Experimental Hematology

Experimental Hematology 2018;61:10–25

REVIEW

Venetoclax: A new wave in hematooncology

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(Received 13 November 2017; revised 31 January 2018; accepted 5 February 2018)

Inhibitors of antiapoptotic proteins of the BCL2 family can successfully restart the deregulated process of apoptosis in malignant cells. Whereas nonselective agents have been limited by their affinity to different BCL2 members, thus inducing excessive toxicity, the highly selective BCL2 inhibitor venetoclax (ABT-199, Venclexta™) has an acceptable safety profile. To date, it has been approved in monotherapy for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) with 17p deletion. Extension of indications can be expected in monotherapy and in combination regimens. Sensitivity to venetoclax is not common in lymphomas, but promising outcomes have been achieved in the mantle cell lymphoma group. Venetoclax is also active in multiple myeloma patients, especially in those with translocation t(11;14), even if high-risk features such as del17p are also present. Surprisingly, positive results are being obtained in elderly acute myeloid leukemia patients, in whom inhibition of BCL2 is able to substantially increase the efficacy of low-dose cytarabine or hypomethylating agents. Here, we provide a summary of available results from clinical trials and describe a specific mechanism of action that stands behind the efficacy of venetoclax in hematological malignancies.

Eukaryotic cells can die in many ways, including physiological and mostly beneficial modes of death (e.g., apoptosis, necroptosis, and pyroptosis), as well as nonphysiological and harmful necrotic cell destruction [1]. The classical form of cell death, apoptosis, is a gene-directed process of cell suicide characterized by specific biochemical and morphological changes including activation of proteolytic enzymes, caspases, cell shrinkage, membrane blebbing, chromatin condensation, and nuclear fragmentation. In this process, the cellular content is not released, so apoptosis is noninflammatory and the remaining apoptotic bodies are removed by phagocytes [2]. Apoptosis plays vital roles in embryogenesis, tissue homeostasis, defense against pathogens, and elimination of neoplastic cells. However, deregulated apoptotic processes might promote the development of autoimmune, neurodegenerative, and oncologic diseases as well as resistance of cancer cells to chemotherapy [3,4].

Apoptosis is triggered by two independent signaling pathways, intrinsic or extrinsic. Although both pathways in the last steps rely on the same executioner caspases (caspase-3, caspase-6, and caspase-7), each pathway is activated differently [5,6]. The extrinsic pathway is set off by membrane death receptors belonging to the tumor necrosis factor (TNF) receptor superfamily, which recognize their cognate extracellular ligands (e.g., FasR/FasL or CD95/CD95L, TNFR1/TNFα, DR3/TL1A, DR4/TRAIL-RI, and DR5/TRAIL-RII) [7]. Conversely, the intrinsic (mitochondrial) pathway is activated by excessive cellular stress and other pro-apoptotic events (e.g., heat, radiation, nutrient deprivation, viral infection, hypoxia, increased intracellular calcium concentration, and DNA mutations) and is orchestrated by proteins of the BCL2 family [3]. Each BCL2 family member harbors one or more BCL2 homology (BH) domains (BH1-4), that mediate protein–protein interactions. The BCL2 family is divided into two major functional groups. The first group includes the

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0301-472X/
https://doi.org/10.1016/j.exphem.2018.02.002

pro-apoptotic (pro-death) proteins BAD, BIK, NOXA, BMF, PUMA, BIM, BID, and HRK (BH3-only proteins) that activate the apoptotic effectors BAX and BAK. The second group contains the anti-apoptotic (prosurvival) proteins BCL2, BCL-XL, BCL-W, A1, and MCL-1 that bind and sequester members of the first group to prevent apoptosis. Mechanistically, when the cell receives the right signals to undergo apoptosis, the BH3-only proteins oligomerize with the effectors BAX and BAK and cause permeabilization of mitochondrial outer membrane. As a result, cytochrome c is released from mitochondria and activates caspase-dependent cell death [8–13].

Clearly, enhanced function of anti-apoptotic proteins would make cells more resistant to apoptosis induction. Indeed, deregulation of BCL2 and other anti-apoptotic proteins has been demonstrated to be an important resistance mechanism in solid tumors [14–16] and hematologic malignancies [17–20]. For instance, the main player, BCL2, is often overexpressed due to 18q21 translocations; for example, t(14;18)(q32;q21), which juxtaposes the BCL2 gene under the constitutive activation of the immunoglobulin heavy-chain gene promoter [20] or due to various chromosome amplifications and deletions [17,21,22]. Alternatively, the cells can acquire an anti-apoptotic advantage indirectly via mechanisms involving tumor suppressor protein p53. As a transcription factor, p53 is able to induce transcription of BAX [23] and some BH3-only proteins (PUMA, NOXA, BID) [24,25] directly or even act as a BH3-only protein itself [26,27]. Therefore, mutations of the *TP53* gene interfering with these p53 functions can inactivate mitochondrial apoptotic pathway. Similarly, the proto-oncogene c-MYC regulates apoptosis by inducing expression of pro-apoptotic genes (BAX, BAK, BIM, PUMA and NOXA) [28–30] and suppressing expression of anti-apoptotic (BCL2 and BCL-XL) genes [31]. However, in cancer cells that overexpress mutated c-MYC, the apoptotic safety mechanism is blocked by inappropriate expression of some anti-apoptotic molecules (BCL2, BCL-XL, and MCL-1) [32–34].

Because impaired apoptosis plays a key role in cancer resistance to therapy, pharmacologic inhibition of anti-apoptotic proteins, especially BCL2, represents an attractive way to force clonal cells to die. Indeed, a number of chemical agents, the so-called BH3 mimetics, which are targeted to anti-apoptotic proteins, have been designed and tested in recent years. These drugs include nonselective inhibitors (AT-101, TW37, apogossypolone [ApoG2], obatoclax [GX15-070], ABT-737) and the BH3-only mimetic, navitoclax (ABT-263) [35–38]. Although navitoclax binds effectively only to BCL2, BCL-XL, and MCL-1, its high affinity to BCL-XL limits its clinical use due to significant thrombocytopenia that restricts dose escalation and safe anticancer administration [39–41].

In this review, we focus on the highly selective BCL2 inhibitor venetoclax and its use in hematological malignancies. We present a brief summary of molecular mechanisms, principles of resistance, and main toxicities accompanied by an overview of available clinical studies (Tables 1–6).

Venetoclax: mechanism of action

Venetoclax (ABT-199, GDC-0199, Venclexta™) is a unique, small, and highly selective orally bioavailable molecule that was designed to target specifically the BH3 domain of BCL2 [42]. As a BH3 mimetic, venetoclax displays a high affinity to the BH3-binding groove of BCL2 and is able to displace pro-apoptotic BH3-only proteins (e.g., BIM) bound to BCL2. Therefore, free BH3-only proteins can activate apoptotic effectors (BAX and BAK) or inhibit other anti-apoptotic members (MCL-1). Therefore, venetoclax triggers and restores apoptosis in tumor cells by releasing pro-apoptotic proteins from BCL2 [43] (Fig. 1).

Venetoclax is highly bound to plasma proteins (>99%), with a terminal half-life of 16–19 hours [44,45]. Peak concentrations have been observed after 4–5 hours and have been delayed by approximately 2 hours when taken with a meal (high-fat meal) [46]. Venetoclax is metabolized by CYP3A4 and CYP3A5 and it is a substrate for the P-glycoprotein efflux pump [45,47]. Concomitant therapy with strong CYP3A inhibitors or P-glycoprotein inhibitors should be avoided, but if they are necessary, then venetoclax reduction is required (≥75% and 50% dose reduction in concomitant use of CYP3A and P-glycoprotein inhibitors). There is only minimal excretion of the intact drug in urine [45] and its clearance does not appear to be affected in patients with mild to moderate renal or hepatic impairment [48]. However, it has not been studied in patients with severe abnormalities of kidney or liver functions.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia arising from clonal mature B lymphocytes with a characteristic immunophenotype [49]. Although it is an indolent malignancy, its clinical course is variable and prognosis is predicted according to present genetic lesions. More than 80% of CLL cases have classified genomic aberrations, including the most frequent deletions (del)13q (55%), del11q (18%), del17p (8%), and trisomy 12 (12–16%) [21].

Investigation of the BCL2 protein has revealed that nearly all patients have increased BCL2 expression in CLL cells [50–52]. Translocations such as t(14;18)(q32;q21), t(2;18)(p11;q21.3), and t(18;22)(q21.3;q11) are rarely detected [53]. Another reason for BCL2 overexpression is the loss of the tumor suppressor genes microRNA 15 (miR15) and miR16, which are located on the 13q14 chromosome region. miR15 and miR16 interact directly with and inhibit BCL2 and several other oncogenes (e.g., MCL1 and BMl1). Therefore, del 13q14 results in the loss of miR15 and miR16 function and enables increase of BCL2 protein in 50% of CLL patients [17,19,54].

In April 2016, the U.S. Food and Drug Administration approved venetoclax as monotherapy for the treatment of relapsed/refractory (RR) CLL with del17p. The overall response rate (ORR) in the initial phase 1 study in patients with RR CLL/SLL (median of three previous therapies) was

Table 1. Results of phase 1 and 2 studies in chronic lymphocytic leukemia

Title	Regimen	EN	*N*	Condition	ORR% (*N*)	CR% (*N*)	PR% (*N*)	MRD	PFS	OS	Identifier, Phase (Reference)
A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma	Venetoclax	116	116	RR CLL/SLL	79% (92/116)	20% (23/116)	NA	35% (6/17) BM	66% (15th mo)	84% (24th mo)	NCT01328626, Phase 1 (Roberts et al., 2016)
A Phase 2 Open-Label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukemia (CLL) Subjects With Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy	Venetoclax	120	64 43 21	RR CLL Ibrutinib arm Idelalisib arm	70% (30/43) 57% (10/21)	2% (1/43) 0%	67% (29/43) 47% (10/21)	33% (14/42) PB	72% (12th mo)	90% (12th mo)	NCT02141282. Phase 2 (Jones et al., 2016a)
A Study of the Efficacy of ABT-199 in Subjects With Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia With the 17p Deletion	Venetoclax	158	107	RR CLL/SLL	79% (85/107)	8% (8/107)	77% (77/107)	33% (6/18) BM	72% (12th mo)	87% (12th mo)	NCT01889186, Phase 2 (Stilgenbauer et al., 2016a)
A Phase 1b Study Evaluating the Safety and Tolerability of ABT-199 in Combination With Rituximab in Subjects With Relapsed Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma	Venetoclax Rituximab	50	49	RR CLL	86% (42/49)	51% (25/49)	35% (17/49)	57% (28/49) BM	89% (24th mo)	NA	NCT01682616, Phase 1 (Seymour et al., 2017a)
CLARITY: Assessment of VenetoCLAx (ABT-199) in combination with IbRutInib in relapsed/refracTory Chronic LymphocYtic Leukaemia	Venetoclax Ibrutinib	54	38	RR CLL	100% (38/38)	47% (18/38)	53% (20/38)	37% (15/38) PB 32% (12/38) BM	NA	NA	ISCRTN: 13751862, Phase 2 (Hillmen et al., 2017)

(*continued on next page*)

Table 1. (*continued*)

Title	Regimen	EN	*N*	Condition	ORR% (*N*)	CR% (*N*)	PR% (*N*)	MRD	PFS	OS	Identifier, Phase (Reference)
Venetoclax and Ibrutinib in Patients With Chronic Lymphocytic Leukemia (CLL)	Venetoclax Ibrutinib	78	14	RR CLL	100% (14/14)	64% (9/14)	35% (5/14)	NA	NA	NA	NCT02756897, Phase 2 (Jain et al., 2017)
A Study of Venetoclax in Combination With Rituximab Compared With Bendamustine in Combination With Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia	Venetoclax Rituximab Bendamustin Rituximab	389	194 194	RR CLL	93% (180/194) 68% (132/194)	27% (52/194) 8% (16/194)	67% (129/194) 60% (116/194)	84% (163/194) PB 23% (45/194) PB	84.9% (24th mo) 36.3% (24th mo)	NA	NCT02005471, Phase 3 (Seymour et al., 2017b)
A Study of Venetoclax in Combination With Bendamustine + Rituximab or Bendamustine + Obinutuzumab in Participants With Relapsed/ Refractory or Previously Untreated Chronic Lymphocytic Leukemia (CLL)	Venetoclax Bendamustin Rituximab	100	30	RR CLL	96% (26/27)	26% (7/27)	70% (19/27)	76% (16/21)[a]	NA	NA	NCT01671904, Phase 1 (Stilgenbauer et al., 2016b)
Bcl-2 Inhibitor GDC-0199 in Combination With Obinutuzumab and Ibrutinib in Treating Patients With Relapsed, Refractory, or Previously Untreated Chronic Lymphocytic Leukemia	Venetoclax Ibrutinib Obinutuzumab	68	10	RR CLL	100% (10/10)	20% (2/10)	80% (8/10)	40% (4/10) BM	NA	NA	NCT02427451, Phase 1/2 (Jones et al., 2016b)
Sequential Regimen of Bendamustine-Debulking Followed by ABT-199 and GA101-Induction and -Maintenance in CLL (CLL2-BAG)	Venetoclax Bendamustin Obinutuzumab	66	29	RR CLL	93% (27/29)	10% (3/29)	83% (24/29)	97% (33/34) PB	NA	NA	NCT02758665, Phase 2 (Cramer et al., 2017)

BM = bone marrow; EN = estimated enrollment; *N* = number of patients; MRD = minimal residual disease; NA = not available; PB = peripheral blood; SLL = *small lymphocytic lymphoma.*
Update data were presented at EHA 2017. MRD in peripheral blood evaluated in an entire cohort of 158 patients (RR and untreated).
[a]Not otherwise specified.

Table 2. Results of phase 1 and 2 studies in CLL

Title	Regimen	EN	*N*	Condition	ORR% (*N*)	CR% (*N*)	PR% (*N*)	MRD	PFS	OS	Identifier, Phase (Reference)
A Study of the Efficacy of ABT-199 in Subjects With Relapsed/Refractory or Previously ND Chronic Lymphocytic Leukemia With the 17p Deletion	Venetoclax	158	5	ND CLL	80% (4/5)	40% (2/5)	NA	27% (42/158) PB	100% (12th mo)	100% (12th mo)	NCT01889186, Phase 2 (Stilgenbauer et al., 2017)
A Study of Venetoclax in Combination With Obinutuzumab in Participants With Chronic Lymphocytic Leukemia	Venetoclax Obinutuzumab	82	32	ND CLL	100% (32/32)	56% (17/32)	44% (14/32)	100% (32/32) PB 65% (20/32) BM	100% (12th mo)	NA	NCT01685892, Phase 1 (Flinn et al., 2017)
A Study to Compare the Efficacy and Safety of Obinutuzumab + Venetoclax (GDC-0199) Versus Obinutuzumab + Chlorambucil in Participants With Chronic Lymphocytic Leukemia	Venetoclax Obinutuzumab Chlorambucil Obinutuzumab	445	12	ND CLL	100% (12/12)	66% (8/12)	NA	100% (12/12) PB	NA		NCT02242942, Phase 3 (Fischer et al., 2016)
Venetoclax and Ibrutinib in Patients With Chronic Lymphocytic Leukemia (CLL)	Venetoclax Ibrutinib	78	16	ND CLL	100% (16/16)	56% (9/16)	44% (7/16)	NA	NA	NA	NCT02756897, Phase 2 (Jain et al., 2017)
A Study of Venetoclax in Combination With Bendamustine + Rituximab or Bendamustine + Obinutuzumab in Participants With Relapsed/Refractory or Previously ND Chronic Lymphocytic Leukemia (CLL)	Venetoclax Bendamustin Rituximab	100	17	ND CLL	100% (14/14)	43% (6/14)	57% (8/14)	67% (6/9)[a]	NA	NA	NCT01671904, Phase 1 (Stilgenbauer et al., 2016b)
	Venetoclax Bendamustin Obinutuzumab		8	ND CLL	100% (7/7)	43% (3/7)	57% (4/7)	50% (2/4)[a]	NA	NA	
Bcl-2 Inhibitor GDC-0199 in Combination With Obinutuzumab and Ibrutinib in Treating Patients With Relapsed, Refractory, or Previously ND Chronic Lymphocytic Leukemia	Venetoclax Ibrutinib Obinutuzumab	68	23	ND CLL	100% (23/23)	50% (12/24)	46% (11/23)	58% (14/23)	NA	NA	NCT02427451, Phase 1/2 (Rogers, et al., 2017)
Sequential Regimen of Bendamustine-Debulking Followed by ABT-199 and GA101-Induction and -Maintenance in CLL (CLL2-BAG)	Venetoclax Bendamustin Obinutuzumab	66	34	ND CLL	100% (34/34)	9% (3/34)	91% (31/34)	12% (4/34) BM	NA	NA	NCT02758665, Phase 2 (Cramer et al. , 2017)

SLL = *small lymphocytic lymphoma*, NA = not available, EN = estimated enrollment, *N* = number of patients, MRD = minimal residual disease, PB = peripheral blood, BM = bone marrow, ND = newly diagnosed.

Update data were presented at EHA 2017. MRD in peripheral blood evaluated in an entire cohort of 158 patients (RR and ND).

[a]Not otherwise specified.

Table 3. Ongoing phase 2 and 3 clinical trials in RR and ND CLL

Title	Regimen	EN	Condition	Identifier
A Study Venetoclax in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia in the Presence of 17p Deletion	Venetoclax	70	RR CLL	NCT02966756 Phase 2
A Study Evaluating Venetoclax in Subjects With Chronic Lymphocytic Leukemia Whose Cancer Has Come Back or Who Had No Response to Previous Cancer Treatments Including Subjects Missing Part of Their Chromosome 17, or TP53 Gene Mutation; or Who Received Prior Treatment With a B-Cell Receptor Inhibitor	Venetoclax	200	RR CLL	NCT02980731 Phase 3
A Study of Venetoclax (GDC-0199; ABT-199) in Combination With Obinutuzumab in Participants With Chronic Lymphocytic Leukemia	Venetoclax Obinutuzumab	81	RR CLL	NCT01685892 Phase 1
Venetoclax and Ibrutinib in Patients With Relapsed/Refractory CLL or SLL	Venetoclax Ibrutinib	20	RR CLL/SLL	NCT03045328 Phase 2
Ibrutinib Plus Venetoclax in Patients With Treatment-naive Chronic Lymphocytic Leukemia /Small Lymphocytic Lymphoma	Venetoclax Ibrutinib	150	ND CLL/SLL	NCT02910583 Phase 2
Sequential Regimen of Bendamustine-Debulking Followed by ABT-199 and GA101-Induction and -Maintenance in CLL (CLL2-BAG)	Venetoclax Bendamustin Obinutuzumab	66	RR CLL ND CLL	NCT02401503 Phase 2
Bcl-2 Inhibitor GDC-0199 in Combination With Obinutuzumab and Ibrutinib in Treating Patients With Relapsed, Refractory, or Previously ND Chronic Lymphocytic Leukemia	Venetoclax Ibrutinib Obinutuzumab	68	RR CLL[a] ND CLL	NCT02427451 Phase 1
Trial of Ibrutinib Plus Venetoclax Plus Obinutuzumab in Patients With CLL (CLL2-GiVe)	Venetoclax Ibrutinib Obinutuzumab	40	ND CLL	NCT02758665 Phase 2
Standard Chemoimmunotherapy (FCR/BR) Versus Rituximab + Venetoclax (RVe) Versus Obinutuzumab (GA101) + Venetoclax (GVe) Versus Obinutuzumab + Ibrutinib + Venetoclax (GIVe) in Fit Patients With Previously ND Chronic Lymphocytic leukemia (CLL) Without Del (17p) or TP53 Mutation (GAIA)	FCR BR Venetoclax Rituximab Venetoclax Obinutuzumab Venetoclax Ibrutinib Obinutuzumab	920	ND CLL	NCT02950051 Phase 3

SLL = *small lymphocytic lymphoma*, EN = estimated enrollment, *N* = number of patients, ND = newly diagnosed.
[a]MRD was evaluated either from bone marrow or peripheral blood.

achieved by 79% (92/116) and complete remission (CR) occurred in 20% (23/116). Almost no differences were observed in the subgroup of patients with del17p (ORR and CR were 71% [22/31] and 16% [5/31], respectively) Progression-free survival (PFS) at 15 months was estimated to be 66% (median PFS was 16 months for CLL with del17p and median PFS was not reached for CLL with unmutated chromosome 17) and the 2-year overall survival (OS) for all cohorts was 84%. Compared with other options for RR CLL, 68% and 63% of patients responded to bendamustin plus rituximab (BR) and ibrutinib, respectively, and 83% with del17p response to ibrutinib monotherapy. Clinical tumor lysis syndrome (TLS) occurred in three cases, with one death after step-up to 1200 mg per day. Other most common serious adverse events (AEs) (grade 3–4) were neutropenia, febrile neutropenia, pneumonia, upper respiratory tract infection, and immune thrombocytopenia [44]. In a phase 2 study, 107 patients with RR CLL (median of two previous therapies) with del17p received venetoclax in monotherapy. Response occurred in 79% (85/107), with 8% (8/107) achieving CR. One-year PFS and OS were 72% and 87%, respectively [55]. Another phase 2 study assessed the efficacy of venetoclax monotherapy in the treatment of patients who relapsed after, or were refractory to, a B-cell receptor inhibitor (idelalisib or ibrutinib). In arm A (prior ibrutinib for a median of 17 months), 70% (30/43) of patients responded to the administered drug and 2% (1/43) achieved CR; 57% (10/21) patients in arm B (prior idelalisib for a median of 8 months) responded with partial remission (PR) as the best response. One-year PFS and OS were 72% and 90%, respectively, for all patients. The majority of both arms were refractory to ibrutinib (91%) or idelalisib (67%). Hematological toxicity (neutropenia, anemia, and thrombocytopenia), febrile neutropenia, and pneumonia were the most common grade 3–4 AEs [56].

Venetoclax in combination with rituximab was investigated in a phase 1 study in RR CLL (median of two previous therapies) and the combination regimen was effective in 86% (42/49) of patients, with 51% (25/49) obtaining CR. The 2-year estimated PFS and OS were 82% and 89%, respectively. Toxicity appeared to be similar to venetoclax in monotherapy, including two clinical significant TLS cases, one of which ended in death [57]. Promising outcomes were obtained by untreated and RR CLL patients (median of one previous therapy) who were administered obinutuzumab, ibrutinib, and

Table 4. Results of phase 1 and 2 clinical trials in NHL, MM, and AML

Title	Regimen	EN	*N*	Condition	ORR% (*N*)	CR% (*N*)	PR% (*N*)	PFS (median)	OS (1-year)	Identifier, Phase (Reference)
A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma	Venetoclax	106	106	RR NHL	44% (47/106)	13% (14/106)	31% (33/106)	6 m 14 m	70% 82%	NCT01328626, Phase 1 (Davids et al., 2017)
			28	MCL	75% (21/28)	21% (6/28)	54% (15/28)	11 m 1 m	100% 32%	
			29	FL	38% (11/29)	14% (4/29)	24% (7/29)	NA NA	NA NA	
			34	DLBCL	18% (6/34)	12% (4/34)	6% (2/34)	NA	NA	
			7	RT	43% (3/7)	0%	43% (3/7)			
			4	WM	100% (4/4)	0%	100% (4/4)			
			3	MZL	67% (2/3)	0%	67% (2/3)			
A Safety and Pharmacokinetics Study of GDC-0199 (ABT-199) in Patients With Non-Hodgkin's Lymphoma	Venetoclax R-CHOP	248	21	NHL RR/Untreated	86% (18/21)	67% (14/21)	14% (3/21)	NA	NA	NCT02055820, Phase 1 (Zelenetz et al., 2016)
	Venetoclax G-CHOP		21		81% (17/21)	62% (13/21)	19% (4/21)			
ABT-199 & Ibrutinib in Mantle Cell Lymphoma (AIM) (AIM)	Venetoclax Ibrutinib	24	23 1	RR MCL ND MCL	71% (17/24)	63% (15/24)	17% (4/24)	NA	NA	NCT02471391, Phase 2 (Tam et al., 2017)
Study Evaluating ABT-199 in Subjects With Relapsed or Refractory MM	Venetoclax Venetoclax Dexamethasone	84	66	RR MM	21% (14/66)	6% (4/66)	15% (10/66)	NA	NA	NCT01794520, Phase 1 (Kumar et al., 2016)
A Study Evaluating ABT-199 in Multiple Myeloma Subjects Who Are Receiving Bortezomib and Dexamethasone as Standard Therapy	Venetoclax Bortezomib Dexamethasone	66	66	RR MM	68% (44/65)	17% (11/66)	51% (33/66)	NA	NA	NCT01794507, Phase 1 (Moreau et al., 2016)
A Study Evaluating Venetoclax in Combination With Low-Dose Cytarabine in Treatment-Naïve Subjects With Acute Myelogenous Leukemia (AML)	Venetoclax LD-Cytarabine	91	61	Elderly ND AML	61% (37/61)	62% (38/61)	2% (1/61)	NA	46%	NCT02287233, Phase 1/2 (Wei et al., 2017)
Phase 1b Acute Myelogenous Leukemia (AML) Study With ABT-199 + Decitabine or Azacitidine (Chemo Combo)	Venetoclax 5-Azacitidine Venetoclax Decitabine	260	145	Elderly ND AML	68% (97/145)	NA	NA	17.5 m	NA	NCT02203773, Phase 1 (DiNardo et al., 2017)

EN = estimated enrollment, LD = low-dose, ND = newly diagnosed, *N* = number of patients.

Table 5. Ongoing clinical trials in NHL, MM, and AML

Title	Regimen	EN	Condition	Identifier
Non-Hodgkin lymphoma				
A Study Evaluating the Safety and Efficacy of GDC-0199 Plus Bendamustine + Rituximab (BR) in Comparison With BR or GDC-0199 Plus Rituximab in Participants With Relapsed and Refractory Follicular Non-Hodgkin's Lymphoma (fNHL)	Venetoclax Rituximab Venetoclax BR BR	165	RR FL	NCT02187861 Phase 2
Ibrutinib and Venetoclax in Relapsed and Refractory Follicular Lymphoma	Venetoclax Ibrutinib	41	RR FL	NCT02956382 Phase 2
Combination of Obinutuzumab and Venetoclax in Relapsed or Refractory DLBCL	Venetoclax Obinutuzumab	21	RR DLBCL	NCT02987400 Phase 2
Study of Venetoclax in Combination With Carfilzomib and Dexamethasone in Subjects With Relapsed or Refractory MM	Venetoclax Carfilzomib Dexamethasone	40	RR MM	NCT02899052 Phase 2
Study of Ibrutinib Combined With Venetoclax in Subjects With Mantle Cell Lymphoma (SYMPATICO)	Venetoclax Venetoclax Ibrutinib Ibrutinib	287	RR MCL	NCT03112174 Phase 3
MM				
A Study Evaluating Venetoclax (ABT-199) in Multiple Myeloma Subjects Who Are Receiving Bortezomib and Dexamethasone as Standard Therapy	Venetoclax Bortezomib Dexamethasone Placebo Bortezomib Dexamethasone	240	RR MM	NCT02755597 Phase 3
Acute myeloid leukemia				
A Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy	Venetoclax 5-Azacitidine Placebo 5-Azacitidine	400	Elderly ND AML	NCT02993523 Phase 3
A Study of Venetoclax in Combination With Low Dose Cytarabine Versus Low Dose Cytarabine Alone in Treatment Naïve Patients With Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy	Venetoclax LD-Cytarabine Placebo LD-Cytarabine	175	Elderly ND AML	NCT03069352 Phase 3
Study of the BCL-2 Inhibitor Venetoclax in Combination With Standard Intensive Acute Myeloid Leukemia (AML) Induction/Consolidation Therapy With FLAG-IDA in Patients With Newly Diagnosed or Relapsed/ Refractory Acute Myeloid Leukemia (AML)	Venetoclax FLAG-IDA	56	ND or RR AML	NCT03214562 Phase 1/2
A Study of Venetoclax in Combination With Cobimetinib and Venetoclax in Combination With Idasanutlin in Patients Aged >/=60 Years With Relapsed or Refractory Acute Myeloid Leukemia Who Are Not Eligible for Cytotoxic Therapy	Venetoclax cobimetinib Venetoclax Idasanutlin	140	Elderly RR AML	NCT02670044 Phase 1/2

BR = bendamustin plus rituximab, ND = newly diagnosed, LD = low dose, FLAG-IDA = fludarabine, cytosinearabinoside, idarubicine, EN = estimated enrollment.

venetoclax. At the time of data analysis, 10 RR patients had completed eight cycles (ORR and CR were 100% [10/10] and 20% [2/10], respectively) [56] and 32 untreated patients completed six cycles (ORR and CR were 100% [32/32] and 56% [17/32], respectively) [58]. Observed toxicities for the combination were consistent with those reported for the single agents, with neutropenia, lymphopenia, hypertension, and fatigue as the most common AEs and no cases of TLS [56]. Untreated and RR CLL (median of one previous therapy) were enrolled in a phase 1 study of standard chemoimmunotherapy: BR combined with venetoclax. In the group of untreated and RR CLL, ORR reached 100% (14/14) and 96% (26/27) with 43% (6/14) and 26% (7/27) of CR, respectively. In the same study, bendamustin plus obinutuzumab (BG) and venetoclax were administered to seven untreated CLL patients with similar outcomes to BR plus venetoclax (ORR 100%, CR 43% [3/7]). Hematologic toxicity was the most serious across all groups and diarrhea with fatigue appeared most often as a nonhematologic toxicity [59]. Outcomes of a phase 2 study with the same combination (BG plus venetoclax) were presented at the European Haematology Association (EHA) 2017 meeting. Responses were similar to the phase 1 study (ORR 100% [34/34] and 93% [27/29], CR 9% [3/34] and 10% [3/29] for untreated and RR CLL, respectively). More AEs occurred in the RR cohort than in untreated patients [60]. A randomized phase 3 trial (CLL14) compares the efficacy and safety of obinutuzumab and venetoclax with obinutuzumab and chlorambucil in patients with previously untreated CLL

Table 6. Chemotherapeutic and targeted agents, monoclonal antibodies, and combined regimens

Chemical name	Agent	Pharmacology	Regimen
Rituximab	mAb, anti-CD20	Induction of CDC, ADCC	FCR, BR, R-CHOP, RClb
Obinutuzumab	mAb, anti-CD20	Induction of direct cell death, ADCC, ADCP, CDC	R-CHOP, G-CHOP
Cyclophosphamide	Alkylating agent	Inhibition of DNA synthesis	R-CHOP, G-CHOP
Chlorambucil	Alkylating agent	Inhibition of DNA synthesis	RClb
Bendamustine	Alkylating agent	Inhibition of DNA and RNA synthesis, Induction of apoptosis, activation of p53	BR
Doxorubicin	Anthracycline antibiotic	Inhibition of DNA and RNA synthesis	R-CHOP, G-CHOP
Cytarabine	Antimetabolite—pyrimidine analogue	Inhibition of DNA polymerase	LDAC
Fludarabine	Antimetabolite—purine analogue	Inhibition of DNA polymerase and ribonucleotide reductase	FCR
5-azacytidine	Antimetabolite—pyrimidine analogue, demethylation agent	Hypomethylation of DNA, impairment of trna	5-Aza
Decitabine	Antimetabolite -cytidine analogue, demethylation agent	Hypomethylation of DNA, arrest of DNA synthesis	Decitabine
Vincristine	Vinca alkaloid	Arrest tumor cells in metaphase	R-CHOP, G-CHOP
Dexamethasone	Synthetic glucocorticoid	Inhibition of DNA synthesis	VD
Prednisone	Synthetic glucocorticoid	Inhibition of DNA synthesis	R-CHOP, G-CHOP
Ibrutinib	B-cell receptor inhibitor	Inhibition of Bruton's tyrosine kinase	Ibrutinib
Idelalisib	B-cell receptor inhibitor	Inhibition of Phosphatidylinositol 3-kinase	Idelalisib
Venetoclax	Inhibitor of anti-apoptotic proteins	BCL2 inhibitor	Venetoclax
Bortezomib	Proteasome inhibitor	Inhibition of the 26S proteasome	VD

R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, G-CHOP = obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone, FCR = fludarabine, cyclophosphamide, rituximab, RClb = rituximab, chlorambucil, BR = bendamustin, rituximab, LDAC = low-dose cytarabine, VD = bortezomib, dexamethasone, 5-Aza = 5-azacytidine, CDC = complement-dependent cytotoxicity, ADCC = antibody-dependent cellular cytotoxicity, ADCP = antibody-dependent cellular phagocytosis, mAb = monoclonal antibody.

with coexisting medical conditions (CIRS > 6). Response was obtained by all patients, with 66% (8/12) of patients obtaining CR and neither progression nor death at 15 months of treatment monitored [61]. Early results of phase 2 study in RR CLL (median of two previous therapies) suggest a potent synergy between ibrutinib and venetoclax (ORR and CR were 100% [38/38] and 47% [18/38], respectively) with acceptable toxicity and TLS only in two patients thus far [62]. Similar

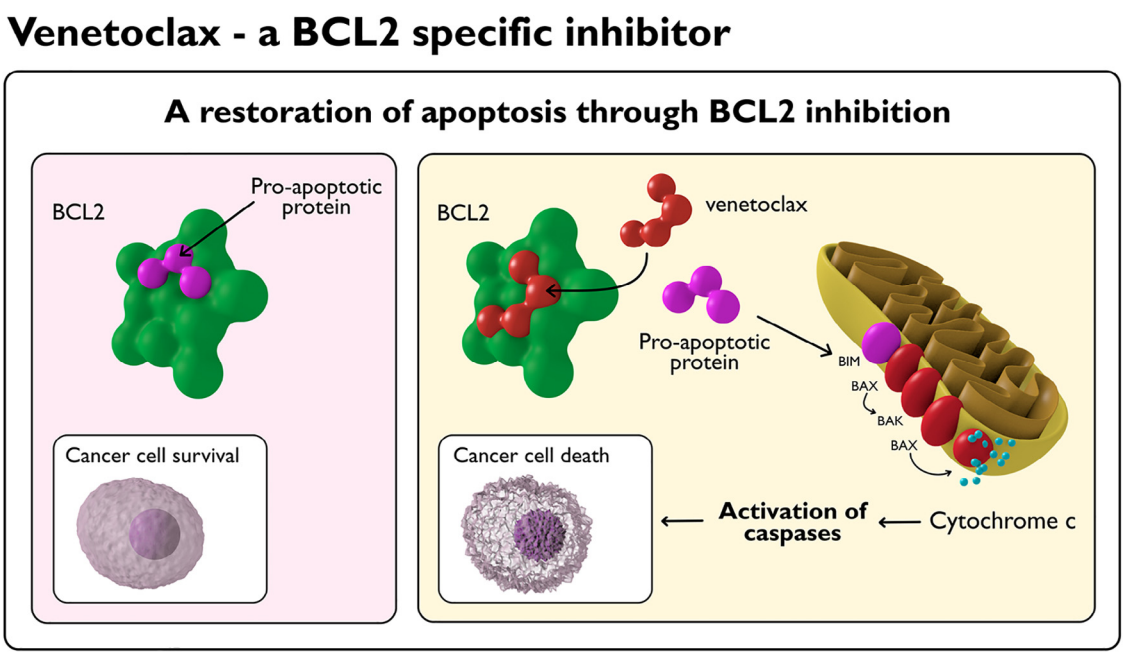

Figure 1. In cancer cells, the anti-apoptotic protein BCL22 sequesters and blocks the function of BH3-only pro-apoptotic proteins (e.g., BIM) and therefore prevents apoptosis. The BH3-only mimetic compound venetoclax displaces and reactivates pro-apoptotic proteins bound to the BH3-binding groove of BCL2. Consequently, released pro-apoptotic proteins associate with the apoptotic effectors BAX and BAK and induce permeabilization of the mitochondrial outer membrane. Cytochrome c released from mitochondria then activates caspases and triggers cell death.

results were achieved in RR patients (ORR and CR were 100% [14/14] and 64% [9/14], respectively) and untreated patients (ORR and CR were 100% [19/19] and 56% [9/16], respectively) in another trial with the same combination [63].

There is an ongoing phase 3 trial comparing a combination regimen of venetoclax plus monoclonal antibody (rituximab or obinutuzumab) or venetoclax, ibrutinib plus obinutuzumab with standard chemoimmunotherapy, BR and FCR (fludarabine, cyclophosphamide, and rituximab). All available results of completed and ongoing clinical trials are summarized in Tables 1–3.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is usually represented as an aggressive B-cell lymphoma developing from naive B cells [64]. It is associated with translocation t(11;14)(q13;q32), resulting in overexpression of cyclin D1 in 70–95% of cases [65–67]. Despite the presence of this aberration, additional genetic changes (loss of tumor suppressor genes *TP53, ATM*, and *CDKN2A* or gain of oncogenes *BCL2, C-MYC*, *SYK*) are usually required for malignant transformation [68].

Nearly all (95%) clonal cells are BCL2 positive in MCL [65]. Benz et al. identified amplification of the 18q21–22 locus in several cases and also pointed out the presence of del13q14 that was shown to be responsible for BCL2 activation in CLL [69]. Gain of c-MYC, which is involved in oncogenesis, might contribute to BCL2 overexpression as well [70].

In an initial phase 1 study of RR non-Hodgkin's lymphoma (NHL) (106 patients), the cohort of RR MCL (median of three previous therapies) was one of the best responding groups achieving ORR and CR in 75% (21/28) and 21% (6/28), respectively. One-year OS was demonstrated in 82% and median PFS was 14 months. The most common grade 3–4 toxicity was hematological (anemia, neutropenia, and thrombocytopenia) and only a few cases of hyponatremia and infections (lower respiratory tract infection and influenza) occurred during treatment. No clinical TLS was observed [71]. The combination of venetoclax and ibrutinib was investigated in a phase 2 study in RR MCL (95%, median of two previous therapies, 30% failed to autologous stem cell transplantation) and untreated MCL (5%). ORR and CR were achieved in 71% (17/24) and 63% (15/24) of all patients and estimates of PFS and OS were 74% and 81%, respectively, at 8 months. TLS occurred in two cases with high tumor burden, leading to revision of the protocol (venetoclax starting dose from 50 to 20 mg per day) [72]. A phase 3 trial comparing venetoclax plus ibrutinib with ibrutinib or venetoclax monotherapy is ongoing (Table 5).

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma morphologically classified by the diffuse growth of mature neoplastic large B lymphoid cells [73]. It comprises several distinct histologic, immunophenotypic, and genetic subgroups. The most common aberrations involve mutations of the *BCL6* (30%), *BCL2 (20–30%), and* c-MYC *(*5–22%) genes [74–76]. Translocation t(14;18)(q32;q21) and amplification of 18q21-23 are responsible for BCL-2 overexpression in 20–30% and 21% of DLBCL, respectively [18,20]. Double-hit DLBCL is a subgroup with poor clinical outcome that harbors concurrent gene rearrangement of c-MYC and the BCL2, BCL6, or BCL3 proto-oncogene. It represents less than 10% of DLBCL, with the most frequent MYC/BCL2 subtype carrying translocation of c-MYC and t(14;18)(q32;q21) [77].

In a phase 1 study, venetoclax monotherapy was administered to 34 patients with RR DLBCL (median of three previous therapies). The drug was effective in 18% (6/34) and 12% (4/34) of patients reached CR. However, the responses did not last long and were the shortest among all types of RR NHL. Median PFS was 1 month and 1-year OS was achieved by 12%. Venetoclax was well tolerated and no TLS was observed [71].

Preliminary data of combination therapy, venetoclax plus R-CHOP/G-CHOP (rituximab/obinutuzumab, cyclophosphamide, doxorubicin, vincristine and prednisone) were published at ASH 2016. Patients (24 follicular lymphoma [FL], 17 DLBCL, five marginal zone lymphoma [MZL], 10 others) with untreated disease (91%) or RR disease (9%, one previous therapy) were enrolled. Demonstrated results were presented for all NHL (untreated and RR) types together and they were nearly the same in both cohorts (R-CHOP and G-CHOP). Patients treated with venetoclax plus R-CHOP achieved ORR and CR in 86% (18/21) and 67% (14/21) of patients, respectively, and in the arm with venetoclax plus G-CHOP, ORR and CR were 81% (17/21) and 62% (13/21), respectively. Toxicity seemed to be higher than in venetoclax monotherapy and mainly presented as neutropenia, febrile neutropenia, and thrombocytopenia without TLS [78].

FL

FL represents an indolent lymphoproliferative disease arising from malignant germinal center B cells (centrocytes and centroblasts) [79] undergoing histologic transformation (typically to DLBCL) in 30–40% of cases [80]. Translocation t(14;18)(q32;q21) is present in 80–90% cases [81], but other aberrations might be caused by various genes, including c-MYC and TP53 [82].

In a phase 1 study of RR NHL, venetoclax in monotherapy was given to 29 patients with RR FL (median of three previous therapies). Treatment was successful in 38% (11/29) and 14% (4/29) of CRs were observed. All patients were alive in the first year and the estimated median PFS was 11 months. Toxicity was acceptable and similar to all groups/types of NHL [71].

Combination of venetoclax plus standard immunochemotherapy (R-CHOP/G-CHOP) was investigated in a phase 1 study in 24 patients with untreated or RR FL (one previous therapy). Preliminary results were published for the whole cohort of NHL together. ORR and CR

were 86% (18/21) and 67% (14/21) versus 81% (17/21) and 62% (13/21), respectively, in venetoclax plus R-CHOP versus enetoclax plus G-CHOP. Most common grade 3–4 AEs (neutropenia, febrile neutropenia, and thrombocytopaenia) occurred more frequently than in venetoclax monotherapy [78]. Finally, several studies with rituximab, ibrutinib, bendamustine, and rituximab were designed to find the best combination for venetoclax (Table 5).

MZL

MZL is an indolent lymphoma that arises from memory B cells that are present in the marginal zone of lymphoid tissue. Chromosomal changes such as trisomy 3, trisomy 18, and t(11;18)(q21;q21) are commonly seen in the extranodal subtype and other specific mutations such as t(1;14)(p22;q32), t(14;18)(q32;q21), t(3;14)(p14;q32) and del17p13 are recorded only rarely [83].

Several subtypes of MZL are BCL2 positive (nodal and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue), whereas others (splenic) are negative [84], but little is known about the pathogenesis of BCL2 expression in MZL. In the initial study for RR NHL, venetoclax has shown efficacy in 67% (2/3) of patients, with PR as the best response. To correctly interpret outcomes of venetoclax treatment, a bigger cohort of patients must be assessed [71].

Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM) is a B-cell neoplasm manifested by accumulation of the monoclonal immunoglobulin M secreted by lymphoplasmacytic cells. Malignancy is associated with somatic mutations of *MYD88* and *CXCR4* in 90% and 30% of cases, respectively [85,86].

In several in vitro experiments, overexpressed BCL2 was detected in malignant cells [87,88]. Subsequently, venetoclax demonstrated effective induction of apoptosis alone and in combination with either ibrutinib or idelalisib ex vivo (including WM cells with CXCR4 mutation), so it is speculated that it will be able to overcome the resistance of *CXCR4-mutated WM in vivo as well* [89]. All four RR WM patients (median of four previous therapies) responded to venetoclax monotherapy, with PR as the best response. Toxicity was the same as in the whole group of NHL [71].

Multiple myeloma

Multiple myeloma (MM) is a genetically heterogeneous malignant disorder caused by the proliferation and accumulation of clonal plasma cells and is almost always associated with the presence of monoclonal immunoglobulin in the serum and/or urine [90,91].

MM is a heterogeneous disease due to its dependence on anti-apoptotic proteins such as BCL2, BCL_XL, or MCL-1 and it is currently not known what proportion of MM patients are likely to be BCL2 dependent [92]. Nevertheless, it has been demonstrated in MM cell lines and primary patient samples that venetoclax is highly effective in a specific subset of MM with translocation t(11;14), mainly due to the higher BCL2/MCL-1 mRNA ratio. Interestingly, venetoclax remains active in this subgroup of MM even if the high-risk 17p deletion is present [93,94]. Moreover, it has been shown that this drug works synergistically with dexamethasone and is able to increase the expression of BCL2 and BIM, so MM cells become more sensitive to venetoclax [95].

In a phase 1 clinical trial with venetoclax monotherapy, 66 RR MM patients with a median of five previous therapies were enrolled overall. The ORR for all patients was 21% (14/66), with 15% (10/66) reaching very good partial response (VGPR, decrease of more than 90% of M-protein) or better. In the subset of MM patients with t(11;14), ORR was 40% (12/30), with 27% (8/30) achieving VGPR or better. Conversely, in patients without t(11;14), almost no responses were observed (ORR: 6%) [96]. In another phase 1b trial, the combination of venetoclax with bortezomib and dexamethasone was investigated in the cohort of 66 RRMM patients with a median of three previous therapies. The ORR was 67% for all patients (44/66), with 42% (28/66) of patients reaching VGPR or better. The ORR for patients with or without t(11;14) was 78% versus 65% and with or without del(17p) was 47% versus 73%, respectively. Venetoclax alone or in combination had an acceptable safety profile in both of these phase 1 trials, with the most common AEs grade 3/4 being thrombocytopenia, anemia, neutropenia, and infectious complications [97]. There is an ongoing phase 3 clinical trial comparing bortezomib and dexamethasone plus venetoclax versus bortezomib and dexamethasone plus placebo (Table 5).

Acute myeloid leukemia

Acute myeloid leukemia (AML) is a biologically heterogeneous clonal disorder of undifferentiated myeloid precursors resulting in impaired hematopoiesis and bone marrow failure [98,99].

AML cells are dependent on BCL2 for survival [43]. Overexpression of this anti-apoptotic protein is also implicated in chemotherapy resistance, even though the mechanism of overexpression has not yet been fully described [100]. Importantly, venetoclax spares normal hematopoietic stem cells that are more dependent on MCL-1 for their survival [101,102]. The first evidence of venetoclax efficacy was proposed by Pan et al., who demonstrated selective blast killing in AML cell lines, primary patient samples, and murine primary xenografts by this agent [102].

Preclinical studies revealed that patients with mutated isocitrate dehydrogenase proteins 1 and 2 (IDH 1/2, approximately 15% of AML) are more likely to respond to BCL2 inhibition by venetoclax [103]. In the first clinical trial investigating venetoclax monotherapy (800 mg daily) in 32 high-risk RR AML patients, the ORR was 19%. However, 38% (12/32) had IDH 1/2 mutations, of whom 33% (4/12) reached CR or CR with incomplete blood count recovery (CRi), confirming this preclinical finding. Common AEs grade 3/4 included nausea, vomiting, diarrhea, febrile neutropenia, and

hypokalemia [104]. Preclinical investigation (by RNA interference drug modifier screens) identified the potential synergistic role of BCL2 family protein inhibitors with 5-azacytidine (5-Aza). Preliminary results of the phase 1 clinical trial investigating the combination of venetoclax plus either 5-Aza or decitabine in newly diagnosed >65-year-old AML patients ineligible for intensive chemotherapy were presented at ASH 2017. Overall, 145 patients were enrolled in four arms (comparing 400 or 800 mg doses of venetoclax with each hypomethylating agent), with the ORR being 67% (97/145).The median OS in all patients was 17.5 months. The emerging clinical and exposure response data demonstrated that 400 mg venetoclax has the best benefit-risk profile. A phase 3 study of 400 mg venetoclax combined with AZA is under way. The most frequent grade 3/4 AEs were hematologic toxicities and febrile neutropenia [105]. Another logical combination of venetoclax is with low-dose cytarabine (LDAC); this is considered as a current standard of care in the elderly AML patient population, with an expected ORR of maximum 20%. Sixty-one patients were enrolled in a phase 1/2 study with 600 mg venetoclax; 62% (38/61) of these patients achieved CR/CRi with a median duration of CR/CRi of 14.9 months. Treatment-emergent grade 3/4 AEs (in ≥20% of 61 patients) were thrombocytopenia (59%), neutropenia (46%), febrile neutropenia (36%), and anemia (28%). One case (2%) of TLS occurred [106]. These promising results led to the initiation of randomized phase 3 trials that are currently ongoing. One compares venetoclax plus 5-Aza versus 5-Aza alone; the other one compares venetoclax plus LDAC versus LDAC alone (Table 5).

Conclusions

The intrinsic apoptotic pathway deregulated due to the overexpression of anti-apoptotic proteins is found in a variety of tumor types. It has been demonstrated that the blockade of these proteins leading to the release of pro-apoptotic proteins might restart the process of cell suicide in malignant cells. To date, the most effective molecule is venetoclax, the BH3-only mimetic and the first selective BCL2 inhibitor. It has been approved for RR CLL patients with del17p in monotherapy. However, expanded indications may be assumed in this malignancy. FL was another lymphoproliferative disease with expected efficacy according to a high rate of t(14;18)(q32;q21) in malignant cells (80–90%). Nevertheless, the results of venetoclax monotherapy are not that promising, with responses in less than half of RR FL [71]. Current research identifies BCL2-positive DLBCL (BCG and ABC subtypes) as DLBCL with inferior prognosis [107,108], but it is still not clear why venetoclax, even in combination with standard care (R-CHOP), does not improve outcomes in these patients [78]. Conversely, RR MCL, MZL, and WM have achieved interesting outcomes, even though the final conclusion requires bigger cohorts and longer follow-up [71]. Venetoclax is also active in MM patients, especially in those with translocation t(11;14), and represents an available biomarker predicting the efficacy of this drug. Quite striking results were obtained in elderly AML patients, in whom venetoclax in combination with LDAC or hypomethylating agents (5-Aza or decitabine) induced approximately 60–70% of responses (taking into account that, in the current standard of care, LDAC does not induce more than 20% of responses), resulting in the initiation of phase 3 clinical trials.

The venetoclax toxicity profile was found to be acceptable across all studies. Initially, there was a concern about TLS, but this is well manageable with the recommended prophylactic procedures. Typically, it has occurred in CLL with two deaths demonstrated to date (venetoclax monotherapy at 1200 mg and venetoclax plus rituximab at 50 mg) [44,57]. To mitigate the risk, a dose ramp-up period (initial dose of 20 mg in CLL and 50 mg in NHL with dose escalation every week during the first months), along with prophylactic hydration and urate lowering therapy, is recommended [109]. Relatively frequent hematological toxicity might be explained by the presence of anti-apoptotic members in the immature stages of hematopoietic cells during their maturation. Anti-apoptotic proteins let immature cells survive and differentiate into mature forms [110–113], but this process is interrupted prematurely when anti-apoptotic inhibitors are administered. Grade of cytopenia depends on both the selectivity of the inhibitor and the ratio of protein members (BCL/MCL-1 and BCL2/BCL-XL). For instance, it has been proven that venetoclax does not induce limiting thrombocytopenia because megakaryopoesis is controlled by the BCL-XL protein [114].

Despite promising results in preclinical tests and initial trials with venetoclax, there are already signs of resistance [44]. Therefore, it is of high importance to establish additional prognostic markers that can predict the sensitivity to venetoclax and further explore potential resistance mechanisms, which will be likely diverse in individual groups of patients. Given the high venetoclax specificity to BCL2, upregulated BCL-XL and MCL1 can sequester proapoptotic protein BIM and lead to resistance [115]. Preclinical data indicate that BCL2/BCL-XL and BCL2/MCL1 ratios could be used in response prediction and thus should be included in routine clinical pipelines. Interestingly, low expression of miR-377 was inversely correlated with high expression of BCL-XL and might also be of potential prognostic importance [116]. Additional mechanisms of venetoclax resistance include increased BCL2 phosphorylation [117] and mutations in BH3 domain of BCL2 [5], which displace BIM from BCL2 or prevent inhibitor binding. The complexity of venetoclax resistance in B-cell malignancies has been broadly described in other studies [118,119] and additional mechanisms can be uncovered by modern screening approaches [120].

The ratio of different anti-apoptotic proteins within malignant cells has an impact on venetoclax resistance. The combination of different molecules such as some of the B-cell receptor inhibitors is being used to try to solve this issue. For example, ibrutinib (a Bruton's tyrosine kinase inhibitor) mobilizes lymphocytes expressing BCL-XL and A1

(dominantly) from lymph nodes into the peripheral blood. In circulation, clonal cells lose protecting microenvironment signals, reduce BCL-XL and A1, and increase BCL2 protein expression [119,121,122]. In MM, the overexpressed MCL-1 protein may be reduced by proteasome inhibitors and synergized with venetoclax activity [123]. Various other kinase inhibitors such as entospletinib (GS-9973), sunitinib (SU11248), cerdulatinib (PRT062070), CC-115 (TORK and DNA-PK inhibitor), and inhibitors of cyclin-dependent kinases (CDK2, CDK9), are able to block MCL-1 and might become the right partners for venetoclax treatment [120,124–128]. A therapeutic challenge is double-hit DLBCL expressing BCL2 but also other anti-apoptotic proteins (e.g., MCL-1 and BCL-XL) that have been effectively blocked by combination of venetoclax plus carfilzomib, 5-Aza, or BR101801 (PI3K and DNA-PK inhibitor) in some in vitro studies [129–131].

In conclusion, venetoclax is a targeted drug with a novel mechanism of action that has already demonstrated highly promising activity in a variety of hematological malignancies. Due to its effect on the restoration of the apoptotic pathway, it can also be used successfully in patients with high-risk genetic features and nonfunctional p53. Taking all this and its low toxicity into consideration, venetoclax might become an important part of the treatment armamentarium against a substantial number of blood cancers.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgments

The authors thank Shira Timilsina, M.D., for English language editing and Michal Kupka, M.D., for illustrations.

This work was supported by grants from the Ministry of Health (DRO-FNOs/2017) and the Ministry of Health [17-30089A); the Institutional Development Plan of University of Ostrava [IRP201550), SGS18/PrF/2017–2018; and Strengthening International Cooperation in Science, Research and Education (project ID: 01211/2016/RRC).

References

1. Fink SL, Cookson BT. Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun. 2005;73:1907–1916.
2. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer. 1972;26:239–257.
3. Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. Nat Rev Cancer. 2002;2:647–656.
4. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.
5. Huang DCS, Hahne M, Schroeter M, et al. Activation of Fas by FasL induces apoptosis by a mechanism that cannot be blocked by Bcl-2 or Bcl-xL. Proc Natl Acad Sci USA. 1999;96:14871–14876.
6. Strasser A, Harris AW, Huang DC, Krammer PH, Cory S. Bcl-2 and Fas/APO-1 regulate distinct pathways to lymphocyte apoptosis. EMBO J. 1995;14:6136–6147.
7. Guicciardi ME, Gores GJ. Life and death by death receptors. FASEB J. 2009;23:1625–1637.
8. Chen L, Willis SN, Wei A, et al. Differential targeting of prosurvival Bcl-2 proteins by their BH3-only ligands allows complementary apoptotic function. Mol Cell. 2005;17:393–403.
9. Chittenden T. BH3 domains: intracellular death-ligands critical for initiating apoptosis. Cancer Cell. 2002;2:165–166.
10. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat Rev Mol Cell Biol. 2014;15:49–63.
11. Huang DC, Strasser A. BH3-Only proteins-essential initiators of apoptotic cell death. Cell. 2000;103:839–842.
12. Willis SN, Chen L, Dewson G, et al. Proapoptotic Bak is sequestered by Mcl-1 and Bcl-xL, but not Bcl-2, until displaced by BH3-only proteins. Genes Dev. 2005;19:1294–1305.
13. Willis SN, Fletcher JI, Kaufmann T, et al. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science. 2007;315:856–859.
14. Gazzaniga P, Gradilone A, Vercillo R, et al. bcl-2/bax mRNA expression ratio as prognostic factor in low-grade urinary bladder cancer. Int J Cancer. 1996;69:100–104.
15. Jiang S-X, Sato Y, Kuwao S, Kameya T. Expression of bcl-2 oncogene protein is prevalent in small cell lung carcinomas. J Pathol. 1995;177:135–138.
16. Joensuu H, Pylkkänen L, Toikkanen S. Bcl-2 protein expression and long-term survival in breast cancer. Am J Pathol. 1994;145:1191–1198.
17. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA. 2002;99:15524–15529.
18. Monni O, Joensuu H, Franssila K, Knuutila S. DNA copy number changes in diffuse large B-cell lymphoma–comparative genomic hybridization study. Blood. 1996;87:5269–5278.
19. Pekarsky Y, Croce CM. Role of miR-15/16 in CLL. Cell Death Differ. 2015;22:6–11.
20. Tsujimoto Y, Finger LR, Yunis J, Nowell PC, Croce CM. Cloning of the chromosome breakpoint of neoplastic B cells with the t (14;18) chromosome translocation. Science. 1984;226:1097–1099.
21. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910–1916.
22. Edelmann J, Holzmann K, Miller F, et al. High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. Blood. 2012;120:4783–4794.
23. Toshiyuki M, Reed JC. Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell. 1995;80:293–299.
24. Nakano K, Vousden KH. PUMA, a novel proapoptotic gene, is induced by p53. Mol Cell. 2001;7:683–694.
25. Yu J, Wang Z, Kinzler KW, Vogelstein B, Zhang L. PUMA mediates the apoptotic response to p53 in colorectal cancer cells. Proc Natl Acad Sci USA. 2003;100:1931–1936.
26. Petros AM, Gunasekera A, Xu N, Olejniczak ET, Fesik SW. Defining the p53 DNA-binding domain/Bcl-x (L)-binding interface using NMR. FEBS Lett. 2004;559:171–174.
27. Zilfou JT, Lowe SW. Tumor suppressive functions of p53. Cold Spring Harb Perspect Biol. 2009;1:a001883.
28. Dansen TB, Whitfield J, Rostker F, Brown-Swigart L, Evan GI. Specific requirement for Bax, not Bak, in Myc-induced apoptosis and tumor suppression in vivo. J Biol Chem. 2006;281:10890–10895.
29. Egle A, Harris AW, Bouillet P, Cory S. Bim is a suppressor of Myc-induced mouse B cell leukemia. Proc Natl Acad Sci USA. 2004;101:6164–6169.
30. Nikiforov MA, Riblett M, Tang WH, et al. Tumor cell-selective regulation of NOXA by c-MYC in response to proteasome inhibition. Proc Natl Acad Sci USA. 2007;104:19488–19493.

31. Hoffman B, Liebermann DA. Apoptotic signaling by c-MYC. Oncogene. 2008;27:6462–6472.
32. Meyer N, Kim SS, Penn LZ. The Oscar-worthy role of Myc in apoptosis. Semin Cancer Biol. 2006;16:275–287.
33. Nieminen AI, Partanen JI, Klefstrom J. c-Myc blazing a trail of death: coupling of the mitochondrial and death receptor apoptosis pathways by c-Myc. Cell Cycle. 2007;6:2464–2472.
34. Nilsson JA, Cleveland JL. Myc pathways provoking cell suicide and cancer. Oncogene. 2003;22:9007–9021.
35. Kipps TJ, Eradat H, Grosicki S, et al. A phase 2 study of the BH3 mimetic BCL2 inhibitor navitoclax (ABT-263) with or without rituximab, in previously untreated B-cell chronic lymphocytic leukemia. Leuk Lymphoma. 2015;56:2826–2833.
36. Nguyen M, Marcellus RC, Roulston A, et al. Small molecule obatoclax (GX15-070) antagonizes MCL-1 and overcomes MCL-1-mediated resistance to apoptosis. Proc Natl Acad Sci USA. 2007;104:19512–19517.
37. Nguyen M, Cencic R, Ertel F, et al. Obatoclax is a direct and potent antagonist of membrane-restricted Mcl-1 and is synthetic lethal with treatment that induces Bim. BMC Cancer. 2015;15:568.
38. Sun Y, Wu J, Aboukameel A, et al. Apogossypolone, a nonpeptidic small molecule inhibitor targeting Bcl-2 family proteins, effectively inhibits growth of diffuse large cell lymphoma cells in vitro and in vivo. Cancer Biol Ther. 2008;7:1418–1426.
39. Roberts AW, Seymour JF, Brown JR, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. J Clin Oncol. 2012;30:488–496.
40. Tse C, Shoemaker AR, Adickes J, et al. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. Cancer Res. 2008;68:3421–3428.
41. Wilson WH, O'Connor OA, Czuczman MS, et al. Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity. Lancet Oncol. 2010;11:1149–1159.
42. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013;19:202–208.
43. Konopleva M, Contractor R, Tsao T, et al. Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. Cancer Cell. 2006;10:375–388.
44. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:311–322.
45. Salem AH, Agarwal SK, Dunbar M, Enschede SLH, Humerickhouse RA, Wong SL. Pharmacokinetics of venetoclax, a novel BCL-2 inhibitor, in patients with relapsed or refractory chronic lymphocytic leukemia or non-Hodgkin lymphoma. J Clin Pharmacol. 2017;57:484–492.
46. Salem AH, Agarwal SK, Dunbar M, et al. Effect of low- and high-fat meals on the pharmacokinetics of venetoclax, a selective first-in-class BCL-2 inhibitor. J Clin Pharmacol. 2016;56:1355–1361.
47. Agarwal SK, Hu B, Chien D, Wong SL, Salem AH. Evaluation of rifampin's transporter inhibitory and CYP3A inductive effects on the pharmacokinetics of venetoclax, a BCL-2 inhibitor: results of a single- and multiple-dose study. J Clin Pharmacol. 2016;56:1335–1343.
48. Freise KJ, Jones AK, Eckert D, et al. Impact of venetoclax exposure on clinical efficacy and safety in patients with relapsed or refractory chronic lymphocytic leukemia. Clin Pharmacokinet. 2017;56:515–523.
49. Ginaldi L, De Martinis M, Matutes E, Farahat N, Morilla R, Catovsky D. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. J Clin Pathol. 1998;51:364–369.
50. Hanada M, Delia D, Aiello A, Stadtmauer E, Reed JC. bcl-2 gene hypomethylation and high-level expression in B-cell chronic lymphocytic leukemia. Blood. 1993;82:1820–1828.
51. O'Brien S, Moore JO, Boyd TE, et al. Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2007;25:1114–1120.
52. Schena M, Larsson LG, Gottardi D, et al. Growth- and differentiation-associated expression of bcl-2 in B-chronic lymphocytic leukemia cells. Blood. 1992;79:2981–2989.
53. Dyer MJ, Zani VJ, Lu WZ, et al. BCL2 translocations in leukemias of mature B cells. Blood. 1994;83:3682–3688.
54. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci USA. 2005;102:13944–13949.
55. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17:768–778.
56. Jones J, Choi MY, Mato AR, et al. Venetoclax (VEN) monotherapy for patients with chronic lymphocytic leukemia (CLL) who relapsed after or were refractory to ibrutinib or idelalisib. Blood. 2016;128:637.
57. Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. Lancet Oncol. 2017;18:230–240.
58. Rogers KA, Huang Y, Stark A, Jones JA. Initial results of the phase 2 treatment-naïve cohort in a phase 1b/2 study of obinutuzumab, ibrutinib, and venetoclax in CLL. Available at https://ash.confex.com/ash/2017/webprogram/Paper107539.html [Cited 2018 Jan 9].
59. Stilgenbauer S, Morschhauser F, Wendtner CM, et al. Phase Ib study (GO28440) of venetoclax with bendamustine/rituximab or bendamustine/obinutuzumab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia. Blood. 2016;128:4393.
60. Cramer P, von Tresckow J, Bahlo J, et al. Bendamustine (B), followed by obinutuzumab (G, GA101) and venetoclax (A, ABT-199) in patients with chronic lymphocytic leukemia (CLL): CLL2-BAG Phase-II-trial of the German CLL study group (GCLLSG) EHA Learning Center. Available at https://learningcenter.ehaweb.org/eha/2017/22nd/181751/paula.cramer.bendamustine.28b29.followed.by.obinutuzumab.28g.ga10129.and.html?f=m3e1181 [Cited 2017 Jun 17].
61. Fischer K, Al-Sawaf O, Fink A-M, Dixon M, Bahlo J, Hallek M. Safety and efficacy of venetoclax and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia (CLL) and coexisting medical conditions: final results of the run-in phase of the randomized CLL14 Trial (BO25323). Available at https://ash.confex.com/ash/2016/webprogram/Paper94946.html [Cited 2017 Feb 9].
62. Hillmen P, Munir T, Rawstron A, et al. Initial results of ibrutinib plus venetoclax in relapsed, refractory CLL (Bloodwise TAP CLARITY Study): high rates of overall response, complete remission and MRD eradication after 6 months of combination therapy. Blood. 2017;130:428.
63. Jain N, Thompson PA, Ferrajoli A, et al. Combined venetoclax and ibrutinib for patients with previously untreated high-risk CLL, and relapsed/refractory CLL: a phase II trial. Blood. 2017;130:429.
64. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–2390.
65. Ives Aguilera NS, Bijwaard KE, Duncan B, et al. Differential expression of cyclin D1 in mantle cell lymphoma and other non-Hodgkin's lymphomas. Am J Pathol. 1998;153:1969–1976.
66. Leroux D, Marc'hadour FL, Gressin R, et al. Non-Hodgkin's lymphomas with t (11;14) (q13;q32): a subset of mantle zone/intermediate lymphocytic lymphoma? Br J Haematol. 1991;77:346–353.
67. Vandenberghe E, De Wolf Peeters C, Wlodarska I, et al. Chromosome 11q rearrangements in B non-Hodgkin's lymphoma. Br J Haematol. 1992;81:212–217.

68. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. Blood. 2009;114:1469–1476.
69. Bentz M, Plesch A, Bullinger L, et al. t (11;14)-positive mantle cell lymphomas exhibit complex karyotypes and share similarities with B-cell chronic lymphocytic leukemia. Genes Chromosomes Cancer. 2000;27:285–294.
70. Hemann MT, Bric A, Teruya-Feldstein J, et al. Evasion of the p53 tumour surveillance network by tumour-derived MYC mutants. Nature. 2005;436:807–811.
71. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. J Clin Oncol. 2017;35:826–833.
72. Tam CSL, Roberts AW, Anderson MA, et al. Combination ibrutinib (Ibr) and venetoclax (Ven) for the treatment of mantle cell lymphoma (MCL): primary endpoint assessment of the phase 2 AIM study. J Clin Oncol. 2017;35:7520.
73. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117:5019–5032.
74. Kramer MH, Hermans J, Wijburg E, et al. Clinical relevance of BCL2, BCL6, and MYC rearrangements in diffuse large B-cell lymphoma. Blood. 1998;92:3152–3162.
75. Li S, Lin P, Young KH, Kanagal-Shamanna R, Yin CC, Medeiros LJ. MYC/BCL2 double-hit high-grade B-cell lymphoma. Adv Anat Pathol. 2013;20:315–326.
76. Saito M, Gao J, Basso K, et al. A signaling pathway mediating downregulation of BCL6 in germinal center B cells is blocked by BCL6 gene alterations in B cell lymphoma. Cancer Cell. 2007;12:280–292.
77. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. Blood. 2011;117:2319–2331.
78. Zelenetz AD, Salles GA, Mason KD, et al. Results of a phase Ib Study of venetoclax plus R- or G-CHOP in patients with B-cell non-Hodgkin lymphoma. Blood. 2016;128:3032.
79. Kridel R, Mottok A, Farinha P, et al. Cell of origin of transformed follicular lymphoma. Blood. 2015;126:2118–2127.
80. Montoto S, Fitzgibbon J. Transformation of indolent B-cell lymphomas. J Clin Oncol. 2011;29:1827–1834.
81. Horsman DE, Gascoyne RD, Coupland RW, Coldman AJ, Adomat SA. Comparison of cytogenetic analysis, southern analysis, and polymerase chain reaction for the detection of t (14; 18) in follicular lymphoma. Am J Clin Pathol. 1995;103:472–478.
82. Lossos IS, Alizadeh AA, Diehn M, et al. Transformation of follicular lymphoma to diffuse large-cell lymphoma: alternative patterns with increased or decreased expression of c-myc and its regulated genes. Proc Natl Acad Sci USA. 2002;99:8886–8891.
83. Braggio E, Dogan A, Keats JJ, et al. Genomic analysis of marginal zone and lymphoplasmacytic lymphomas identified common and disease-specific abnormalities. Mod Pathol. 2012;25:651–660.
84. Ortolani C. Flow cytometry of hematological malignancies. New York: John Wiley & Sons; 2011.
85. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;123:1637–1646.
86. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367:826–833.
87. Chng WJ, Schop RF, Price-Troska T, et al. Gene-expression profiling of Waldenström macroglobulinemia reveals a phenotype more similar to chronic lymphocytic leukemia than multiple myeloma. Blood. 2006;108:2755–2763.
88. Hatjiharissi E, Mitsiades CS, Bryan CT, et al. Comprehensive molecular characterization of malignant and microenvironmental cells in Waldenstrom's macroglobulinemia by gene expression profiling. Blood. 2007;110:3174.
89. Cao Y, Yang G, Hunter ZR, et al. 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;170:134–138.
90. Jelinek T, Hajek R. PD-1/PD-L1 inhibitors in multiple myeloma: the present and the future. Oncoimmunology. 2016;5:e1254856.
91. Jelinek T, Hajek R. Monoclonal antibodies: a new era in the treatment of multiple myeloma. Blood Rev. 2016;30:101–110.
92. Touzeau C, Ryan J, Guerriero J, et al. BH3 profiling identifies heterogeneous dependency on Bcl-2 family members in multiple myeloma and predicts sensitivity to BH3 mimetics. Leukemia. 2016;30:761–764.
93. Touzeau C, Dousset C, Le Gouill S, et al. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t (11;14) multiple myeloma. Leukemia. 2014;28:210–212.
94. Touzeau C, Le Gouill S, Mahé B, et al. Deep and sustained response after venetoclax therapy in a patient with very advanced refractory myeloma with translocation t (11;14). Haematologica. 2017;102:e112–e114.
95. Matulis SM, Gupta VA, Nooka AK, et al. Dexamethasone treatment promotes Bcl-2 dependence in multiple myeloma resulting in sensitivity to venetoclax. Leukemia. 2016;30:1086–1093.
96. Kumar S, Vij R, Kaufman JL, et al. Venetoclax monotherapy for relapsed/refractory multiple myeloma: safety and efficacy results from a phase I study. Blood. 2016;128:488.
97. Moreau P, Chanan-Khan AA, Roberts AW, et al. Venetoclax combined with bortezomib and dexamethasone for patients with relapsed/refractory multiple myeloma. Blood. 2016;128:975.
98. Jelinek T, Mihalyova J, Kascak M, Duras J, Hajek R. PD-1/PD-L1 inhibitors in haematological malignancies: update 2017. Immunology. 2017;152:357–371.
99. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374:2209–2221.
100. Saygin C, Carraway HE. Emerging therapies for acute myeloid leukemia. J Hematol Oncol. 2017;10:93.
101. Opferman JT, Iwasaki H, Ong CC, et al. Obligate role of anti-apoptotic MCL-1 in the survival of hematopoietic stem cells. Science. 2005;307:1101–1104.
102. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. Cancer Discov. 2014;4:362–375.
103. Chan SM, Thomas D, Corces-Zimmerman MR, et al. Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. Nat Med. 2015;21:178–184.
104. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov. 2016;6:1106–1117.
105. DiNardo CD, Pollyea DA, Jonas BA, et al. Updated safety and efficacy of venetoclax with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2017;130:2628.
106. Wei A, Strickland SA, Roboz GJ, et al. 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.
107. Szafer-Glusman E, Peale FV, Lei G, et al. BCL2 expression identifies a population with unmet medical need in previously untreated (1L) patients with DLBCL. Blood. 2017;130:418.
108. Tsuyama N, Sakata S, Baba S, et al. BCL2 expression in DLBCL: reappraisal of immunohistochemistry with new criteria for therapeutic biomarker evaluation. Blood. 2017;130:489–500.

109. Coiffier B, Altman A, Pui C-H, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26:2767–2778.
110. Leverson JD, Phillips DC, Mitten MJ, et al. Exploiting selective BCL-2 family inhibitors to dissect cell survival dependencies and define improved strategies for cancer therapy. Sci Transl Med. 2015;7:279ra40.
111. Motoyama N, Kimura T, Takahashi T, Watanabe T, Nakano T. bcl-x prevents apoptotic cell death of both primitive and definitive erythrocytes at the end of maturation. J Exp Med. 1999;189:1691–1698.
112. Socolovsky M, Fallon AE, Wang S, Brugnara C, Lodish HF. Fetal anemia and apoptosis of red cell progenitors in Stat5a-/-5b-/- mice: a direct role for Stat5 in Bcl-X (L) induction. Cell. 1999;98:181–191.
113. Villunger A, O'Reilly LA, Holler N, Adams J, Strasser A. FAS ligand, Bcl-2, granulocyte colony-stimulating factor, and p38 mitogen-activated protein kinase. J Exp Med. 2000;192:647–658.
114. Zhang H, Nimmer PM, Tahir SK, et al. Bcl-2 family proteins are essential for platelet survival. Cell Death Differ. 2007;14:943–951.
115. Choudhary GS, Al-Harbi S, Mazumder S, et al. MCL-1 and BCL-xL-dependent resistance to the BCL-2 inhibitor ABT-199 can be overcome by preventing PI3K/AKT/mTOR activation in lymphoid malignancies. Cell Death Dis. 2015;6:e1593.
116. Al-Harbi S, Choudhary GS, Ebron JS, et al. miR-377-dependent BCL-xL regulation drives chemotherapeutic resistance in B-cell lymphoid malignancies. Mol Cancer. 2015;14:185.
117. Song T, Chai G, Liu Y, Yu X, Wang Z, Zhang Z. Bcl-2 phosphorylation confers resistance on chronic lymphocytic leukaemia cells to the BH3 mimetics ABT-737, ABT-263 and ABT-199 by impeding direct binding. Br J Pharmacol. 2016;173:471–483.
118. Bodo J, Zhao X, Durkin L, et al. Acquired resistance to venetoclax (ABT-199) in t (14;18) positive lymphoma cells. Oncotarget. 2016;7:70000–70010.
119. Vogler M, Butterworth M, Majid A, et al. Concurrent up-regulation of BCL-XL and BCL2A1 induces approximately 1000-fold resistance to ABT-737 in chronic lymphocytic leukemia. Blood. 2009;113:4403–4413.
120. Oppermann S, Ylanko J, Shi Y, et al. High-content screening identifies kinase inhibitors that overcome venetoclax resistance in activated CLL cells. Blood. 2016;128:934–947.
121. Cervantes-Gomez F, Lamothe B, Woyach JA, et al. Pharmacological and protein profiling suggests venetoclax (ABT-199) as optimal partner with ibrutinib in chronic lymphocytic leukemia. Clin Cancer Res. 2015;21:3705–3715.
122. Hillmen P, Rawstron A, Munir T, et al. The initial report of the bloodwise tap clarity study combining ibrutinib and venetoclax in relapsed, refractory cll shows acceptable safety and promising early indications of efficacy. Available at https://learningcenter.ehaweb.org/eha/2017/22nd/182057/peter.hillmen.the.initial.report.of.the.bloodwise.tap.clarity.study.combining.html?f=m3 [Cited 2017 Aug 19].
123. Punnoose EA, Leverson JD, Peale F, et al. Expression profile of BCL-2, BCL-XL, and MCL-1 predicts pharmacological response to the BCL-2 selective antagonist venetoclax in multiple myeloma models. Mol Cancer Ther. 2016;15:1132–1144.
124. Bojarczuk K, Sasi BK, Gobessi S, et al. BCR signaling inhibitors differ in their ability to overcome Mcl-1-mediated resistance of CLL B cells to ABT-199. Blood. 2016;127:3192–3201.
125. Choudhary GS, Tat TT, Misra S, et al. Cyclin E/Cdk2-dependent phosphorylation of Mcl-1 determines its stability and cellular sensitivity to BH3 mimetics. Oncotarget. 2015;6:16912–16925.
126. Flynn J, Jones J, Johnson AJ, et al. Dinaciclib is a novel cyclin-dependent kinase inhibitor with significant clinical activity in relapsed and refractory chronic lymphocytic leukemia. Leukemia. 2015;29:1524–1529.
127. Hamlin PA, Flinn I, Wagner-Johnston N, et al. Clinical and correlative results of a phase 1 study of cerdulatinib (PRT062070) a dual SYK/JAK inhibitor in patients with relapsed/refractory B cell malignancies. Blood. 2015;126:3929.
128. Thijssen R, ter Burg J, Garrick B, et al. Dual TORK/DNA-PK inhibition blocks critical signaling pathways in chronic lymphocytic leukemia. Blood. 2016;128:574–583.
129. Crombie J, Lossos C, Sarosiek K, et al. Dynamic BH3 profiling reveals novel therapeutic strategies for the treatment of double-hit lymphoma. Blood. 2017;130:2764.
130. Jung HS, Kim NH, Wang J, et al. Combination of BR101801 and venetoclax demonstrates synergistic activity in DLBCL cell lines harboring double hit and double expressor alterations. Blood. 2017;130:4114.
131. Mavis C, Torka P, Zeccola A, et al. Pre-clinical development of targeted therapies for double hit (DH) diffuse large B-cell lymphoma (DLBCL). Blood. 2017;130:1542.