVATE study. J Clin Oncol 2022;40(1):52–62.
[73] IMBRUVICA. (Ibrutinib). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205552s030,210563s006lblPI.pdf. [Accessed 19 October 2021].
[74] Danilov AV, Persky DO. Incorporating acalabrutinib, a selective next-generation Bruton tyrosine kinase inhibitor, into clinical practice for the treatment of haematological malignancies. Br J Haematol 2021;193(1):15–25.
[75] Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M, Kaplan P, Kraychuk I, Illes A, de la Serna J, Dolan S, Campbell P, Musuraca G, Jacob A, Avery E, Lee JH, Liang W, Patel P, Quan C, Jurczzak W. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2020;38(25):2849–61.
[76] Abbas HA, Wierda WG. Acalabrutinib: a selective Bruton tyrosine kinase inhibitor for the treatment of B-cell malignancies. Front Oncol 2021;11:668162.
[77] CALQUENCE (Acalabrutinib). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf. [Accessed 19 October 2021].
[78] Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, Kamdar M, Munir T, Walewska R, Corbett G, Fogliatto LM, Herishanu Y, Banerji V, Courte S, Follows G, Walker P, Karlsson K, Ghia P, Janssens A, Cymbalista F, Woyach JA, Salles G, Wierda WG, Izumi R, Munugalavadla V, Patel P, Wang MH, Wong S, Byrd JC. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase III trial. Lancet (London, England) 2020;395(10232):1278–91.
[79] Appleby N, Eyre TA, Cabes M, Jackson A, Boucher R, Yates F, Fox S, Rawstron A, Hillmen P, Schuh A. The STELLAR trial protocol: a prospective multicentre trial for Richter's syndrome consisting of a randomised trial investigation CHOP-R with or without acalabrutinib for newly diagnosed RS and a single-arm platform study for evaluation of novel agents in relapsed disease. BMC Cancer 2019;19(1):471.
[80] Smolewski P, Robak T. Current treatment of refractory/relapsed chronic lymphocytic leukemia: a focus on novel drugs. Acta Haematol 2021;144(4):365–79.
[81] Isfort S, Crysandt M, Gezer D, Koschmieder S, Brümmendorf TH, Wolf D. Bosutinib: a potent second-generation tyrosine kinase inhibitor. Recent Results Cancer Res 2018;212:87–108.
[82] Brümmendorf TH, Gambacorti-Passerini C, Bushmakin AG, Cappelleri JC, Viqueira A, Reisman A, Isfort S, Mamolo C. Relationship between molecular response and quality of life with bosutinib or imatinib for chronic myeloid leukemia. Ann Hematol 2020;99(6):1241–9.
[83] Brümmendorf TH, Cortes JE, Milojkovic D, Gambacorti-Passerini C, Clark RE, le Coutre P, Garcia-Gutierrez V, Chuah C, Kota V, Lipton JH, Rousselot P, Mauro MJ, Hochhaus A, Monroy RH, Leip E, Purcell S, Yver A, Viqueira A, Deininger MW, BFORE study investigators. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. Leukemia 2022;36(7):1825–33.
[84] Réa D, Mauro MJ, Boquimpani C, Minam Y, Lomaia E, Voloshin S, Turkina A, Kim D-W, Apperley JF, Abdo A, Fogliatto LM, Kim DDH, le Courte P, Saussele A, Annunziata M, Hughes TP, Chaudhri N, Sasaki K, Chee L, Garcia-Gutierrez V, Cortes JE, Aimone P, Allepuz A, Quenet S, Bedoucha V, Hochhause A. A phase III, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021;138(21):2031–41.
[85] Hochhaus A, Réa D, Boquimpani C, Minami Y, Cortes JE, Hughes TP, Apperley JF, Lomaia E, Voloshin S, Turkina A, Kim D-W, Abdo A, Fogliatto LM, le Courte P, Sasaki K, Kim DDH, Saussele S, Annunziata M, Chaudhri N, Chee L, Garcia-Gutierrez V, Kapoor S, Allepuz A, Quenet S, Bedoucha V, Mauro MJ. Asciminib

vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia 2023;37(3):617–26.
[86] Chuah C, Koh LP, Numbenjapon T, Zang DY, Ong KH, Do YR, Ohkura M, Ono C, Viqueira A, Cortes JE, Brummendorf TH. Efficacy and safety of bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia in the Asian subpopulation of the phase 3 BFORE trial. Int J Hematol 2021;114(1):65–78.
[87] Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, Milojkovic D, le Coutre P, Garcia-Gutierrez V, Crescenzo R, Mamolo C, Reisman A, Hochhaus A, Brummendorf TH, BFOR Study Investigators. Patient-reported outcomes in the phase 3 BFORE trial of bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia. J Cancer Res Clin Oncol 2019;145(6):1589–99.
[88] Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol 2020;95(6):691–709.
[89] Yue X, Hincapie AL, Li Y, Guo JJ. Safety and cost-effectiveness of ponatinib versus other tyrosine kinase inhibitors as second-line therapy in patients with chronic myeloid leukemia in the United States. Leuk Lymphoma 2022;63(4):946–54.
[90] Hoy SM. Ponatinib: a review of its use in adults with chronic myeloid leukaemia or Philadelphia chromosome-positive acute lymphoblastic leukaemia. Drugs 2014;74(7):793–806.
[91] Cortes J, Apperley J, Lomaia E, Moiraghi B, Undurraga Sutton M, Pavlovsky C, Chuah C, Sacha T, Lipton JH, Schiffer CA, McCloskey J, Hochhaus A, Rousselot P, Rosti G, de Lavallade H, Turkina A, Chr R, ChrKA A, Maness L, Talpaz M, Mauro M, Hall T, Lu V, Srivastava S, Deininger M. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood 2021;138(21):2042–50.
[92] Ribera JM, García-Calduch O, Ribera J, Montesinos P, Cano-Ferri I, Martínez P, Esteve J, Esteban D, García-Fortes M, Alonso N, González-Campos J, Bermúdez A, Torrent A, Genescà E, Mercadal S, Martínez-Lopez J, García-Sanz R. Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Adv 2022;6(18):5395–402.
[93] Devos T, Havelange V, Theunissen K, Meers S, Benghiat FS, Gadisseur A, Vanstraelen G, Vellemans H, Bailly B, Granacher N, Lewalle P, De Becker A, Van Eygen K, Janssen M, Triffet A, Vrelust I, Deeren D, Mazare D, Bekaert J, Beck M, Selleslag D. Clinical outcomes in patients with Philadelphia chromosome-positive leukemia treated with ponatinib in routine clinical practice—data from a Belgian registry. Ann Hematol 2021;100(7):1723–32.
[94] Shamroe CL, Comeau JM. Ponatinib: A new tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Pharmacother 2013;47(11):1540–6.
[95] Starr P. Midostaurin the first targeted therapy to improve survival in AML: potentially practice-changing. Am Health Drug Benefits 2016;9:1–21.
[96] Schlenk RF, Sabine KS. Midostaurin: a multiple tyrosine kinases inhibitor in acute myeloid leukemia and systemic Mastocytosis. Recent Results Cancer Res 2018;212:199–214.
[97] Lu H, Weng X-Q, Sheng Y, Wu J, Xi H-M, Cai X. Combination of midostaurin and ATRA exerts dose-dependent dual effects on acute myeloid leukemia cells with wild type FLT3. BMC Cancer 2022;22:749.
[98] Tremblay G, Cariou C, Recher C, Dolph M, Brandt P, Blanc AS, Forsythe A. Cost-effectiveness of midostaurin in the treatment of newly diagnosed FLT3-mutated acute myeloid leukemia in France. Eur J Health Econ 2020;21(4):543–55.
[99] Stein E, Xie J, Duchesneau E, Bhattacharyya S, Vudumula U, Ndife B, Bonifacio G, Guerin A, Li N, Joseph G. Cost effectiveness of midostaurin in the treatment of newly diagnosed FLT3-mutated acute myeloid leukemia in the United States. Pharmacoeconomics 2019;37(2):239–53.
[100] Tzogani K, Yu Y, Meulendijks D, Herberts C, Hennik P, Verheijen R, Wangen T, Hakonsen GD, Kaasboll T, Dalhus M, Bolstad B, Salmonson T, Gisselbrecht C, Pignatti F. European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis. ESMO Open 2019;4(6):e000606.
[101] Jaramillo S, Schlenk RF. Update on current treatments for adult acute myeloid leukemia: to treat acute myeloid leukemia intensively or non-intensively? That is the question. Haematologica 2023;108(2):342–52.
[102] Döhner H, Weber D, Krzykalla J, Fiedler W, Wulf G, Salih H, Lübbert M, Kühn MWM, Schroeder T, Salwender H, Götze K, Westermann J, Fransecky L, Mayer K, Hertenstein B, Ringhoffer M, Tischler H-J, Machherndl-

Spandl S, Schrade A, Paschka P, Gaidzik VI, Thies F, Thol F, Heuser M, Schlenk RF, Bullinger L, Saadati M, Benner A, Larson R, Stone R, Döhner K, Ganser A. Midostaurin plus intensive chemotherapy for younger and older patients with AML and FLT3 internal tandem duplications. Blood Adv 2022;6(18):5345–55.

[103] Döhner K, Thiede C, Jahn N, Panina E, Gambietz A, Larson RA, Prior TW, Marcucci G, Jones D, Krauter J, Heuser M, Voso MT, Ottone T, Nomdedeu JF, Mandreker SJ, Klisovic RB, Wei AH, Sierra J, Sany MA, Brandwein JM, de Witte T, Jansen JH, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Gathmann I, Benner A, Palland C, Stone RM, Döhner H, Bloomfield CD. Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. Blood 2020;135(5):371–80.

[104] Kayser S, Levis MJ. Updates on targeted therapies for acute myeloid leukaemia. Br J Haematol 2022;196 (2):316–28.

[105] Mori M, Kaneko N, Ueno Y, Yamada M, Tanaka R, Saito R, Shimada I, Mori K, Kuromitsu S. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Investig Drugs 2017;35:556–65.

[106] Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, McQuitty M, Hunter DS, Levy R, Knoops L, Cervantes F, Vannucchi AM, Barbui T, Barosi G. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787–98.

[107] Tarver TC, Hill JE, Rahmat L, Perl AE, Bahceci E, Mori K, Smith CC. Gilteritinib is a clinically active FLT3 inhibitor with broad activity against FLT3 kinase domain mutations. Blood Adv 2020;4:514–24.

[108] Pulte ED, Norsworthy KJ, Wang Y, Xu Q, Qosa H, Gudi R, Przepiorka D, Fu W, Okusanya OO, Goldberg KB, De Claro RA, Farrell AT, Pazdur R. FDA approval summary: gilteritinib for relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Clin Cancer Res 2021;27(13):3515–21.

[109] Zhu R, Li L, Nguyen B, Seo J, Wu M, Seale T, Levis M, Duffield A, Hu Y, Small D. FLT3 tyrosine kinase inhibitors synergize with BCL-2 inhibition to eliminate FLT3/ITD acute leukemia cells through BIM activation. Signal Transduct Target Ther 2021;6:186.

[110] Brinton LT, Zhang P, Williams K, Canfield D, Orwick S, Sher S, Wasmuth R, Beaver L, Cempre C, Skinner J, Cannon M, Govade M, Harrington B, Lehman A, Byrd JC, Lapalombella R, Blachly JS. Synergistic effect of BCL2 and FLT3 co-inhibition in acute myeloid leukemia. J Hematol Oncol 2020;13:139.

[111] Ma J, Zhao S, Qiao X, Knight T, Edwards H, Polin L, Kushner J, Dzinic SH, White K, Wang G, Zhao L, Lin H, Taub JW, Ge Y. Inhibition of Bcl-2 synergistically enhances the antileukemic activity of midostaurin and gilteritinib in preclinical models of FLT3-mutated acute myeloid leukemia. Clin Cancer Res 2019;25:6815–26.

[112] Daver N, Perl AE, Maly J, Levis M, Ritchie E, Litzow M, McCloskey J, Smith CC, Schiller G, Bradley T, Tiu RV, Naqvi K, Dail M, Brackman D, Siddani S, Wang J, Chyla B, Lee P, Altman JK. Venetoclax plus gilteritinib for FLT3-mutated relapsed/refractory acute myeloid leukemia. J Clin Oncol 2022;40:4048–59.

[113] DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E, Havelange V, Leber B, Esteve J, Wang J, Pejsa V, Hájek R, Porkka K, Illes A, Lavie D, Lemoli RM, Yamamoto K, Yoon S-S, Jang J-H, Yeh S-P, Turgut M, Hong W-J, Zhou Y, Potluri J, Pratz KW. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383:617–29.

[114] National Comprehensive Cancer Network—NCCN. Clinical Practice Guidelines in Oncology (NCCN GuidelinesR): myelodysplastic syndromes Version 3.2021., 2021, www.nccn.org/professionals/physiciangls/pdf/mds.pdf.

[115] Short NJ, Daver N, Dinardo CD, Kadia T, Nasr LF, Macaron W, Yilmaz M, Borthakur G, Motalban-Bravo G, Garcia-Manero G, Issa GC, Chien KS, Jabbour E, Nasnas C, Huang X, Qiao W, Matthews J, ChrJ S, Patel KP, Abramova R, Thankachan J, Konopleva M, Kantarjian H, Ravadi F. Azacitidine, venetoclax, and gilteritinib in newly diagnosed and relapsed or refractory FLT3-mutated AML. J Clin Oncol 2024;1–10.

[116] Bewersdorf JP, Jaszczur SM, Afifi S, Zhao JC, Zeidan AM. Beyond ruxolitinib: fedratinib and other emergent treatment options for myelofibrosis. Cancer Manag Res 2019;11:10777–90.

[117] Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, Catalano JV, Deininger M, Miller C, Silver RT, Talpaz M, Winton EF, Harvey JH, Arcasoy MO, Hexner E, Lyons RM, Paquette R, Raza A, Vaddi K, Erickson-Viitanen S, Koumenis IL, Sun W, Sandor V, Kantarjian HM. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799–807.

[118] Gerds AT, Yu J, Scherber RM, Paranagama D, Kish JK, Visaria J, Singhal M, Verstovsek S, Pemmaraju N. Ruxolitinib re-treatment in patients with myelofibrosis: real-world evidence on patient characteristics and outcomes. Acta Haematol 2022;145(4):448–53.
[119] Ajayi S, Becker H, Reinhardt H, Engelhardt M, Zeiser R, von Bubnoff N, Wäsch R. Ruxolitinib. Recent Results Cancer Res 2018;212:119–32.
[120] Pardanani A, Tefferi A, Jamieson C, Gabrail NY, Lebedinsky C, Gao G, Liu F, Xu C, Cao H, Talpaz M. A phase 2 randomized dose-ranging study of the JAK2-selective inhibitor fedratinib (SAR302503) in patients with myelofibrosis. Blood Cancer J 2015;5:e335.
[121] Harrison CN, Schaap N, Vannucchi AM, Kiladjian J-J, Passamonti F, Zweegman S, Talpaz M, Verstovsek S, Rose S, Zhang J, Sy O, Mesa RA. Safety and efficacy of fedratinib, a selective oral inhibitor of Janus kinase-2 (JAK2), in patients with myelofibrosis and low pretreatment platelet counts. Br J Haematol 2022;198(2):317–27.
[122] Tremblay D, Mascarenhas J. Pharmacotherapeutic advances for splenomegaly in myelofibrosis. Expert Opin Pharmacother 2023;24(5):577–85.
[123] Waksal JA, Harrison CN, Mascarenhas JO. Novel therapeutics and targets in myelofibrosis. Leuk Lymphoma 2022;63(5):1020–33.
[124] Ragheb M, Harrison CN, McLornan DP. Current and future role of fedratinib in the treatment of myelofibrosis. Fut Oncol (Lond, Engl) 2020;16(6):175–86.
[125] Brown JR, Byrd JC, Coutre SE, Benson DM, Flinn IW, Wagner-Johnston ND, Spurgeon SE, Kahl BE, Bello C, Webb HK, Johnson DM, Peterman S, Li D, Jahn TM, Lannutti B, Ulrich RG, Yu AS, Miller LL, Furman RR. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. Blood 2014;123:3390–9.
[126] Markham A. Copanlisib: first global approval. Drugs 2017;77(18):2057–62.
[127] Frustaci AM, Tedeschi A, Deodato M, Zamprogna G, Cairoli R, Montillo M. Duvelisib for the treatment of chronic lymphoytic leukemia. Expert Opin Pharmacother 2020;21(11):1299–309.
[128] Zirlik K, Veelken H. Idelalisib. Recent results. Cancer Res 2018;212:243–64.
[129] Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, Barrientos JC, Zelenetz AD, Kipps TJ, Finn I, Ghia P, Eradat H, Ervin T, Lamanna N, Coiffier B, Pettitt AR, Ma S, Stigenbauer S, Cramer P, Aiello M, Johnson DM, Miller LL, Li D, Jahn TM, Dansey RD, Hallek M, O'Brien SM. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014;370:997–1007.
[130] O'Brien SM, Lamanna N, Kipps TJ, Flinn I, Zelenetz AD, Burger JA, Keating M, Mirta S, Holes L, Yu AS, Johnson DM, Miller LL, Kim Y, Dansey RD, Dubowy RL, Courte SE. A phase 2 study of idelalisib plus rituximab in treatment-naive older patients with chronic lymphocytic leukemia. Blood 2015;126(25):2686–94.
[131] Madanat Y, Smith M, Almasan A, Hill B. Idelalisib therapy of indolent B-cell malignancies: chronic lymphocytic leukemia and small lymphocytic or follicular lymphomas. Blood Lymph Cancer: Targ Ther 2016;6:1–6.
[132] Huang X, You L, Nepovimova E, Psotka M, Malinak D, Valko M, Sivak L, Korabecny J, Heger Z, Adam V, Wu Q, Kuca K. Inhibitors of phosphoinositide 3-kinase (PI3K) and phosphoinositide 3-kinase-related protein kinase family (PIKK). J Enzyme Inhib Med Chem 2023;38(1):2237209.
[133] Zelenetz AD, Barrientos J, Brown J, Coiffer B, Delgado J, Egyed M, Pristupa AS, Robak T, Sharman JP, Simpson D, Smolej L, Tausch E, Adewoye AH, Dreiling LK, Kim Y, Stilgenbauer S, Hillmen P. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2017;18(3):297–311.
[134] Banerjee T, Kim MS, Haslam A, Prasad V. Clinical trials portfolio and regulatory history of idelalisib in indolent non-Hodgkin lymphoma: asystematic review and meta-analysis. JAMA Intern Med 2023;183(5):435–41.
[135] Shah A, Mangaonkar A. Idelalisib: a novel PI3Kδ inhibitor for chronic lymphocytic leukemia. Ann Pharmacother 2015;49(10):1162–70.
[136] Barrientos JC. Idelalisib for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma. Fut Oncol (Lond, Engl) 2016;12(18):2077–94.
[137] Liu W, Ping L, Xie Y, Sun Y, Du T, Niu Y, Cisternas G, Huang F, Garcia-Vargas J, Childs BH, Mehra A, Reschke S, Wang X, Song Y, Zhu J. A phase I pharmacokinetic study of copanlisib in Chinese patients with relapsed indolent non-Hodgkin lymphoma. Cancer Chemother Pharmacol 2022;89(6):825–31.
[138] Tang X, Chen X, Zhang T, Jiang J. Copanlisib plus rituximab combination therapy vs. rituximab monotherapy for relapsed indolent non-Hodgkin lymphoma: a cost-effectiveness analysis. Ann Transl Med 2022;10(6):352.

[139] Matasar MJ, Capra M, Özcan M, Lv F, Li W, Yañez E, Sapunarova K, Lin T, Jin J, Jurczak W, Hamed A, Wang M-C, Baker R, Bondarenko I, Zhang Q, Feng J, Geissler K, Lazaroiu M, Saydam G, Szomor A, Bouabdallah K, Galiulin R, Uchida T, Soler LM, Cao A, Hiemeyer F, Mehra A, Childs BH, Shi Y, Zinzani PL. Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2021;22(5):678–89.
[140] Magagnoli M, Carlo-Stella C, Santoro A. Copanlisib for the treatment of adults with relapsed follicular lymphoma. Expert Rev Clin Pharmacol 2020;13(8):813–23.
[141] Grunenberg A, Kaiser LM, Woelfle S, Schmelzle B, Viardot A, Möller P, Barth TFE, Muche R, Dreyhaupt J, Raderer M, Kiesewetter B, Chr B. A phase II study of the PI3K inhibitor copanlisib in combination with the anti-CD20 monoclonal antibody rituximab for patients with marginal zone lymphoma: treatment rationale and protocol design of the COUP-1 trial. BMC Cancer 2021;21(1):749.
[142] Rodrigues DA, Sagrillo FS, Fraga CAM. Duvelisib: A 2018 novel FDA-approved small molecule inhibiting phosphoinositide 3-kinases. Pharmaceuticals (Basel) 2019;12(2):69.
[143] Flinn IW, O'Brien S, Kahl B, Patel M, Oki Y, Foss FF, Porcu P, Jones J, Burger JA, Jain N, Kelly VM, Allen K, Douglas M, Sweeney J, Kelly P, Horwitz S. Duvelisib, a novel oral dual inhibitor of PI3K-δ, γ, is clinically active in advanced hematologic malignancies. Blood 2018;131:877–87.
[144] Izutsu K, Kato K, Kiyoi H, Yamamoto G, Shimada K, Akashi K. Phase I study of duvelisib in Japanese patients with relapsed or refractory lymphoma. Int J Hematol 2020;112(4):504–9.
[145] Lolli G, Casadei B, Pellegrini C, Argnani L, Cocito F, Zinzani PL. Duvelisib as bridge to allotransplantation in refractory peripheral T-cell lymphoma with T-follicular helper phenotype: case report. Tumori 2021;107(6): NP105–7.
[146] Lee HZ, Kwitkowski VE, Del Valle PL, Ricci MS, Saber H, Habtemariam BA, Bullock J, Bloomquist E, Shen YL, Chen X-H, Brown J, Mehrotra N, Dorff S, Charlab R, Kane RC, Kaminskas E, Justice R, Farrell AT, Pazdur R. FDA approval: belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Clin Cancer Res 2015;21:2666–70.
[147] Laubach JP, Schjesvold F, Mariz M, Dimopoulos MA, Lech-Maranda E, Spicka I, Hungria VTM, Shelekhova T, Abdo A, Jacobasch L, Polprasert C, Hajek R, Illes A, Wrobel T, Sureda A, Beksac M, Goncalves I, Blade J, Rajkumar SV, Chari A, Lonial S, Spencer A, Maison-Blanche P, Moreau P, San-Miguel JF, Richardson PG. Efficacy and safety of oral panobinostat plus subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma (PANORAMA 3): an open-label, randomised, phase 2 study. Lancet Oncol 2021;22(1):142–54.
[148] Zhang L, Zhang J, Jiang Q, Zhang L, Song W. Zinc binding groups for histone deacetylase inhibitors. J Enzyme Inhib Med Chem 2018;33:714–21.
[149] El Omari N, Bakrim S, Khalid A, Albratty M, Abdalla AN, Lee L-H, Goh KW, Ming LC, Bouyahya A. Anticancer clinical efficiency and stochastic mechanisms of belinostat. Biomed Pharmacother 2023;165:115–212.
[150] O'Connor O, Masszi T, Savage K, Pinter-Brown L, Foss F, Popplewell L, Cashen AF, Doordujn J, Chawla S, Knoblauch P, Zinzani PL, Brown P, Hess G, Van Hoof A, Horwitz SM, Shustov AR. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): results from the BELIEF trial. J Clin Oncol 2013;31(15):8507.
[151] Sawas A, Radeski D, Owen A, O'Connor O. Belinostat in patients with refractory or relapsed peripheral T-cell lymphoma: a perspective review. Therap Adv Hematol 2015;6(4):202–8.
[152] Juergens R, Wrangle J, Vendetti F, Murphy S, Zhao M, Coleman B, Sebree R, Rodgers K, Hooker CM, Franco N, Lee B, Tsai S, Delgalo IE, Rudek MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM. Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. Cancer Discov 2011;1(7):598–607.
[153] Wolf JL, Siegel D, Goldschmidt H, Hazell K, Bourquelot PM, Bengoudifa BR, Matous J, Vij R, de Magalhaes-Silverman M, Abonour R, Anderson KC, Lonial S. Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. Leuk Lymphoma 2012;53(9):1820–3.
[154] San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, Jedrzejczak WW, Günther A, Nakorn TN, Siritanaratkul N, Corradini P, Chuncharunee S, Lee J-J, Schlossman RL, Shelekhova T, Tong K, Tan D, Numbenjapon T, Cavenagh JD, Hou J, LeBlanc R, Nahi H, Qiu L, Salwender H, Pulini S, Moreau P, Warzocha K, White D, Blade J, Ocio EM, Veskovski L, Sohn SK, Wang M-C, Lee JH, Einsele H, Sopala M, Corrado C, Bengoudifa B-R, Binlich F, Richardson PG. Panobinostat plus bortezomib and dexamethasone versus placebo

plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15(11):1195–206.
[155] Eleutherakis-Papaiakovou E, Kanellias N, Kastritis E, Gavriatopoulou M, Terpos E, Dimopoulos MA. Review article efficacy of panobinostat for the treatment of multiple myeloma. Hindawi J Oncol 2020;2020:7131802.
[156] Kaufman JL, Mina R, Jakubowiak AJ, Zimmerman TL, Wolf JJ, Lewis C, Gleason C, Sharp C, Martin T, Heffener LT, Nooka AK, Harvey RD, Lonial S. Combining carfilzomib and panobinostat to treat relapsed/refractory multiple myeloma: results of a multiple myeloma research consortium phase i study. Blood Cancer J 2019;9(1):3.
[157] Chari A, Cho HJ, Dhadwal A, Morgan G, La L, Zaychta K, Catamero D, Florendo E, Stevens N, Verina D, Chan E, Leshchenko V, Lagana A, Perumal D, Mei AH-C, Tung K, Fukui J, Jagannath S, Parekh S. A phase 2 study of panobinostat with lenalidomide and weekly dexamethasone in myeloma. Blood Adv 2017;1(19):1575–83.
[158] Popat R, Brown SR, Flanagan L, Hall A, Gregory W, Kishore B, Streetly M, Oakervee H, Yong K, Cook G, Low E, Cavenagh J, Myeloma UK Early Phase Clinical Trial Network. Bortezomib, thalidomide, dexamethasone, and panobinostat for patients with relapsed multiple myeloma (MUK-six): a multicentre, open-label, phase 1/2 trial. Lancet Haematol 2016;3(12):e572–80.
[159] Gao L, Gao M, Yang G, Tao Y, Kong Y, Yang R, Meng X, Ai G, Wei R, Wu H, Wu X, Shi J. Synergistic activity of carfilzomib and panobinostat in multiple myeloma cells via modulation of ROS generation and ERK1/2. Biomed Res Int 2015;9:459052.
[160] Berdeja JG, Hart LL, Mace JR, Arrowsmith ER, Essell JH, Owera RS, Hainsworth JD, Flinn IW. Phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma. Haematologica 2015;100(5):670–6.
[161] Waitkus MS, Diplas BH, Yan H. Isocitrate dehydrogenase mutations in gliomas. Neuro-Oncology 2016;18:16–26.
[162] Norsworthy KJ, Luo L, Hsu V, Gudi R, Dorff SE, Przepiorka D, Deisseroth A, Shen Y-L, ChrM S, Charlab R, Williams GM, Goldberg KB, Farrell AT, Pazdur R. FDA approval summary: ivosidenib for relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-1 mutation. Clin Cancer Res 2019;25:3205–9.
[163] Amatangelo MD, Quek L, Shih A, Stein EM, Roshal M, David MD, Marteyn B, Farnoud NR, de Botton S, Bernard OA, Wu B, Yen KE, Tallman MS, Papaemmanuil E, Penard-Lacronique V, Thakurta A, Vyas P, Levine R. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. Blood 2017;130:732–41.
[164] Fathi AT, Kim HT, Soiffer RJ, Levis MJ, Li S, Kim AS, DeFilipp Z, El-Jawahri A, McAfee SL, Brunner AM, Amrein PC, Mims AS, Knight LW, Kelley D, Bottoms AS, Perry LH, Wahl JL, Brock J, Breton E, Marchoine DM, Ho VT, Chen Y-B. Multicenter phase I trial of Ivosidenib as maintenance treatment following allogeneic hematopoietic cell transplantation for IDH1-mutated acute myeloid leukemia. Clin Cancer Res 2023;29(11):2034–42.
[165] Liu X, Gong Y. Isocitrate dehydrogenase inhibitors in acute myeloid leukemia. Biomark Res 2019;7:22.
[166] Klink AJ, Gajra A, Knoth RL, Marshall L, Hou Y, McBride A, Copher R. Real-world clinical outcomes with enasidenib in relapsed or refractory acute myeloid leukemia. Leuk Res 2022;122:106946.
[167] Cai SF, Huang Y, Lance JR, Mao HC, Dunbar AJ, McNulty SN, Druley T, Li Y, Baer MR, Stock W, Kovacsovics T, Blum WG, Schiller GJ, Olin RL, Foran JM, Litziw M, Lin T, Patel P, Foster MC, Boyiadzis M, Collins RH, Chervin J, Shoben A, Vergilio J-A, Heerema NA, Rosenberg L, Chen TL, Yocum AO, Druggan F, Marcus S, Stefanos M, Druker BJ, Mims AS, Borate U, Burd A, Byrd JC, Levine RL, Stein EM. A study to assess the efficacy of enasidenib and risk-adapted addition of azacitidine in newly diagnosed IDH2-mutant AML. Blood Adv 2024;8(2):429–40.
[168] Venugopal S, Takahashi K, Daver N, Maiti A, Borthakur G, Loghavi S, Short NJ, Ohanian M, Masarova L, Issa G, Wang X, Carlos B-R, Yilmaz M, Kadia T, Andreeff M, Ravandi F, Konopleva M, Kantarjian HM, DiNardo CD. Efficacy and safety of enasidenib and azacitidine combination in patients with IDH2 mutated acute myeloid leukemia and not eligible for intensive chemotherapy. Blood Cancer J 2022;12(1):10.
[169] Bewersdorf JP, Patel KK, Goshua G, Shallis RM, Podoltsev NA, Stahl M, Stein EM, Huntington SF, Zeidan AM. Cost-effectiveness of azacitidine and ivosidenib in newly diagnosed older, intensive chemotherapy-ineligible patients with IDH1-mutant acute myeloid leukemia. Leuk Lymphoma 2023;64(2):454–61.
[170] Italiano A, Soria JC, Toulmonde M, Michot J-M, Lucchesi C, Varga A, Coindre J-M, Blakemore SJ, Clawson A, Suttle B, McDonald AA, Woodruff M, Ribich S, Hedrick E, Keilhack H, Thomson B, Owa T, Copeland RA, Ho PTC, Ribrag V. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. Lancet Oncol 2018;19:649–59.

[171] Ribrag V, Soria J-C, Michot J-M. Phase 1 study of Tazemetostat (EPZ-6438), an inhibitor of enhancer of Zeste-homolog 2 (EZH2): preliminary safety and activity in relapsed or refractory non-Hodgkin lymphoma (NHL) patients. Blood 2015;126:473.
[172] Munakata W, Shirasugi Y, Tobinai K, Onizuka M, Makita S, Suzuki R, Maruyama D, Kawai H, Izutsu K, Nakanishi T, Shiba S, Hojo S, Ando K. Phase 1 study of tazemetostat in Japanese patients with relapsed or refractory B-cell lymphoma. Cancer Sci 2021;112(3):1123–31.
[173] Izutsu K, Ando K, Nishikori M, Shibayama H, Teshima T, Kuroda J, Kato K, Imaizumi Y, Nosaka K, Sakai R, Hojo S, Nakanishi T, Rai S. Phase II study of tazemetostat for relapsed or refractory B-cell non-Hodgkin lymphoma with EZH2 mutation in Japan. Cancer Sci 2021;112(9):3627–35.
[174] Batlevi CL, Park SL, Phillips TJ, Amengual J, Andorsky DJ, Campbell P, McKay P, Leonard JP, Sondhi M, Yang J, Chen Y, O'Connor H, Slatcher P, Morschhauser F. Updated interim analysis of the randomized phase 1b/3 study of tazemetostat in combination with lenalidomide and rituximab in patients with relapsed/refractory follicular lymphoma. J Clin Oncol 2022;40(16_suppl):7572.
[175] Lyko F. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. Nat Rev Genet 2017;19:81–92.
[176] Schapira M. Structural chemistry of human RNA methyltransferases. ACS Chem Biol 2016;11:575–82.
[177] Keating GM. Azacitidine. Drugs 2012;72:1111–36.
[178] European Medicines. Agency Vidaza: EPAR—product information. Available from: [Accessed 6 March 2023].
[179] Serizawa K, Tanaka H, Morita Y, Taniguchi T, Ashida T, Matsumura I. Immunemodulatory effects of 5-azacitidin through expansion of functional regulatory T cells on paraneoplastic inflammation associated with myelodysplastic syndromes: a case report. Front Oncol 2018;8:204.
[180] Food and Drug. Administration VIDAZA® (azacitidine). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050794s011lbl.pdf [Accessed 6 March 2023].
[181] Yamauchi H, Yokoyama M, Mishima Y, Nishimura N, Ueda K, Kusano Y, Inoue N, Takahashi A, Terui Y, Hatake K. Azacitidine is effective in the therapy related myelodysplastic syndrome. Blood 2016;128(22):5554.
[182] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, Schoch R, Gattermann N, Sanz G, List A, Gore SD, Seymour JF, Bennett JM, Byrd J, Backstorm J, Zimmerman L, McKenzie D, Cl B, Silverman LR. Efficacy of Azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223–32.
[183] Fenaux P, Haase D, Santini V, Sanz GF, Platzbecker U, Mey U. Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32(2):142–56.
[184] ONUREG (Azacitidine). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214120s000lbl.pdf. [Accessed 15 September 2021].
[185] US Food and Drug Administration. ONUREG (azacitidine) tablets. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214120s000lbl.pdf. [Accessed 6 March 2023. European Medicines Agency. Onureg: EPAR—product information. Available from: https://www.ema.europa.eu/en/documents/product-information/onureg-epar-product-nformation_en.pdf [Accessed 6 March 2023].
[186] Tabah A, Huggar D, Wang S-T, Johnson SJ, Ronda M, Copher RM, O'Connell T, McBride A, LeBlanc TW. Indirect treatment comparison of oral versus injectable azacitidine as maintenance therapy for acute myeloid leukemia. Future Oncol 2022;18(37):4089–99.
[187] Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, Ravandi F, Sayar H, Jang JH, Porkka K, Selleslag D, Sandhu I, Turgut M, Giai V, Ofran Y, Cakar MK, de Sousa AB, Rybka J, Ch F, Borin L, Beltrami G, Cernak J, Ossenkoppele GJ, La Torre I, Skikne B, Kumar K, Dong Q, Roboz GJ. The QUAZAR AML-001 Maintenance Trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission. Blood 2019;134:LBA-3.
[188] Zeidan AM, Salimi T, Robert S, Epstein RE. Real-world use and outcomes of hypomethylating agent therapy in higher-risk myelodysplastic syndromes: why are we not achieving the promise of clinical trials? Fut Oncol 2021;17(36):5163–74.
[189] Garcia-Manero G, Döhner H, Wei AH, La Torre I, Skikne B, Beach CL, Santin V. Oral azacitidine (CC-486) for the treatment of myeloid malignancies. Clin Lymph Myeloma Leuk 2022;22(4):236–50.
[190] Witlox W, Grimm S, Howick J, Armstrong N, Ahmadu C, McDermot K, Otten T, Noake C, Wolff R, Manuela JM. Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics 2023;41(8):857–67.

[191] Ravandi F, Roboz GJ, Wei AH, Döhner H, Pocock C, Selleslag D, Montesinos P, Sayar H, Musso M, Figuera-Alvarez A, Sayar H, Musso M, Figuera-Alvarez A, Safah H, Tse W, Sohn SK, Hiwase D, Chevassut T, Pierdomenico F, La Torre I, Skikne B, Bailey R, Zhong J, Beach CL, Dombret H. Management of adverse events in patients with acute myeloid leukemia in remission receiving oral azacitidine: experience from the phase 3 randomized QUAZAR AML-001 trial. J Hematol Oncol 2021;14(1):133.
[192] Decitabine NDA #021790. Drugs@FDA: FDA-approved drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021790. [Accessed 4 October 2021].
[193] Plimack ER, Kantarjian HM, Issa JP. Decitabine and its role in the treatment of hematopoietic malignancies. Leuk Lymphoma 2007;48:1472–81.
[194] Thota S, Oganesian A, Azab M, Elizabeth A, Griffiths EA. Role of cedazuridine/decitabine in the management of myelodysplastic syndrome and chronic myelomonocytic leukemia. Fut Oncol 2021;17(16):2077–87.
[195] Norsworthy KJ, By K, Subramaniam S, Zhuang L, Del Valle PL, Przepiorka D, Shen Y-L, ChrM S, Liu C, Leong R, Goldberg KB, Farrell AT, Pazdur R. FDA approval summary: glasdegib for newly diagnosed acute myeloid leukemia. Clin Cancer Res 2019;25:6021–5.
[196] Solem CT, Bell TJ, Kwon Y. A quality-adjusted survival time without symptoms or toxicities analysis of glasdegib plus low-dose cytarabine versus low-dose cytarabine as initial therapy for acute myeloid leukemia in patients who are not considered candidates for intensive chemotherapy. Cancer 2020;126(19):4315–21.
[197] Cortes JE, Heide FH, Hellmann A, Fiedler W, Smith BD, Robak T, Montesinos P, Pollyea DA, DesJardins P, Ottmann O, Ma WW, Shaik MN, Laird AD, Zeremski M, O'Connell A, Chan G, Heuser M. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia 2019;33:379–89.
[198] Thomas X, Heiblig M. An evaluation of glasdegib for the treatment of acute myelogenous leukemia. Expert Opin Pharmacother 2020;21:523–30.
[199] Li J, Cai H, Li H, Liu Y, Wang Y, Shi Y, Sun Y, Song H, Wang D. Combined inhibition of sonic hedgehog signaling and histone deacetylase is an effective treatment for liver cancer. Oncol Rep 2019;41(3):1991–7.
[200] Kurnia Wijaya J, Djawad K, Wahab S, Nurdin A, Anwar AI. Vismodegib and sonidegib in locally advanced and metastatics basal cell carcinoma: update on hedgehog pathway inhibitors. Actas Dermo-Sifiliogr 2022;113(5):t443–50.
[201] Woltsche N, Pichler N, Wolf I, Di Meo N, Zalaudek I. Managing adverse effects by dose reduction during routine treatment of locally advanced basal cell carcinoma with the hedgehog inhibitor vismodegib: a single centre experience. J Eur Acad Dermatol Venereol 2019;33(4):e144–5.
[202] Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Carton ND, Chen J, Dayton BD, Ding H, Enschede SL, Fairbrother WJ, Huang DCS, Hymowitz SG, Jin S, Khaw SL, Kovar PJ, Lam LT, Lee J, Maecker HL, Marsh KC, Mason KD, Mitten MJ, Nimmer PM, Oleksijew A, Park CH, Park C-M, Phillips DC, Roberts AW, Sampath D, Seymour JF, Smith ML, Sullivan GM, Tahir SK, Tse C, Wendt MD, Xiao Y, Xue JC, Zhang H, Humerickhouse RA, Rosenberg SH, Elmore SW. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013;19:202–8.
[203] Konopleva M, Contractor R, Tsao T, Samudio I, Ruvolo PP, Kitada S, Deng X, Zhai D, Shi Y-X, Sneed T, Verhaegen M, Soengas M, Ruvolo VR, McQueen T, Schober WD, Watt JC, Jiffar T, Ling X, Marini FC, Harris D, Dietrich M, Estrov Z, McCubrey J, May WS, Reed JC, Andreeff M. Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. Cancer Cell 2006;10:375–88.
[204] Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, Kipps TJ, Anderson MA, Brown JR, Gressick L, Wong S, Dunbar M, Zhu M, Desai MB, Cerri E, Enschede SH, Humerickhouse RA, Wierda WG, Seymour JF. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:311–22.
[205] Stilgenbauer S, Eichhorst B, Schetelig J, Courte S, Seymour JF, Munir T, Puvvada SD, Wendtner C-M, Roberts AW, Jurczak W, Mulligan SP, Bottcher S, Mobaster M, Zhu M, Desai M, Chyla B, Verdugo M, Enschede SH, Cerri E, Humerickhouse R, Gordon G, Hallek M, Wierda WG. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016;17:768–78.
[206] Jelinek T, Hajek R. PD-1/PD-L1 inhibitors in multiple myeloma: the present and the future. Onco Targets Ther 2016;5:e1254–6.
[207] Touzeau C, Dousset C, Le Gouill S, Sampath D, Leverson JD, Souers AJ, Maïga S, Bene MC, Moreau P, Pellat-Deceunynck C, Amiot M. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t(11;14) multiple myeloma. Leukemia 2014;28:210–2.

[208] Touzeau C, Le Gouill S, Mahé B, Boudreault JS, Gastinne T, Blin N, Cailon H, Chr D, Amiot M, Moreau P. Deep and sustained response after venetoclax therapy in a patient with very advanced refractory myeloma with translocation t(11;14). Haematologica 2017;102:e112–4.
[209] Matulis SM, Gupta VA, Nooka AK, Hollen HV, Kaufman JL, Lonial S, Boise LH. Dexamethasone treatment promotes Bcl-2 dependence in multiple myeloma resulting in sensitivity to venetoclax. Leukemia 2016;30:1086–93.
[210] Kumar S, Vij R, Kaufman JL, Mikhael J, Facon T, Pegourie B, Benboubker L, Gasparetto C, Amiot M, Moreau P, Alzate S, Ross J, Dunbar M, Xu T, Agarwal S, Leverson J, Maciag P, Verdugo M, Touzeau C. Venetoclax monotherapy for relapsed/refractory multiple myeloma: safety and efficacy results from a phase I study. Blood 2016;128:48.
[211] Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, McKeegan E, Salem AH, Zhu M, Ricker JL, Blum W, DiNardo CD, Kadia T, Dunbar M, Kirby R, Falotico N, Leverson J, Humerickhouse R, Marby M, Stone R, Kantarjian H, Letai A. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov 2016;6:1106–17.
[212] DiNardo CD, Pollyea DA, Jonas BA, Konopleva M, Pullarkat V, Wei A, Kantarjian HM, Pigneux A, Chr R, Seymour JF, Dunbar M, Xu T, Mabry M, Potluri J, Pratz K, Letai A. Updated safety and efficacy of venetoclax with decitabine or azacitidine in treatment naive, elderly patients with acute myeloid leukemia. Blood 2017;130:2628.
[213] Wei A, Strickland SA, Roboz GJ, Hou J-Z, Fiedler W, Lin TL, Walter RB, Enjeti A, Chyla B, Popovic R, Fakouhi K, Shah P, Dunbar M, Xu T, Marby M, Hayslip J. Phase 1/2 study of venetoclax with low-dose cytarabine in treatment-naive, elderly patients with acute myeloid leukemia unfit for intensive chemotherapy: 1-year outcomes. Blood 2017;130:890.
[214] Cao Y, Yang G, Hunter ZR, Liu X, Xu L, Chen J, Tsakmaklis N, Hatjiharissi E, Kanan S, Davids MS, Castillo JJ, Treon SP. The BCL2 antagonist ABT-199 triggers apoptosis, and augments ibrutinib and idelalisib mediated cytotoxicity in CXCR4 wild-type and CXCR4 WHIM mutated Waldenstrom macroglobulinaemia cells. Br J Haematol 2015;170:134–8.
[215] Seymour JF, Ma S, Brander DM, Choi MY, Barrientos J, David MS, Anderson MA, Beaven AW, Rosen ST, Tam CS, Prine B, Agarwal SK, Munasinghe W, Zhu M, Lash LL, Desai M, Cerri E, Verdugo M, Kim SY, Humerickhouse RA, Gordon GB, Kipps T, Roberts AW. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. Lancet Oncol 2017;18:230–40.
[216] Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, Owen C, Gerecitano J, Robak T, De la Serna J, Jaeger U, Carton G, Montillo M, Humerickhouse R, Punnoose EA, Li Y, Boyer M, Humphrey K, Mobasher M, Kater AP. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2018;378(12):1107–20.
[217] Munir T, Cairns DA, Bloor A, Allsup D, Cwynarski K, Pettitt A, Paneesha S, Fox CP, Eyre TA, Forconi F, Elmusharaf N, Ben K, Gribben J, Pemberton N, Sheehy O, Preston G, Schuh A, Walewska R, Duley L, Howard D, Hockaday A, Jackson S, Greatorex N, Girvan S, Bell S, Brown JM, Webster N, Dalal S, de Tute R, Rawstron A, Patten PEM, Hillmen P, National Cancer Research Institute Chronic Lymphocytic Leukemia Subgroup. Chronic lymphocytic leukemia therapy guided by measurable residual disease. N Engl J Med 2024;390(4):326–37.
[218] Jones J, Choi MY, Mato AR, Furman RR, Davids MS, Heffen LT, Cheson BD, Lamanna N, Barr PM, Eradat H, Halwani A, Chyla B, Zhu M, Verdugo M, Humerickhouse RA, Potluri J, Wierda WG, Courte SE. Venetoclax (VEN) monotherapy for patients with chronic lymphocytic leukemia (CLL) who relapsed after or were refractory to ibrutinib or idelalisib. Blood 2016;128:63.
[219] Rogers KA, Huang Y, Stark A, Jones JA. Initial results of the phase 2 treatment-naive cohort in a phase 1b/2 study of obinutuzumab, ibrutinib, and venetoclax in CLL. Blood 2017;130(suppl 1).
[220] Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, Robrecht S, Warburton S, Humphrey K, Samoylova O, Liberati AM, Pinila-Ibarz J, Opat S, Sivcheva L, Le Du K, Fogliatto LM, Niemann CU, Weinkove R, Robison S, Kipps TJ, Boettcher S, Tausch E, Humerickhouse R, Eichhorst B, Wendtner C-M, Langerak AW, Kreuzer K-A, Ritgen M, Goede V, Stilgenbauer S, Mobasher M, Hallek M. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med 2019;380(23):2225–36.
[221] Eichhorst E, Niemann C, Kater AP, Fürstenau M, von Tresckow J, Zhang C, Robrecht S, Gregor M, Juliusson G, Patrick Thornton P, Philipp B, Staber PB, Tamdor T, Lindstrom V, da Cunha-Bang C, Chr S, ChrB P, Th I,

Schotther B, Th N, Janssens A, Christiansen I, Baumann M, Frederiksen H, van der Klift M, Jager U, MBL L, Hoogendoorn M, Lotfi K, Hebart H, Gaska T, Koene H, Enggaard L, Goede J, Regelink JC, Winmer A, Simon F, De Silva N, Fink A-M, Bahlo J, Fischer K, Wendtner C-M, Kreuzer KA, Ritgen M, Bruggemann M, Tausch E, Levin M-D, van Oers M, Chr G, Stilgenbauer S, Hallek M, GCLLSG, the HOVON and Nordic CLL Study Groups, the SAKK, the Israeli CLL Association, and Cancer Trials Ireland. First-line venetoclax combinations in chronic lymphocytic leukemia. N Engl J Med 2023;388(19):1739–54.

[222] DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letia A, Fenaux P, Koller E, Havelange V, Leber B, Esteve J, Wang J, Pejsa V, Hajek R, Porkka K, Illes A, Lavie D, Lemoli RM, Yamamoto K, Yoon S-S, Jang J-H, Yeh S-P, Turgut M, Hong W-J, Zhou Z, Potluri J, Pratz KW. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383:617–29.

[223] Mihalyova J, Jelineka T, Growkova K, Hrdinka M, Simicek M, Hajek R. Venetoclax: a new wave in hematooncology. Exp Hematol 2018;61:10–25.

[224] Vogl DT, Dingli D, Cornell RF, Huff CA, Jagannath S, Bhutani D, Zonder J, Baz R, Nooka A, Ritcher J, Cole C, Vij R, Jakubowiak A, Abonour R, Schiller G, Parker TL, Costa LJ, Kaminetzky D, Hoffman JE, Yee AJ, Chari A, Siegel D, Fonesca R, Van Wier S, Ahmann G, Lopez I, Kauffman M, Schacham S, Saint-Martin J-R, Picklesimer CD, Choe-Juliak C, Stewart AK. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. J Clin Oncol 2018;36:859–66.

[225] Gupta A, Saltarski JM, White MA, Scaglioni PP, Gerber DE. Therapeutic targeting of nuclear export inhibition in lung cancer. J Thorac Oncol 2017;12(9):1446–50.

[226] Argueta C, Kashyap T, Klebanov B, Unger TJ, Guo C, Harrington S, Baloglu E, Lee M, Senapedis W, Shacham S, Landesman Y. Selinexor synergizes with dexamethasone to repress mTORC1 signaling and induce multiple myeloma cell death. Oncotarget 2018;9(39):25529–44.

[227] Giliberto M, Govinda T, Raj DB, Cremaschi A, Skanland SS, Gade A, Tjonnfjord GE, Schjesvold F, Munthe LA, Tasken K. Ex vivo drug sensitivity screening in multiple myeloma identifies drug combinations that act synergistically. Mol Oncol 2022;16(6):1241–58.

[228] Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, Moreau P, Dingli D, Cole C, Lonial S, Dimopoulos M, Stewart AK, Richter J, Vij R, Tuchman S, Raab MS, Weisel KC, Delforge M, Cornell RF, Kaminetzky D, Hoffman JE, Costa LJ, Parker TL, Levy M, Schreder M, Meuleman N, Frenzel L, Mohty M, Choquet S, Schiller G, Comenzo RL, Engelhardt M, Illmer T, Vlummens P, Doyen C, Facon T, Karlin L, Perrot A, Podar K, Kauffman MG, Shacham S, Li L, Tang S, Picklesimer C, Saint-Martin J-R, Crocjiere M, Chang H, Samir P, Landesman Y, Shah J, Richardson PG, Jagannath S. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med 2019;381(8):727–38.

[229] Karyopharm Therapeutics Inc. XPOVIO® (selinexor) tablets, for oral use, US prescribing information 2022. [Accessed 23 February 2023]. Available from: https://www.karyopharm.com/wp-content/uploads/2019/07/NDA-212306-SN-0071-Prescribing-Information-01July2019.pdf.

[230] Stemline Therapeutics BV Selinexor summary of product characteristics. 2023. [Accessed 23 February 2023]. Available from: https://www.ema.europa.eu/en/documents/product-information/nexpovio-epar-product-information_en.pdf.

[231] Grosicki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M, Pylypenko H, Auner HW, Leleu X, Doronin V, Usenko G, Bahlis NJ, Hajek R, Benjamin R, Dolai TK, Sinha DK, ChrP V, Garg M, Gironella M, Jurczyszyn A, Robak P, Galli M, Wallington-Beddoe C, Radinoff A, Salogub G, Stevens DA, Basu S, Liberati AM, Quach H, Goranova-Marinova VS, Bila J, Katodritou E, Oliynyk H, Korenkova S, Kumar J, Jagannath S, Moreau P, Levy M, White D, Gatt ME, Facon T, Mateos MV, Cavo M, Reece D, Anderson Jr LD, Saint-Martin J-R, Jeha J, Joshi AA, Chai Y, Li L, Peddagali V, Arazy M, Shah J, Shacham S, Kauffman MG, Dimopoulos MA, Richardson PG, Delimpasi S. Once-per-week selinexor, BTZ, and DEX versus twice-per-week BTZ and Dex in patients with MM (BOSTON): a randomised, open-label, phase 3 trial. Lancet 2020;396(10262):1563–73.

[232] White DJ, LeBlanc R, Baljevic M, Bahlis N, Lentzsch S, Venner CP, Gasparetto C, ChrI C, Lipe BC, Tuchman SA, Sutherland HJ, Kotb R, Sebag M, Callander NS, Bensinger WI, Rossi AC, Biran N, Sheehan H, Van Domelen D, Zhou T, Kai K, Shah J, Shacham S, Kauffman MG, Schiller GJ. Selinexor, lenalidomide and Dex (SRd) for patients with relapsed/refractory and newly diagnosed multiple myeloma. Blood 2020;136(Suppl 1):18–9.

[233] White DJ, Chen CI, Baljevic M, Tuchman SA, Bahlis NJ, Schiller GJ, Lipe B, Kotb R, Sutherland HJ, Bensinger WI, Madan S, Sebag M, Lentzsch S, Callander NS, Biran N, ChrP V, Leblanc R, Monge J, Chubar E, Tamdor T, Lavi N, Leiba M, De Castro A, Van Domenelen DR, Zhang C, Mishal M, Bentur OS, Shah JJ, Shacham S, Kauffman MG, Gasparetto CJ. Once weekly oral selinexor, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma. Blood 2021;138(Suppl 1):2748.

[234] Gasparetto C, Lentzsch S, Schiller G, Callander N, Tuchman S, Chen C, White D, Kotb R, Sutherland H, Sebag M, Baljevic M, Bensinger W, LeBlanc R, Venner C, Bahlis N, Rossi A, Biran N, Sheehan H, Saint-Martin J-R, Van Domelen D, Kai K, Shah J, Shacham S, Kauffman M, Lipe B. Selinexor, daratumumab, and dexamethasone in patients with relapsed or refractory multiple myeloma. EJHaem 2021;2(1):56–65.
[235] Rodríguez-Otero P, De La Calle GV, Sureda A, De Arriba F, Reinoso Segura RM, Ribas P, Gonzalez AP, Gonzalez-Montes Y, Oriol A, Martínez-López J, Gonzalez MS, Hernández MT, Sirvent M, Creixenti JB, Lahuerta JJ, San-Miguel JF, Mateos M-V. Selinexor in combination with daratumumab-bortezomib and dexamethasone for the treatment of relapse or refractory multiple myeloma: initial results of the phase 2, open-label, multicenter GEM-selibordara study. Blood 2021;138(Suppl 1):1677.
[236] Nguyen N, Chaudhry S, Totiger TM, Diaz R, Roberts E, Montoya S, Pardo G, Afaghani J, Affer M, Jahn J, Bradley T, Maura F, Kazandjian D, Bilbao D, Champan J, Landgren O, Hoffman J, Taylor J. Combination venetoclax and selinexor effective in relapsed refractory multiple myeloma with translocation t(11;14). NPJ Precis Oncol 2022;6(1):73.
[237] XPOVIO (Selinexor). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212306s005lbl.pdf. [Accessed 20 September 2021].
[238] Adams J. Proteasome inhibition in cancer: development of PS-341. Semin Oncol 2001;28(6):613–9.
[239] Adams J. Discovery—velcade®: a new tool in the fight against multiple myeloma. Available from: National Cancer Institute; 2014 [2022 June 07] https://www.cancer.gov/research/progress/discovery/velcade.
[240] Davis C, Spaller BL, Matouschek A. Mechanisms of substrate recognition by the 26S proteasome. Curr Opin Struct Biol 2021;67:161–9.
[241] Mao Y. Structure, dynamics and function of the 26S proteasome. Subcell Biochem 2021;96:1–151.
[242] Wang X, Cimermancic P, Yu C, Schweitzer A, Chopra N, Engel JL, Greenberg C, Huszagh AS, Beck F, Sakata E, Yang Y, Novitski EJ, Leitener A, Nanni P, Kahraman A, Guo X, Dixon JE, Rychnovsky SD, Aebersold R, Baumeister W, Sali A, Huang L. Molecular details underlying dynamic structures and regulation of the human 26S proteasome. Mol Cell Proteomics 2017;16:840–54.
[243] Schweitzer A, Aufderheide A, Rudack T, Beck F, Pfeifer G, Plitzko JM, Plitzko JM, Sakata E, Schulten K, Förster F, Baumeister W. Structure of the human 26S proteasome at a resolution of 3.9 Å. Proc Natl Acad Sci U S A 2016;113:7816–21.
[244] Jakubowiak AJ, Griffith KA, Reece DE, Hofmeister CC, Lonial S, Zimmerman TM, Campagnaro EL, Schlossman RL, Laubach JP, Raje NS, Anderson T, Mietzel MA, Harvey CK, Wear SM, Barrickman JC, Tender CL, Esseltine D-L, Kelley SL, Kaminski MS, Anderson KC, Richardson PG. Lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone in newly diagnosed multiple myeloma: a phase 1/2 Multiple Myeloma Research Consortium trial. Blood 2011;118:535–43.
[245] Yau NK, Fong AY, Leung HF, Verhoeft KR, Lim QY, Lam WY, Wong ICK, VWYA L. Pan-Cancer review of ALK mutations: implications for carcinogenesis and therapy. Curr Cancer Drug Targets 2015;15:327–36.
[246] Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, Tageja N, Kazandijan D, Mailankody S, Wu P, Morrison C, Costello R, Zhang Y, Burton D, Mulqiun M, Zuchlinski D, Lamping L, Carpenter A, Wall Y, Carter G, SchC C, Gouden V, Sissung TM, Peer C, Maric I, Calvo KR, Braylan R, Yuan C, Stetler-Stevenson M, Arthur DC, Kong KA, Weng L, Faham M, Lindenberg L, Kurdziel K, Choyke P, Steinberg SM, Figg W, Landgren O. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA. Oncologia 2015;1:746–54.
[247] Vesole DH, Bilotti E, Richter JR, McNeill A, McBride L, Raucci L, Anand P, Bednarz U, Ivanovski K, Smith J, Barta V, Aleman A, Sims T, Guerrero L, Mato A, Siegel DS. Phase I study of carfilzomib, lenalidomide, vorinostat, and dexamethasone in patients with relapsed and/or refractory multiple myeloma. Brit J Haematol 2015;171(1):52–9.
[248] Richardson PG, Baz R, Wang M, Jakubowiak AJ, Lach JP, Harvey RD, Talpaz M, Berg D, Liu G, Yu J, Gupta N, Di Bacco A, Hui A-M, Lonial S. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. Blood 2014;124:1038–46.
[249] Alwahsh M, Farhat J, Talhouni S, Hamadneh L, Hergenröder R. Bortezomib advanced mechanisms of action in multiple myeloma, solid and liquid tumors along with its novel therapeutic applications. EXCLI J 2023;22:146–68.
[250] Tutt A, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, Gelber RD, de Azambuja E, Fielding A, Balmaña J, Domchek SM, Gelmon KA, Hollingsworth SJ, Korde L, Linderholm B, Bandos H, Senkus E, Suga JM, Shao Z, Pippas AW, Nowecki Z, Huzarski T, Ganz PA, Lucas PC, Baker N, Loibl S, McConnel R, Piccart M, Schmutzler R, Steger GG, Constantino JP, Arahmati A, Wolmark N, McFadden E, Karantza V, Lakhani SR, Yothers G, Chr

C, Geyer Jr CE, OlimpiA Clinical Trial Streering Committee and Investigators. Olympi A: a phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. J Clin Oncol 2021;39 (18_Suppl):LBA1–LBA.
[251] Ibata S, Sato T, Kuroda H, Nagamachi Y, Iyama S, Fujimi A, Kamihara Y, Konuma Y, Yoshida M, Tatekoshi A, Hashimoto A, Horiguchi H, Ono K, Musare K, Takada K, Miyanishi K, Konube M, Hirayama Y, Kato J. A phase II trial of small-dose bortezomib, lenalidomide and dexamethasone (sVRD) as consolidation/maintenance therapy in patients with multiple myeloma. Cancer Chemother Pharmacol 2016;78:1041–9.
[252] NINLARO (Ixazomib). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf. [Accessed 21 September 2021].
[253] KYPROLIS (Carfilzomib). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202714s030lbl.pdf. [Accessed 21 September 2021].
[254] Parlati F, Lee SJ, Aujay M, Suzuki E, Levitsky K, Lorens JB, Micklem DR, Ruus P, Sylvan C, Lu Y, Shenk KD, Bennett MK. Carfilzomib can induce tumor cell death through selective inhibition of the chymotrypsin-like activity of the proteasome. Blood 2009;114(16):3439–47.
[255] Gupta N, Hanley MJ, Xia C, Labotka R, Harvey RD, Venkatakrishnan K. Clinical pharmacology of Ixazomib: the first oral proteasome inhibitor. Clin Pharmacokinet 2019;58:431–49.
[256] Engelhardt M, Szymaniak-Vits M, Ajayi S, Dold SM, Müller SJ, Scheubeck S, Wäsch R. Carfilzomib. Recent Results Cancer Res 2018;212:265–83.
[257] Imtiaz H, Khan M, Ehsan H, Wahab A, Rafae A, Khan AY, Jamil A, Sana MKM, Jamal A, Ali TJ, Ansar I, Khan MM, Khouri J, Anwer F. Efficacy and toxicity profile of carfilzomib-based regimens for treatment of newly diagnosed multiple myeloma: a systematic review. Onco Targets Ther 2021;14:4941–60.
[258] Millennium Pharmaceuticals Inc. NINLARO® (ixazomib) capsules, for oral use. United States prescribing Information., 2016, https://www.ninlaro.com/prescribing-information.pdf. [Accessed 1 June 2018].
[259] Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, Sandhu I, Ganly P, Baker BW, Jackson SR, Stoppa A-M, Simpson DR, Gimsing P, Palumbo A, Garderet L, Cavo M, Kumar S, Touzeau C, Baudi KF, Laubach JP, Berg D, Lin J, Di Bacco A, Hui A-M, van de Velde H, Richardson PG, TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374 (17):1621–34.
[260] Chen Y, Li S. Omacetaxine mepesuccinate in the treatment of intractable chronic myeloid leukemia. Onco Targets Ther 2014;7:177–86.
[261] Alvandi F, Kwitkowski VE, Ko CW, Rothmann MD, Ricci S, Saber H, Ghosh D, Brown J, Pfeiler E, Chikhale E, Grillo J, Bullock J, Kane R, Kaminskas E, Farrell AT, Pazdur RUS. Food and Drug Administration approval summary: omacetaxine mepesuccinate as treatment for chronic myeloid leukemia. Oncologist 2013;19(1):94–9.
[262] Gandhi V, Plunkett W, Cortes JE. Omacetaxine: a protein translation inhibitor for treatment of chronic myelogenous leukemia. Clin Cancer Res 2014;20(7):1735–40.
[263] Rehman W, Arfons LM, Lazarus HM. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. Ther Adv Hematol 2011;2(5):291–308.
[264] Gini G, Tani M, Tucci A, Marcheselli L, Cesaretti M, Bellei M, Pascarella A, Ballerini F, Petrini M, Merli F, Olivieri A, Lanza F, Annibali O, Zilioli VR, Liberati AM, Tisi MC, Arcari A, Marino D, Musucara G, Pavone V, Fabbri A, Pozzi S, Mannina D, Plenteda C, Celli M, Luminari S. Lenalidomide plus rituximab for the initial treatment of frail older patients with DLBCL: the FIL_ReRi phase 2 study. Blood 2023;142(17):1438–47.
[265] Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011;86:57–65.
[266] Weisel K, Kanz L. Lenalidomide. Recent Results Cancer Res 2014;201:347–57.
[267] Chanan-Khan AA, Swaika A, Paulus A, Kumar SK, Mikhael JR, Rajkumar SV, Dispenzieri A, Lacy MQ. Pomalidomide: the new immunomodulatory agent for the treatment of multiple myeloma. Blood Cancer J 2013;3:e143.
[268] POMALYST (Pomalidomide). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204026s024lbl.pdf. [Accessed 28 September 2021].
[269] Ríos-Tamayo R, Martín-García A, Alarcón-Payer C, Sánchez-Rodríguez D, del Valle Díaz de la Guardia AM, CGG C, Morales AJ, Chacón MJ, Barrera JC. Pomalidomide in the treatment of multiple myeloma: design, development and place in therapy. Drug Des Devel Ther 2017;11:2399–408.

[270] Richardson PG, Oriol A, Beksac M, Liberati AM, Galli M, Schjesvold F, Lindsay J, Weisel K, White D, Facon T, Miguel JS, Sunami K, O'Gorman P, Sonneveld P, Robak P, Semochkin S, Schey S, Yu X, Th D, Bensmaine A, Biyukov T, Peluso T, Zaki M, Anderson K, Dimopoulos M, OPTIMISMM Trial Investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:781–94.
[271] Siegel DS, Schiller GJ, Song KW, Agajanian R, Stockerl-Goldstein K, Kaya H, Sebag M, Chr S, Malek E, Talamo G, ChrS S, Mouro J, Pierceall WE, Zafar F, Chung W, Srinivasan S, Agarwal A, Bahlis NJ. Pomalidomide plus low-dose dexamethasone in relapsed refractory multiple myeloma after lenalidomide treatment failure. Br J Haematol 2020;188:501–10.
[272] Wester R, Dinmohamed AG, van der Holt B, Zweegman S, Minnema M, Croockewit S, Mark-David L, Libourel E, de Waal E, Sonneveld P, Cornelissen J, Blijlevens N, Broijl A. Pomalidomide in patients with relapsed and/or refractory multiple myeloma: a prospective study within the Nationwide Netherlands Cancer Registry. HemaSphere 2022;6(2):e683.
[273] Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, Siegel D, Borello I, Rajkumar SV, Chanan-Khan AA, Lonial S, Yu Z, Patin J, Olesnyckyj M, Zeldis JB, Knight RD, Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133–42.
[274] Richardson P, Anderson K. Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma. J Clin Oncol 2002;22:3212–4.
[275] Posner J, Barrington P, Brier T, Datta-Mannan A. Monoclonal antibodies: past, present and future. Handb Exp Pharmacol 2019;260:81–141.
[276] Bayer V. An overview of monoclonal antibodies. Semin Oncol Nurs 2019;35(5):150927.
[277] Duell J, Abrisqueta P, Andre M, Gaidano G, Gonzales-Barca E, Jurczak W, Kalakonda N, Liberati AM, Maddocks KJ, Menne T, Nagy Z, Tournilhac O, Chr K, Bakuli A, Amin A, Gurbanov K, Salles G. Tafasitamab for patients with relapsed or refractory diffuse large B-cell lymphoma: final 5-year efficacy and safety findings in the phase II L-MIND study. Haematologica 2024;109(2):553–66.
[278] Weiner GJ. Rituximab: mechanism of action. Semin Hematol 2010;47(2):115–23.
[279] Onrust SV, Lamb HM, Balfour JA. Rituximab. Drugs 1999;58(1):79–90.
[280] Rierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab—The World's First Oncology Monoclonal Antibody Therapy. Front Oncol 2018;8(163).
[281] TRUXIMA (Rituximab-abbs). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761088s000lbl.pdf. [Accessed 8 October 2021].
[282] RUXIENCE (Rituximab-pvvr). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761103s000lbl.pdf. [Accessed 8 October 2021].
[283] RIABNI (Rituximab-arrx). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761140s000lbl.pdf. [Accessed 8 October 2021].
[284] USA FDA. [Last accessed on 2013 Nov 20]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125486s000lbl.pdf.
[285] GAZYVA (Obinutuzumab). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125486s017s018lbl.pdf. [Accessed 8 October 2021].
[286] National Cancer Institute at the National Institutes of Health. [Last accessed on 2013 Nov20]. Available from: http://www.cancer.gov/drugdictionary?cdrid=570643.
[287] Owen C, Stewart DA. Obinutuzumab for the treatment of lymphoproliferative disorders. Expert Opin Biol Ther 2012;12:343–51.
[288] Cartron G, Watier H. Obinutuzumab: what is there to learn from clinical trials? Blood 2017;130(5):581–9.
[289] Sachdeva M, Dhingra S. Obinutuzumab: a FDA approved monoclonal antibody in the treatment of untreated chronic lymphocytic leukemia. Int J Appl Basic Med Res 2015;5(1):54–7.
[290] Davies A, Kater AP, Sharman JP, Stilgenbauer S, Vitolo U, Klein C, Parreira J, Salles G. Obinutuzumab in the treatment of B-cell malignancies: a comprehensive review. Fut Oncol 2022;18(26):2943–66.
[291] US Food and Drug Administration. FDA approves Darzalex for patients with previously treated multiple myeloma. Press Release. November 16, 2015 www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm472875.htm. [Accessed 19 December 2015].

[292] DARZALEX FASPRO (Daratumumab and hyaluronidase-fihj). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761145s002lbl.pdf. [Accessed 11 October 2021].
[293] Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, Belch A, Krishnan A, Vescio RA, Mateos MV, Mazumder A, Orlowski RZ, Sutherland HJ, Bladé J, Scott EC, Oriol A, Berdeja J, Gharibo M, Stevens DA, LeBlanc R, Sebag M, Callander N, Jakubowiak A, White D, de la Rubia J, Richardson PG, Lisby S, Feng H, Uhlar CM, Khan I, Ahmadi T, Voorhees PM. Phase II study of daratumumab (DARA) monotherapy in patients with ≥3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius), J Clin Oncol 2015;33(18).
[294] Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, Minnema MC, Lassen U, Krejcik J, Palumbo A, van de Donk NWCJ, Ahmadi T, Khan I, Uhlar CM, Wang J, Sasser AK, Losic N, Lisby S, Basse L, Brun N, Richardson PG. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015;373:1207–19.
[295] Raedler LA. Darzalex (Daratumumab): first anti-CD38 monoclonal antibody approved for patients with relapsed multiple myeloma. Am Health Drug Benefits 2016;9:70–3.
[296] DARZALEXFASPRO (Daratumumab and Hyaluronidase-fihj). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761145s002lbl.pdf. [Accessed 11 October 2021].
[297] SARCLISA (Isatuximab-irfc). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761113s003lbl.pdf. [Accessed 11 October 2021].
[298] Frampton JE. Isatuximab: a review of its use in multiple myeloma. Target Oncol 2021;16(5):675–86.
[299] Ritchie D, Colonna M. Mechanisms of action and clinical development of elotuzumab. Clin Transl Sci 2018;11(3):261–6.
[300] Gentile M, Vigna E, Palmieri S, Galli M, Derudas D, Mina R, Della Pepa R, Zambello R, Martino EA, Bruzzese A, Mangiacavalli S, Zamagni E, Califano C, Musso M, Conticello C, Cerchione C, Mele G, Di Renzo N, Offidani M, Tarantini G, Casaluci GM, Rago A, Ria R, Uccello G, Barilà G, Palumbo G, Pompa A, Vincelli D, Brunori M, Accardi F, Amico V, Amendola A, Fontana R, Bongarzoni V, Rossini B, Cotzia E, Gozzetti A, Rizzi R, Sgherza N, Ferretti E, Bertuglia G, Nappi D, Petrucci MT, Di Raimondo F, Neri A, Morabito F, Musto P. Elotuzumab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma: a multicenter, retrospective, real-world experience with 200 cases outside of controlled clinical trials. Haematologica 2024;109(1):245–55.
[301] Reiss KA, Forde PM, Brahmer JR. Harnessing the power of the immune system via blockade of PD-1 and PD-L1: a promising new anticancer strategy. Immunotherapy 2014;6(4):459–75.
[302] Giulino-Roth L. Pembrolizumab in PMBCL: can it go the distance? Blood 2023;142(2):121–2.
[303] Wang C, Thudium KB, Han M, Wang XT, Huang H, Feingersh D, Garcia C, Wu Y, Kuhne M, Srinivasan M, Singh S, Wong S, Garner N, Leblanc H, Bunch RT, Blanset D, Selby MJ, Korman AJ. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res 2014;2(9):846–56.
[304] Watson S, Marx JB. Mogamulizumab-kpkc: a novel therapy for the treatment of cutaneous T-cell lymphoma. J Adv Pract Oncol 2019;10(8):883–8.
[305] USA Food & Drug Administration. Biologics License Application 761051 product quality review, 2018. Retrieved from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761051Orig1s000ChemR.pdf.
[306] Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, Duvic M. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018;19(9):1192–204.
[307] Duvic M, Pinter-Brown LC, Foss FM, Sokol L, Jorgensen JL, Challagundla P, Kim YH. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. Blood 2015;125(12):1883–9.
[308] Ma J, Mo Y, Tang M, Shen J, Qi Y, Zhao W, Huang Y, Xu Y, Qian C. Bispecific antibodies: from research to clinical application. Front Immunol 2021;12:626616.
[309] Sigmund AM, Sahasrabudhe KD, Bhatnagar B. Evaluating blinatumomab for the treatment of relapsed/refractory ALL: design, development, and place in therapy. Blood Lymphat Cancer 2020;10:7.

[310] Mirfakhraie R, Dehaghi BK, Ghorbi MD, Ghaffari-Nazari H, Mohammadian M, Salimi M, Ardakani MT, Parkhideh S. All about blinatumomab: the bispecific T cell engager immunotherapy for B cell acute lymphoblastic leukemia. Hematol Transfus Cell Ther 2023. S2531-1379(23)00148-7.
[311] Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct Ther 2022;7(93).
[312] Yurkiewicz IR, Muffly L, Liedtke M. Inotuzumab ozogamicin: a CD22 mAb-drug conjugate for adult relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Drug Des Devel Ther 2018;12:2293–300.
[313] Lamb YN. Inotuzumab ozogamicin: first global approval. Drugs 2017;77(14):1603–10.
[314] Huse K, Bai B, Vera I, Hilden V, Bollum LK, Våtsveen TK, Munthe LA, Smeland EB, Irish JM, Wälchli S, Myklebust JH. Mechanism of CD79A and CD79B support for IgM+ B cell fitness through B cell receptor surface expression. J Immunol 2022;209(10):2042–53.
[315] Nikolaenko L, Nademanee A. Brentuximab vedotin and its use in the treatment of advanced Hodgkin's lymphoma. Future Oncol 2020;16(29):2273–82.
[316] ADCETRIS (Brentuximab Vedotin). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125388s097lbl.pdf. [Accessed 18 October 2021].
[317] Bowers JT, Jacob A, Bair SM, Annunzio K, Epperla N, Pullukkara JJ, Gaballa S, Spinner MA, Li S, Messmer MR, Nguyen J, Ayers EC, Wagner CB, Hu B, Di M, Huntington SF, Furqan F, Shah NN, Chr C, Ballard HJ, Hughes ME, Chong EA, Nasta SD, Barta SK, Landsburg DJ, Svoboda J. Brentuximab vedotin plus AVD for Hodgkin lymphoma: incidence and management of peripheral neuropathy in a multisite cohort. Blood Adv 2023;7(21):6630–8.
[318] Cho SF, Anderson KC, Tai YT. Targeting B cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMAbased immunotherapy. Front Immunol 2018;9:1821.
[319] BLENREP (Belantamab Mafodotin-Blmf). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf. [Accessed 18 October 2021].
[320] Wang B, Wu C, Zhong Q. Belantamab mafodotin for the treatment of multiple myeloma. Drugs Today 2021;57:653–63.
[321] Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, Richardson PG, Hoos A, Gupta I, Bragulat V, He Z, Opalinska JB, Cohen AD. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer J 2019;9(4):37.
[322] de la Rubia J, Alonso R, Clavero ME, Askari E, García A, Antón C, Fernández M, Escalante F, García A, Rios-Tamayo R, Conesa V, Bermúdez MA, Merchán B, Velasco AE, Blanchard MJ, Sampol A, Gainza E, Hernández PM, Alegre A. Belantamab mafodotin in patients with relapsed/refractory multiple myeloma: results of the compassionate use or the expanded access program in Spain. Cancers (Basel) 2023;15(11):2964.
[323] Trudel S, McCurdy A, Louzada ML, Parkin S, White D, Chu MP, Kotb R, Mian H, Othman I, Su J, Khan A, Gul E, Reece D. Belantamab mafodotin, pomalidomide and dexamethasone in refractory multiple myeloma: a phase 1/2 trial. Nat Med 2024;30:543–51.
[324] Dhillon S. Moxetumomab Pasudotox: first global approval. Drugs 2018;78(16):1763–7.
[325] LUMOXITI (Moxetumomab Pasudotox-Tdfk). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761104s000lbl.pdf. [Accessed 19 October 2021].
[326] Yurkiewicz IR, Coutre S, Ghesquieres H, Pastan I, Kreitman RJ. Moxetumomab pasudotox as re-treatment for heavily-pretreated relapsed hairy cell leukemia. Leuk Lymphoma 2021;62(11):2812–4.
[327] Kreitman RJ, Dearden C, Giles F. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Leukemia 2018;32:1768–77.
[328] ERWINAZE (Asparaginase Erwinia Chrysanthemi). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125359lbl.pdf. [Accessed 20 October 2021].
[329] ASPARLAS (Calaspargase Pegol—mknl). Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761102s000lbl.pdf. [Accessed 20 October 2021].
[330] Mullard A. FDA approves first CAR-T therapy. Nat Rev Drug Discov 2017;16(10):669.
[331] Awasthi R, Maier HJ, Zhang J, Lim S. Kymriah® (tisagenlecleucel)—an overview of the clinical development journey of the first approved CAR-T therapy. Hum Vaccin Immunother 2023;19(1):2210046.
[332] Rives S, Maude SL, Hiramatsu H, Baruchel A, Bader P, Bittencourt H, Buechner J, Laetsch T, De Moerloose B, Qayed M, Buechner J, Pulsipher MA, Myers GD, Stefanski HE, Martin PL, Nemecek E, Chr P, Yanik G, Khaw

SL, Davis KL, Krueger J, Balduzzi A, Boissel N, Tiwari R, O'Donovan D, Grupp SA. Tisagenlecleucel in pediatric and young adult patients (Pts) with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL): final analyses from the eliana study. HemaSphere 2022;6:1–8.

[333] John S, Pulsipher MA, Moskop A, Hu Z-H, Phillips CL, Hall EM, Margossian SP, Nikiforow S, Martin PL, Oshrine B, Keating AK, Rouce RH, Tiwari R, Redondo S, Willert J, Agarwal A, Pasquini MC, Grupp SA. Real-world outcomes for pediatric and young adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) treated with tisagenlecleucel: update from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry. Blood 2021;138:428.

[334] Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, Sauter C, Wang Y, Santomasso B, Mead E, Roshal M, Maslak P, Davila M, Brentjens R, Sadelian M. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med Overseas Ed 2018;378(5):449–59.

[335] Neelapu SS, Chavez JC, Sehgal AR, Epperla N, Ulrickson M, Bachy E, Munshi PN, Casulo C, Maloney DG, de Vos S, Reshef R, Leslie LA, Oluwole OO, Yakoub-Agha I, Khanal R, Rosenbaltt J, Korn R, Peng W, Chr L, Wulff J, Shen R, Poddar S, Jung AS, Miao H, Beygi S, Jacobson CA. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Blood 2024;143(6):496–506.

[336] Deshpande A, Wang Y, Munoz J, Jain P. Brexucabtagene autoleucel: a breakthrough in the treatment of mantle cell lymphoma. Drugs Today (Barc) 2022;58(6):283–98.

[337] Wang Y, Jain P, Locke FL, Maurer MJ, Frank MJ, Munoz JL, Dahiya S, Jain MD. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in standard-of-care practice: results from the US lymphoma CAR T consortium. J Clin Oncol 2023;41(14).

[338] National Cancer Institute. Surveillance, epidemiology, and end results program. Bethesda, MD: National Cancer Institute; 2023. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html.