



# Venetoclax: Targeting BCL2 in Hematological Cancers

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## Abstract

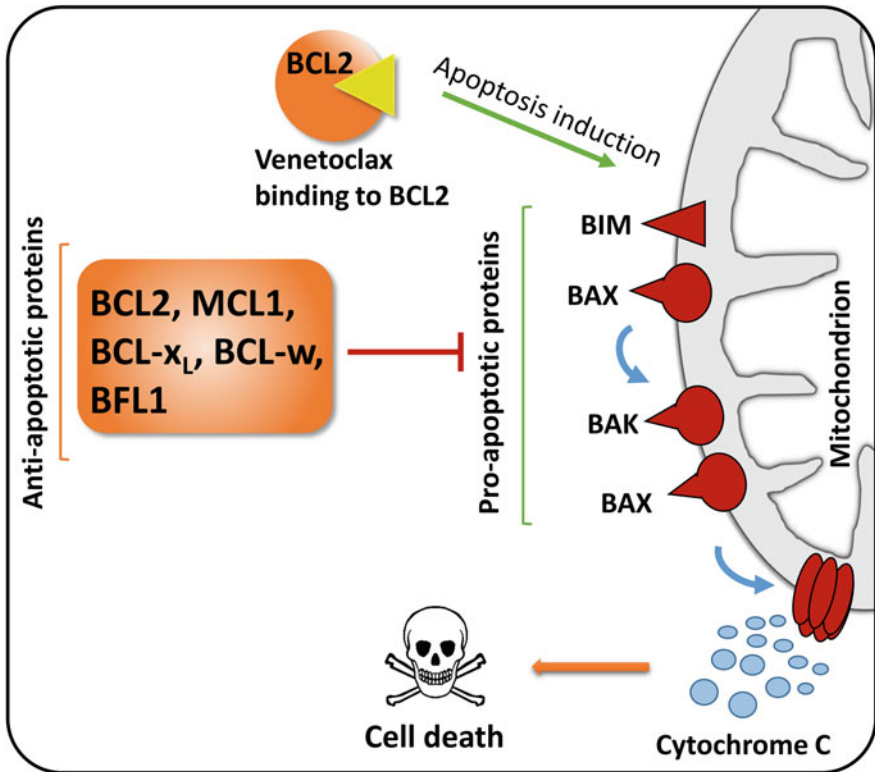
Over the last years, targeted anti-cancer therapy with small-molecule inhibitors and antibodies moved to the forefront as a strategy to treat hematological cancers. These novel agents showed outstanding effects in treatment of patients, often irrespective of their underlying genetic features. However, evolution and selection of subclones with continuous treatment leads to disease relapse and resistance toward these novel drugs. Venetoclax (ABT-199) is a novel, orally bioavailable small-molecule inhibitor for selective targeting of *B-cell lymphoma 2* (BCL2). Venetoclax is in clinical development and shows high efficacy and safety in particular in the treatment of chronic lymphocytic leukemia (CLL), but preliminarily also in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). The most important and impressive outcomes of venetoclax treatment include a rapid induction of apoptosis and drastic reduction of the tumor bulk within a few hours after administration. Venetoclax was approved by the FDA and EMA in 2016 for patients with previously treated CLL with del (17p13) and patients failing B cell receptor signaling inhibitors (EMA only), on the basis of a single-arm phase II trial demonstrating a tremendous response rate of 79% with complete remission in 20% of cases and an estimated 1-year progression-free survival of 72%. This review focuses on the mode of action, the preclinical models, and outcomes from various clinical trials with venetoclax in different hematologic cancers as well as future development.

## Keywords

Venetoclax · BCL2 inhibitors · Hematologic cancer

## 1 Background: The Balance between Anti-apoptotic and Pro-apoptotic Proteins

BCL2 family proteins play a major role in the regulation of cell death, and BCL2 has been the first anti-apoptotic gene discovered in 1985 (Tsujimoto et al. 1985). The BCL2 family is highly conserved and contains more than a dozen proteins that are key regulators of the mechanism of intrinsic programmed cell death. The BCL2 family is clustered into three main functional groups, the pro-survival and anti-apoptotic proteins BCL2, MCL1, BCL-XL and BCL-W (O'Connor et al. 1998; Gibson et al. 1996; Boise et al. 1993; Opferman et al. 2005; Opferman et al. 2003), the multi-BH domain pro-apoptotic proteins BAX and BAK and the pro-apoptotic



**Fig. 1** Overview of pro- and anti-apoptotic molecules. **a** Cell death signals trigger BID and BIM to activate BAX and BAK, which in turn initiate MOMP and lead to apoptosis. **b** Anti-apoptotic molecules, including BCL2, antagonize both activator and effector molecules and block the apoptotic cascade. **c** Cell death signals also activate sensitizer molecules, which antagonize anti-apoptotic molecules and release the block on apoptosis. This physiologic role is pharmacologically recapitulated by BH3-mimetic drugs such as venetoclax

BH3-only proteins BIM, tBID; BAD, PUMA; NOXA and HRK (Inohara et al. 1997; Datta et al. 2002; Oda et al. 2000; O'Connor et al. 1998; Wei et al. 2000; Korsmeyer et al. 2000) that trigger and execute the 'suicidal' cell death. In healthy cells, the balance between cell survival and cell death requires the dynamic binding interactions between the pro-apoptotic and anti-apoptotic proteins (Fig. 1). However, in various malignancies, the anti-apoptotic proteins are frequently overexpressed, leading to defective apoptosis (Robertson et al. 1996).

In cancers, anti-apoptotic BCL2 is upregulated by various mechanisms. The t(14;18) chromosomal translocation which is a genetic hallmark of follicular lymphoma (a subtype of indolent non-Hodgkin lymphoma) includes juxtapositioning of *BCL2* in the IGHV locus, activating *BCL2* at the transcriptional level (Tsujiimoto et al. 1985). Amplification of chromosome 18q21 resulting in high BCL2 levels is observed in small-cell lung cancers (SCLC) (Monni et al. 1997) and mantle cell lymphoma (MCL) (Bentz et al. 2000). In chronic lymphocytic leukemia (CLL), the most common cytogenetic abnormality is the del(13q14), the minimally

deleted region of which includes the *BCL2* repressors, microRNAs 15 and 16 (Cimmino et al. 2005). Moreover, hypomethylation of *BCL2* in CLL also contributes to *BCL2* upregulation due to epigenetic dysregulation (Hanada et al. 1993; Cahill and Rosenquist 2013). On the other hand, defects in expression of pro-apoptotic members result in a loss of the tumor suppressive function and lead to an imbalance between pro- and anti-apoptotic BCL2 family proteins. Homozygous deletions or inactivating mutations of BAX and BID (Meijerink et al. 1998; Lee et al. 2004) or defective expression of BID and PUMA due to loss of p53 function also tip the balance toward anti-apoptotic proteins (Sturm et al. 2000; Miyashita and Reed 1995).

In summary, prevention of apoptosis is one of the hallmarks of cancer cells, which in addition to sustaining survival of the malignant clone, impacts treatment outcome and progression of the disease (Hanahan and Weinberg 2011).

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## 2 Pharmacology and Evolution of BH3 Mimetics

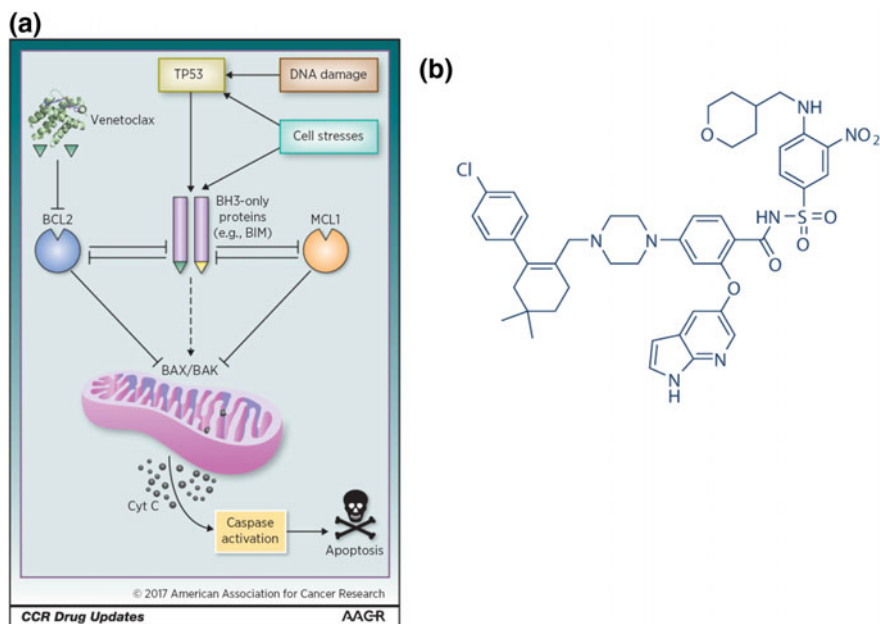
### 2.1 BCL2 Inhibitors

In cancer, apoptosis is prevented by the formation of a heterodimer through binding of the pro-apoptotic protein's BH3 domain into the hydrophobic cleft of anti-apoptotic proteins. The era of BCL2 inhibitors started with the design of anti-sense oligonucleotides to knockdown BCL2 (Reed et al. 1990), followed by BH3 mimetics which bind to the hydrophobic groove of the anti-apoptotic proteins, stabilizing the pro-apoptotic proteins to carry out their function (Fig. 2a).

Oblimersen, the antisense oligonucleotide that was designed to specifically target BCL2 showed only limited efficacy either in monotherapy (O'Brien et al. 2005) or in combination with chemotherapy (O'Brien et al. 2009). Inhibitors of BCL2 derived from natural substances such as AT-101 (Balakrishnan et al. 2009) and synthetic inhibitors such as obatoclax showed modest responses in CLL patients (Brown et al. 2015).

ABT-737 was a highly specific small-molecule inhibitor of BCL-x<sub>L</sub>, BCL2, and BCL-W with EC50 of 78.7, 30.3, and 197.8 nM in cell-free assays. The drug was designed by a strategy of combining screening using nuclear magnetic resonance, structure-based design, and combinatorial chemical synthesis (Oltersdorf et al. 2005). Preclinical data showed ABT-737 to trigger BAX- and BAK-mediated apoptosis in various cancer cell lines and xenograft models (van Delft et al. 2006). Refractoriness to ABT-737 treatment was associated with the upregulation of MCL1 (van Delft et al. 2006). However, the therapeutic use of ABT-737 was limited due to its lack of oral bioavailability and the induction of thrombocytopenia, and higher incidences of transaminitis were observed in the treatment owing to a lower binding affinity of the drugs to BCL2 (Wilson et al. 2010).

A precursor of ABT-199 is navitoclax (ABT-263), a first-in-class dual inhibitor of BCL2 and BCL-x<sub>L</sub>. Navitoclax is structurally related to ABT-737 and inhibits



**Fig. 2** **a** Summary of molecules which interplay in mitochondrial apoptosis. Venetoclax acts as a BH3 mimetic and inhibits BCL2. The activation of BAX and BAK and their delocalization to the outer mitochondrial membrane induces cytochrome c release by depolarization and caspase activation. In healthy cells, BCL2 represses the activation of BAX and BAK. Figure is adopted from Roberts et al. (2017). **b** Chemical structure of venetoclax ( $C_{45}H_{50}ClN_7O_7S(4-(4-\{[2-(2-(4\text{-chlorophenyl})-4,4\text{-dimethylcyclohex-}2H\text{-pyrrolo}[2,3-b]pyridine-5\text{-yloxy)benzamide}))$ )

BCL2 and BCL- $x_L$  with EC50 values of 60 and 20 nM, respectively (Tse et al. 2008). Navitoclax has been evaluated in clinical phase I and II trials in B-cell lymphomas as well as in solid tumors (Gandhi et al. 2011; Tolcher et al. 2015); however, the strong inhibition of BCL- $x_L$  induced a rapid decrease in circulating platelets due to a direct toxic effect. This concentration-dependent grade 3 and 4 thrombocytopenia affected treatment with high drug doses (Gandhi et al. 2011; Kaefer et al. 2014). Navitoclax was explored in a phase I study in relapsed/refractory CLL. In this trial, nine of 29 patients achieved a response with a median PFS of 25 months (Roberts et al. 2012). A phase 2 study of rituximab with or without navitoclax in untreated CLL reported ORR of 55% (Kipps et al. 2015). However, due to the thrombocytopenia, navitoclax never entered clinical phase III trials in spite of being proven efficient in BCL2 dependent malignancies (Roberts et al. 2012).

Venetoclax (ABT-199, GDC-0199) is a selective, potent, orally bioavailable BCL2 inhibitor. The structural formula is  $C_{45}H_{50}ClN_7O_7S(4-(4-\{[2-(2-(4\text{-chlorophenyl})-4,4\text{-dimethylcyclohex-}2H\text{-pyrrolo}[2,3-b]pyridine-5\text{-yloxy)benzamide}))$ , with a molecular mass of  $M_r = 868.4$  g/mol (Fig. 2b). In comparison to navitoclax, venetoclax lacks a thiophenyl unit located at the P4 hotspot which

re-engineers the BH3-binding domain. The pharmacokinetics of venetoclax is described by a  $K_i < 0.01$  nM in cell-free assays, and it has 4800 times higher potency for BCL2 than for BCL-x<sub>L</sub> ( $K_i = 48$  nM) and BCL-W ( $K_i = 245$  nM) (Fig. 2). There is no activity described targeting MCL-1 ( $K_i > 444$  nM) (Souers et al. 2013). The half-life time of venetoclax is 16–19 h (Roberts et al. 2016). ABT-199 was studied in various cellular models and primary patient samples ex vivo, where it induced apoptosis and its sensitivity strongly correlated with the expression of BCL2 (Anderson et al. 2016; Fischer et al. 2015; Varadarajan et al. 2013). The dosing in clinical trials is performed daily and ranges between 300 and 900 mg/day. The peak plasma concentration of venetoclax is achieved 5–8 h after drug uptake. If venetoclax is taken with a fat meal, the mean maximum observed plasma concentration (C<sub>max</sub>) and area under the plasma concentration—time curve (AUC) are fourfold increased as its intestinal uptake and absorbance are accelerated. Venetoclax is metabolized by CYP3A4/5 and is a substrate of the P-glycoprotein pump (Agarwal et al. 2016). The use of CYP3A inhibitors leads to an accumulation and dose increase and therefore should be avoided (Agarwal et al. 2016, 2017). Due to the high degree of specificity and comparatively lower toxicity, only venetoclax among all the BCL2 inhibitors successfully reached the market.

## 2.2 MCL1 Inhibitors

MCL1 is an anti-apoptotic member of the BCL2 family of proteins. MCL1 is frequently upregulated in various cancers and hence considered as a promising therapeutic target. Moreover, transcriptional upregulation or amplification of MCL1 is described to be an important mechanism, driving resistance to BCL2 inhibitors (Beroukhim et al. 2010). As MCL1 has a binding pocket for BAK, several compound screens have been performed to develop competitive inhibitors to disrupt this interaction (Varadarajan et al. 2013). However, MCL1 inhibition is known to be embryonically lethal (Rinkenberger et al. 2000), and MCL1 is also important for survival of hematopoietic stem cells (Opferman et al. 2005), which might limit the therapeutic window due to toxicity. After TW-37 which showed potential efficacy in in vitro models by disruption of MCL1 binding to BAK (Varadarajan et al. 2013), development of an amenable inhibitor had been challenging. Recent findings presented S63845 with potent anti-tumor activity in vitro and in vivo (Kotschy et al. 2016). The inhibitor binds to the BH3 binding groove of MCL1 and was efficacious in the pre-clinical setting in different hematopoietic cancers such as multiple myeloma, acute myeloid leukemia, and lymphomas as well as in solid cancers. Interestingly, S63845 showed no adverse effect on hematopoietic progenitor cells which points to MCL1 as a treatment option for MCL1 dependent tumors and in drug combination with BCL2 inhibitors (Kotschy et al. 2016) (Table 1).

**Table 1** Properties of BCL2 and MCL1 inhibitors and their assessment in clinical trials

| BH3 mimetic          | Proposed targets    | Affects platelets ex vivo | Clinical trial   | Approval | Reference                                       |
|----------------------|---------------------|---------------------------|--|----------|---|
| ABT-737              | BCL2, BCL- $\chi$ L | Yes                       | NCT01440504  | No       | Oltersdorf et al. (2005)                        |
| ABT-263              | BCL2, BCL- $\chi$ L | Yes                       | NCT00406809  | No       | Tse et al. (2008)                               |
| ABT-199              | BCL2                | No                        | NCT01794520<br>NCT02677324<br>NCT03128879<br>NCT02471391 | Yes      | Souers et al. (2013)                            |
| WEHI-539             | BCL- $\chi$ L       | No                        | No   | No       | Lessene et al. (2013)                           |
| BM-1197              | BCL- $\chi$ L       | No                        | No   | No       | Bai et al. (2014)                               |
| AT-101               | pan-BCL2            | No                        | NCT01977209  | No       | Albershardt et al. (2011)                       |
| Obatoclax (GX15-070) | pan-BCL2            | No                        | NCT00719901<br>NCT00521144                               | No       | Albershardt et al. (2011), Nguyen et al. (2007) |
| BXI-62/72            | BCL- $\chi$ L       | No                        | NCT02494583<br>NCT02335411<br>NCT02149225                | No       | Park et al. (2013)                              |
| MIM1, UMI-77         | MCL1                | No                        | No   | No       | Cohen et al. (2012), Abulwerdi et al. (2014)    |
| S63845               | MCL1                | No                        | NCT02979366  | Pending  | Kotschy et al. (2016)                           |

### 3 Preclinical Studies Using Venetoclax

A number of preclinical studies reported the tremendous effects of venetoclax *in vitro*. The major mode of action of venetoclax is the activation of BAK and BAX and subsequent mitochondrial cytochrome C release leading to apoptosis. Treatment with venetoclax was reported in various cellular models to functionally validate its mode of action. Jurkat T-cells lacking BAX showed no response to treatment with different concentrations of venetoclax (Vogler et al. 2013). Apoptosis induction by venetoclax in peripheral blood samples from CLL cases was confirmed by externalization of phosphatidylserine. Comparison of venetoclax with ABT-737 and ABT-263 to analyze their susceptibility to affect platelets showed markedly reduced toxicity of venetoclax in comparison to ABT-737 or ABT-263 (Vogler et al. 2013).

Furthermore, during preclinical development, high single-agent cell-killing was demonstrated in non-Hodgkin's lymphoma (NHL) cell lines including those from diffused large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). Notably, NHL cell lines carrying the t(14;18) BCL2 gain showed higher sensitivity toward ABT-199 treatment than cell lines without the alteration (Souers et al. 2013). Multiple myeloma cell lines showed sensitivity to venetoclax correlating with the expression profile of BCL2, BCL-x<sub>L</sub>, and MCL1 which were predictive for treatment response. Interestingly, the co-expression of BCL2 and BCL-x<sub>L</sub> resulted in resistance to venetoclax monotherapy but still showed response to BCL-x<sub>L</sub> inhibitors.

Remarkable effects were also demonstrated for ABT-199 treatment of AML and pediatric ALL cell lines (Fischer et al. 2015). Also, studies using xenografts of AML (Pan et al. 2014), ALL (Frismantas et al. 2017), and B-cell lymphomas with venetoclax as monotherapy or in combination with rituximab and bendamustine (Souers et al. 2013) highlighted the efficacy of venetoclax as well as its safety in combination treatments. In line with these findings, studies using MLL-rearranged ALL primary samples *in vitro* (Alford et al. 2015) and *in vivo* (Khaw et al. 2016) demonstrated the potent single-agent activity of venetoclax in these tumor entities.

In CLL, treatment with ibrutinib, a novel small-molecule inhibitor of BTK showed impressive clinical activity with durable responses (Byrd et al. 2014; Byrd et al. 2015); however, subsets of patients did not achieve deep remission or cure. To address a possible synergism between venetoclax and ibrutinib, *ex vivo* serial samples of CLL patients under ibrutinib treatment were treated with venetoclax. The combination resulted in high cytotoxicity *in vitro* and confirmed a possible synergy between venetoclax and ibrutinib. Of functional relevance, the decrease of MCL1 and BCL-x<sub>L</sub> mediated by ibrutinib augmented the response to inhibition of BCL2 through venetoclax, strongly endorsing for a clinical trial with this combination therapy (Cervantes-Gomez et al. 2015).

Importantly, on the other hand, various studies were performed to assess the safety profile of venetoclax and their impact on non-tumor hematopoietic lineages using genetically modified murine models. Pre-B-cells and immature B-cells were



found to highly depend on BCL-x<sub>L</sub> (Motoyama et al. 1995) with a low expression of BCL2 in these subsets; however, a gradual switch in BCL2 expression in pro-B-cell precursors directed their maturation (Merino et al. 1994). In order to validate the mode of action of ABT-199 on normal lymphocyte subsets, knockout mice models carrying knockouts of apoptotic players (Bim, Bax, Bak, Puma, Noxa) were analyzed (Khaw et al. 2014).

Analysis of the *in vitro* sensitivity of lymphocyte subsets identified human peripheral B-cells of healthy donors to be more sensitive to venetoclax treatment than CD4+ or CD8+ T-cells and granulocytes. These data were also confirmed by analyzing murine lymphocyte subsets (Khaw et al. 2014). In contrast to cells of the B-cell lineage, the T-cell lineage and granulocytes were resistant to venetoclax treatment. In-depth analysis of T-cell subsets revealed a higher susceptibility of double-negative (CD4- CD8-) thymocytes and mature peripheral T-cells than CD4 and CD8 subsets to venetoclax treatment, correlating with their reliance on BCL2 (Gratiot-Deans et al. 1994; Veis et al. 1993).

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## 4 Clinical Efficacy of Venetoclax in Hematological Malignancies

### 4.1 Venetoclax for Treatment of Poor-Risk CLL

CLL is a B-cell malignancy, where clonal CD5+ CD19+ CD23+ B-cells are present in the peripheral blood and infiltrate lymphoid organs such as lymph nodes, spleen, and bone marrow. The mechanisms underlying CLL pathogenesis are not fully resolved, and the clinical course of CLL is highly diverse. Recently, there was a paradigm change in treatment of CLL from chemoimmunotherapy-based treatments to the use of small-molecule inhibitors targeting key survival mechanisms especially in cases with high-risk genetic aberrations. The three main FDA/EMA approved small-molecule inhibitors with proven efficacy are ibrutinib, targeting BTK; idelalisib, targeting PI3K- $\delta$ ; and venetoclax targeting BCL2.

### 4.2 Phase I and Phase II Trials with Venetoclax as a Single-Agent in CLL

In spite of variations in BCL2 expression levels between patient samples, almost all CLL tumors express high levels of BCL2 primarily due to the prevalence of del (13q14), harboring the BCL2 repressors, miR-15 and miR-16 (Cimmino et al. 2005).

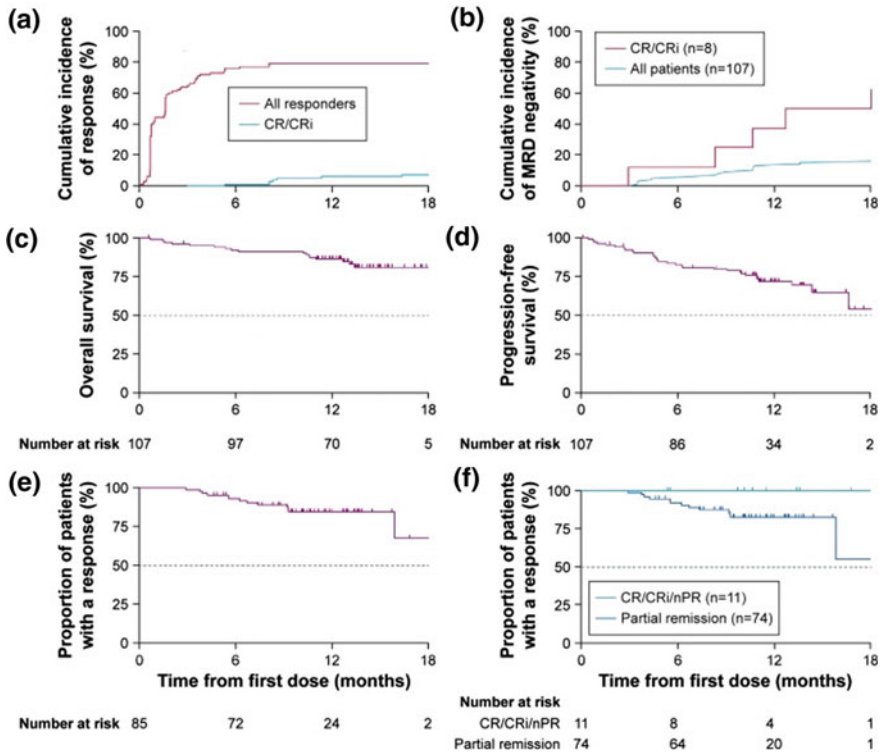
A phase I first-in-human dose escalation clinical trial was initiated to determine the dosings of venetoclax in patients with relapsed/refractory CLL, SLL, or B-NHL (Roberts et al. 2016). To address the safety and pharmacokinetic profile, the first group was treated with an escalating dose, in which 56 patients received treatment

with eight different doses ranging from initial doses between 20 and 50 mg venetoclax and received a weekly increase up to 1200 mg per day. In the second group, 60 patients were treated in a stepwise weekly ramp-up of up to 400 mg per day. Treatment with venetoclax resulted in an overall response rate (ORR) of 79% in the relapsed/refractory CLL with poor prognostic clinical factors (ORR of 77% in the dose escalation cohort, ORR of 82% in the expansion cohort) (Roberts et al. 2016). Strikingly, with venetoclax treatment, a rapid reduction of absolute lymphocyte counts occurred within 6–24 h after a single 20 mg dosing, where apoptotic CLL cells were detected in peripheral blood. Reduction in tumor burden was detected in blood, lymph nodes, and bone marrow; however, tumor lysis syndrome (TLS) occurred only in two patients with lymphadenopathy. Twenty percentage of patients achieved complete remission, and among them, 5% were negative for MRD by flow cytometry, which has never been observed with BTK or PI3 K inhibitors treatments (Woyach and Johnson 2015). Notably, tumor lysis syndrome emerged as dose-limiting toxicity in these early data and dedicated risk mitigation strategies have been implemented including a slow ramp-up dosing and prophylactic measures to allow for safe treatment initiation (for details please see below).

In the dose escalation protocol, 60 patients were treated with a weekly dose ramp-up of 20–400 mg daily and no tumor lysis syndrome was observed. Progression-free survival of 69% was reported after 15 months. The grade 3/4 adverse effects included neutropenia in 40% of the patients and grade 1/2 adverse effects were associated with the gastrointestinal system. Nevertheless, infections due to neutropenia remained lower compared to treatment with chemoimmunotherapy. The efficacy of venetoclax was irrespective of the cytogenetics and *TP53* mutation status. After a median observation time of 17 months, 41 patients (35%) showed progressive disease and among these 18 patients (16%) developed Richter's transformation.

Due to the promising results in poor-risk CLL, a pivotal phase II clinical trial was initiated, accruing relapsed/refractory CLL patients with del(17p). In this multicenter open-label study, 107 patients were enrolled between 2013 and 2014 and treated with venetoclax with a weekly dose escalation from 20 to 400 mg over 4 weeks (20, 50, 100, 200, 400 mg) and continued until disease progression. Overall response after an observation time of 12 months was 79.4% (85 of 107 patients), and in 8% of patients, complete remission was achieved. Estimated PFS and OS after 12 months were 72 and 86.7%, respectively (Fig. 3) (Stilgenbauer et al. 2016).

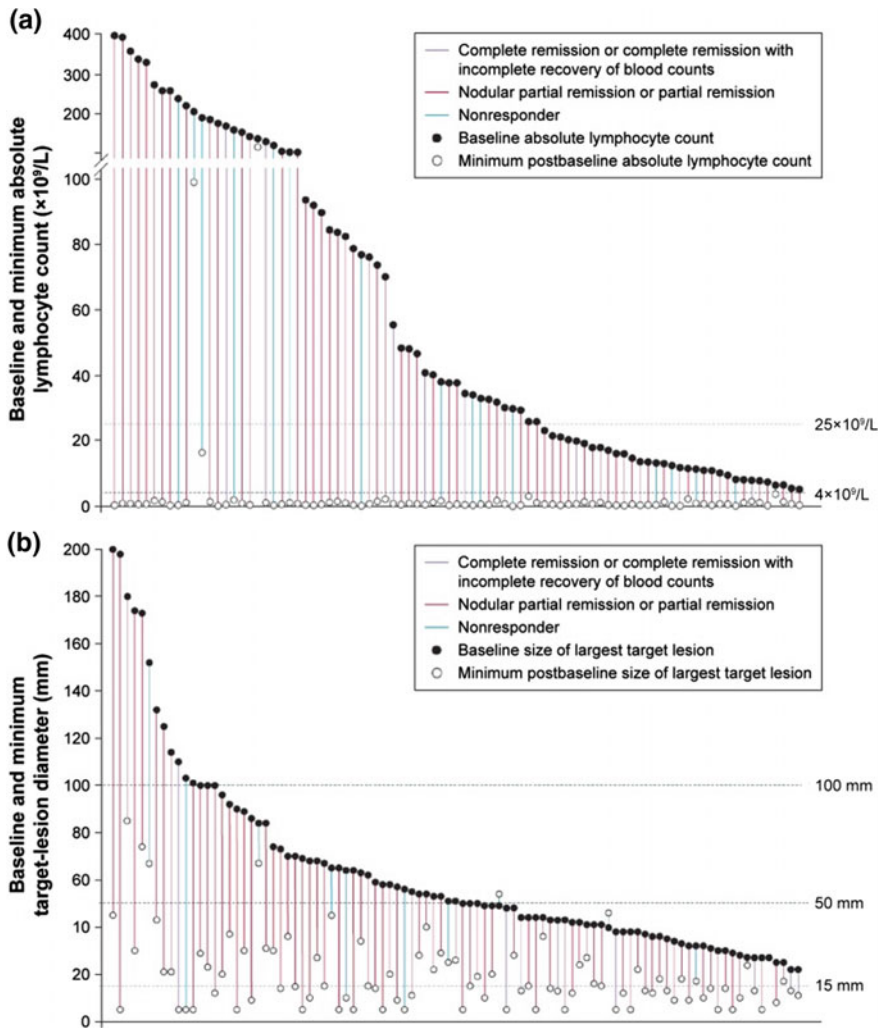
Responses were durable, and majority of the patients showed reduction in absolute lymphocyte count, target lymph node lesion diameter, and bone marrow infiltrate at a median of 0.3 months of treatment (Fig. 4). Management of tumor lysis syndrome was by prophylaxis. Laboratory TLS was observed in five patients during dose escalation and in one patient in the third week; however, no clinical



**Fig. 3** **a** Cumulative incidence of overall response and CR by independent review-committee assessment. **b** Cumulative incidence of minimal residual disease-negative status in peripheral blood for all patients and for patients achieving CR or CRi by independent review-committee assessment. Kaplan–Meier curves for **c** overall survival, **d** progression-free survival ( $n = 107$ ), **e** duration of overall response for all responders by independent review-committee assessment ( $n = 85$ ), and **f** duration of overall response for all responders separated by response subgroups (independently assessed). CR: complete remission; CRi: CR with incomplete recovery of blood counts; nPR: nodular partial response (Stilgenbauer et al 2016; Huber et al. 2017)

TLS appeared in these cases. The most common adverse effect of higher grade was neutropenia in 40% of patients, which was handled with dose reductions, G-CSF administration, or prophylactic antibiotic regimens. The results of this pivotal trial led to FDA approval of venetoclax in April 2016 for the treatment of previously treated CLL patients with the 17p deletion (Deeks 2016).

To date, limited clinical data is available regarding the sequential use of the novel drugs or synergism of inhibitors in combinations. Various drug combinations are currently being tested to improve response rates and with an aim for deep remission or even cure.



**Fig. 4** Absolute change from baseline in peripheral absolute lymphocyte count in patients with a baseline absolute lymphocyte count  $> 5 \times 10^9$  cells/L ( $n = 87$ ) (a) and unidimensional nodal diameter ( $n = 96$ ) (b). Thresholds of  $4 \times 10^9$  cells/L (a) and 15 mm (b) corresponded to requirements for complete remission. Line length indicates absolute best change from baseline; each line represents one patient, with patients arranged in descending order of baseline measurement. Nodal measurements were computed tomography scan-derived, consisting unidimensional diameters of largest target lesions for patients who had at least one follow-up computed tomography scan on study. Response categories were assessed by an independent review committee (Stilgenbauer et al 2016; Huber et al. 2017)

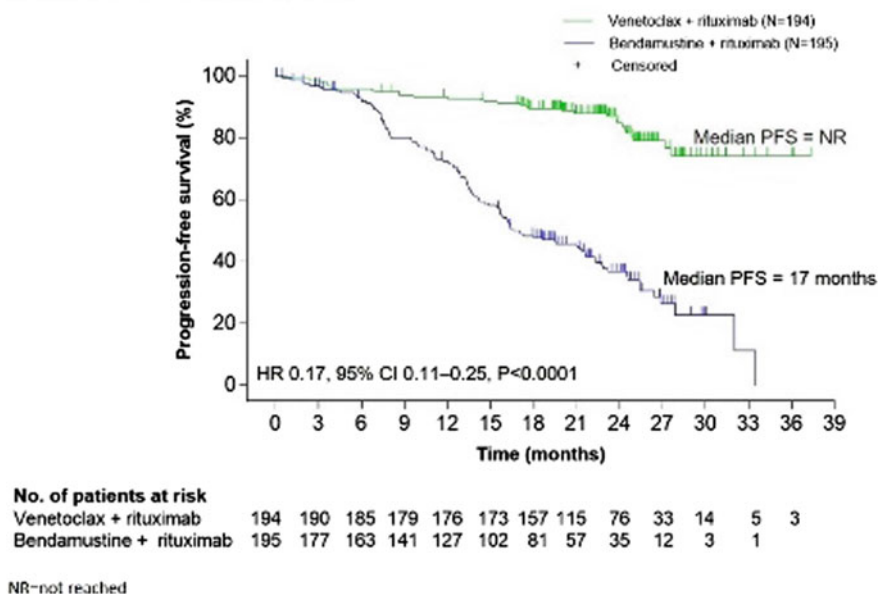
### 4.3 Venetoclax in Combination Therapy for the Treatment of CLL

Since the combination of venetoclax with rituximab enhanced the efficacy of venetoclax in preclinical models, a phase Ib study was initiated where relapsed/refractory CLL patients were continuously treated with venetoclax and received a single dose of rituximab every six weeks. Primary aim of the combination study was to address the maximum tolerable dose and safety of the combination, and further objectives were to assess the pharmacokinetic profile, efficacy, overall response, and PFS (Seymour et al. 2017). Twenty-five (51%) of 49 patients had a complete remission and 28 (57%) patients achieved undetectable bone marrow MRD. The most common adverse effects included grade 1/2 gastrointestinal events and grade 3/4 neutropenia in 26 (53%) patients, similar to that of venetoclax monotherapy. Remarkably, 42 (86%) patients responded (ORR) to the combination, and a 2-year progression-free survival was achieved in 82% (Seymour et al. 2017).

Most recently, the first randomized phase III data on venetoclax became available from the MURANO trial. This showed profound improvement in PFS (primary endpoint), clinical response rate, MRD response, and OS in relapsed/refractory CLL patients treated with venetoclax plus rituximab (VR) compared to bendamustine and rituximab (BR). Of the 389 patients enrolled, 27% had a del(17p13), 60% received one prior therapy, and 15% were refractory to fludarabine. At interim analysis (median follow-up of 23.8 months), PFS was significantly prolonged for VR compared to BR arm (median PFS not reached vs. 17 months, Fig. 5). The ORR for VR was 93.3% compared to 68% for BR, and CR/CRi was achieved in 26.8% versus 8.2%, respectively. MRD negativity was attained in 83.5% of cases treated with VR compared to 23.1% treated with BR. Comparable number of fatal AEs (5%) and Richter's transformation (3%) was observed in both treatment arms. The dramatic efficacy of VR treatment combined with favorable tolerability will lead to approval of this combination therapy for relapsed/refractory CLL (Seymour et al. 2017) (Fig. 5).

Furthermore, a prospective, open-label multicenter randomized phase 3 trial was initiated to compare the efficacy of obinutuzumab combined with venetoclax versus obinutuzumab with chlorambucil (Clb) in the front line treatment of CLL patients with comorbidity (CLL14 trial of the GCLLSG). The safety run-in phase of the trial included 12 patients who received the experimental arm (obinutuzumab with venetoclax). The safety and efficacy of 6 weekly cycles of obinutuzumab and daily treatment with venetoclax appeared well tolerated and showed excellent efficacy; therefore, the randomized phase III trial is currently fully accrued, and follow-up is ongoing (Fischer et al. 2015).

Several lines of evidence support the combination of venetoclax with other small-molecule inhibitors in CLL. Ongoing clinical phase II trials are recruiting participants for combination treatment of ibrutinib, venetoclax, and obinutuzumab for first-line treatment of CLL (CLL13, GAIA trial; NCT02950051). The study protocol compares several combinations such as standard chemotherapy (FCR/BR)



**Fig. 5** Progression-free survival of the interim analysis of the pivotal phase III MURANO trial. The combination of venetoclax with rituximab showed a dramatic prolongation of PFS in comparison to bendamustine and rituximab (Seymour et al. 2017)

versus rituximab with venetoclax (RvE) versus obinutuzumab with venetoclax versus obinutuzumab with ibrutinib and venetoclax (GIVE) in previously untreated fit patients without del(17p13) or *TP53* mutation (NCT02758665). Furthermore, the combination of venetoclax with ibrutinib (NCT02756897) is being studied for the treatment of relapsed/refractory CLL. In the CLL-BAG trial, the sequential regimen of bendamustine for debulking of tumor cells is followed by ABT-199 and GA101-induction and -maintenance therapy. Interim results after the induction phase report tremendous success with an overall response rate in 97% of treated patients and 89% of patients were MRD-negative (NCT02401503) (Cramer et al. 2017). Even more impressive results are expected from these trials on treatment-naïve patients as well as relapsed/refractory diseases (Table 2).

#### 4.4 Venetoclax for the Treatment of Acute Lymphoblastic Leukemia (ALL)

Treatment of pediatric B-cell precursor ALL (BCP-ALL) has evolved to be more and more successful over the past decades as survival rates of patients have improved to more than 80% (Pui et al. 2015). However, decreased tolerance to therapy (toxicity) and minimal residual disease positivity with subsequent relapse remain issues associated with poor outcome. As BCP-ALL is a very heterogeneous

**Table 2** Selection of the important clinical trials in chronic lymphatic leukemia and their adverse effects (grade 3/4)

| Trial name/population                               | Treatment   | Phase | Identifier  | N   | ORR [%]              | Reference                                  | Adverse effects grade 3/4   |
|---|---|-------|-------------|-----|----------------------|--|---|
| Relapsed/refractory CLL                             | Venetoclax monotherapy  | I     | NCT01328626 | 116 | 79%                  | Roberts et al. (2016) NEJM                 | Neutropenia 41% (48)<br>Thrombocytopenia 12% (14)<br>TLS (dose expansion cohort 10/56)  |
| Relapsed/refractory CLL with del (17p)              | Venetoclax monotherapy  | II    | NCT01889186 | 107 | 79.4% (85)           | Stilgenbauer et al. (2016) Lancet Oncology | Neutropenia 40% (43)<br>Anemia 18% (19)<br>Thrombocytopenia 15% (16)<br>Infection 20% (21)  |
| Relapsed/refractory CLL                             | Venetoclax + rituximab  | Ib    | NCT01682616 | 49  | 51% (25)             | Seymour et al. (2017) Lancet Oncology      | Neutropenia 53% (26)<br>Thrombocytopenia 16% (8)<br>Anemia 14% (7)<br>TLS 4% (2)  |
| Untreated CLL, run-in phase CLL14                   | Obinutuzumab combined with venetoclax versus obinutuzumab with chlorambucil | III   | NCT02242942 | 13  | 58% (7)              | Fischer et al. (2015) Blood                | Neutropenia 58% (7)<br>Infections 16.7% (2)<br>Diarrhea 8.3% (1)<br>Leukopenia 8.3% (1)<br>Thrombocytopenia 16.7% (2)<br>Laboratory TLS 16.7% (2) |
| CLL2-BAG (untreated CLL or relapsed/refractory CLL) | Bendamustine, then venetoclax + GA101                                       | II    | NCT02401503 | 66  | 97% (interim result) | Cramer et al. (2017) Hematol. Oncol.       |   |

(continued)

**Table 2** (continued)

| Trial name/population   | Treatment   | Phase         | Identifier  | N   | ORR [%]<br>(interim result)  | Reference                      | Adverse effects grade 3/4   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
|---|---|---------------|-------------|-----|------------------------------|--------------------------------|---|--|-------|-------|-------------|----------------|---------------|--------|---------------|---------------|------------------|--------------|---------------|------------------------|-------------|--------------|-----------|--------------|--------------|
| MURANO<br>(relapsed/refractory<br>CLL with/without del<br>(17p))            | Venetoclax + rituximab versus<br>bendamustine + rituximab | III           | NCT02005471 | 389 | 97.3%<br>(interim<br>result) | Seymour et al.<br>(2017) Blood | <table border="1"> <thead> <tr> <th></th> <th>V + R</th> <th>B + R</th> </tr> </thead> <tbody> <tr> <td>Neutropenia</td> <td>112<br/>(57.7%)</td> <td>73<br/>(38.8%)</td> </tr> <tr> <td>Anemia</td> <td>21<br/>(10.8%)</td> <td>26<br/>(13.8%)</td> </tr> <tr> <td>Thrombocytopenia</td> <td>11<br/>(5.7%)</td> <td>19<br/>(10.1%)</td> </tr> <tr> <td>Febrile<br/>neutropenia</td> <td>7<br/>(3.6%)</td> <td>18<br/>(9.6%)</td> </tr> <tr> <td>Pneumonia</td> <td>10<br/>(5.2%)</td> <td>15<br/>(8.0%)</td> </tr> </tbody> </table> |  | V + R | B + R | Neutropenia | 112<br>(57.7%) | 73<br>(38.8%) | Anemia | 21<br>(10.8%) | 26<br>(13.8%) | Thrombocytopenia | 11<br>(5.7%) | 19<br>(10.1%) | Febrile<br>neutropenia | 7<br>(3.6%) | 18<br>(9.6%) | Pneumonia | 10<br>(5.2%) | 15<br>(8.0%) |
|   | V + R   | B + R         |             |     |                              |                                |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
| Neutropenia   | 112<br>(57.7%)  | 73<br>(38.8%) |             |     |                              |                                |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
| Anemia  | 21<br>(10.8%)   | 26<br>(13.8%) |             |     |                              |                                |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
| Thrombocytopenia  | 11<br>(5.7%)  | 19<br>(10.1%) |             |     |                              |                                |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
| Febrile<br>neutropenia  | 7<br>(3.6%)   | 18<br>(9.6%)  |             |     |                              |                                |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
| Pneumonia   | 10<br>(5.2%)  | 15<br>(8.0%)  |             |     |                              |                                |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |
| CLL2-GIVe<br>(untreated CLL with<br>TP53 deletion (17p-)<br>and/or mutation | Venetoclax + ibrutinib + obinutuzumab                     | II            | NCT02758665 |     | recruiting                   | German CLL<br>Study Group      |   |  |       |       |             |                |               |        |               |               |                  |              |               |                        |             |              |           |              |              |



disease, ideal biomarkers for early stratification of patients into groups which would potentially benefit from treatment with venetoclax are required. In particular, the prognosis of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph (+) ALL) remains unfavorable. Ph(+) ALL occurs in 25% of adults and in only 3% of pediatric ALL patients (Liu-Dumlao et al. 2012). The current treatment regimen includes multi-chemotherapy which is complemented with the kinase inhibitors imatinib or dasatinib. A pre-clinical trial in xenograft mice demonstrated that the combination of dasatinib and venetoclax is synergistic and tolerable in vivo and that the anti-leukemic effects were vastly improved (Leonard et al. 2016).

Two clinical trials are planned to study the efficacy of venetoclax monotherapy in ALL. A phase I study to address the safety and pharmacokinetics of venetoclax monotherapy in pediatric and young adult patients will recruit patients with relapsed/refractory ALL (NCT03236857). Another open-label phase I dose-escalating study will recruit participants and analyze safety and pharmacokinetics of venetoclax, navitoclax, and chemotherapy in relapsed acute lymphoblastic leukemia (NCT03181126).

#### **4.5 Treatment of Non-Hodgkin's Lymphomas (NHL) and Multiple Myeloma (MM) with Venetoclax**

Non-Hodgkin's lymphoma describes a group of B- and T-cell lymphomas, which range from indolent to aggressive types. The low-grade or indolent subtypes include follicular lymphoma (FL) and CLL, while the high-grade or aggressive NHLs include diseases such as diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). While the standard chemo-immuno therapy has improved the outcome of patients diagnosed with aggressive non-Hodgkin's lymphomas, treatment after disease relapse remains challenging.

Venetoclax monotherapy is being assessed in a clinical trial for pediatric and young patients with NHL (NCT03236857), and even further clinical trials are planned to study venetoclax in combination (NCT03181126). A clinical phase III trial is currently investigating in the combination of venetoclax and ibrutinib in MCL patients (NCT03112174). An ongoing phase I single-arm study investigates the combination of venetoclax with bendamustine and rituximab. After completion of the treatment cycles with bendamustine, rituximab, and venetoclax, venetoclax is continued as monotherapy for two more years. In a phase I first in human trial of 106 recruited patients with relapsed/refractory FL (29), DLBCL (34), MCL (28), Waldenstrom macroglobulinemia (4), marginal zone lymphoma (3) and DLBCL derived from Richter's syndrome (3), an ORR of 44% and median PFS of 6 months was achieved. 14 patients had a complete response, 33 patients showed a partial response, and 32 patients had a stable disease. In this dose escalation study, the MCL cases achieved durable response with 800mg while 1200mg was the effective single agent dose of venetoclax for FL and DLBCL patients (Davids et al. 2017).

A follow-up phase II single-arm study is currently recruiting participants for the combination of venetoclax with obinutuzumab in relapsed/refractory DLBCL. Here, the combination treatment is repeated for three cycles, and if complete or partial responses are obtained, the patients will receive stem cell transplantation (NCT02987400). Several trials aiming for the combination treatment of venetoclax with rituximab or obinutuzumab, cyclophosphamide, etoposide, prednisone, and others are under investigation.

Venetoclax demonstrated cell killing in multiple myeloma cell lines and primary tumor cells (Kumar et al. 2015), and several clinical studies with venetoclax are currently ongoing for the treatment of multiple myeloma. Relapsed/refractory patients receive combinations of venetoclax and current standard therapy with dexamethasone and bortezomib (NCT02755597; NCT01794507). Other trials combine venetoclax with daratumumab, a CD38 antibody (NCT03314181). In the monotherapy approach, 21% of patients responded to venetoclax treatment. Notably, 40% of these patients carried the t(11;14) translocation, were refractory to bortezomib and lenalidomide, and were treated with at least four prior regimens (Kumar et al. 2015). Due to good safety and efficacy, a phase Ib trial was initiated to study the combination treatment of venetoclax with bortezomib and dexamethasone. Sixty-six heavily pretreated patients were enrolled. The overall response rate was 66%, and the median time to progression was 9.7 months. The results were irrespective of the t(11;14) status, with manageable adverse effects and an acceptable safety profile (Moreau et al. 2017).

## 4.6 Venetoclax for Treatment of Myeloid Malignancies

Acute myeloid leukemia is an aggressive malignancy of the myeloid progenitor cells. AML cases have variable outcome after chemotherapy due to the enormous clinical and molecular heterogeneity. Over decades, the induction therapy of combined anthracycline plus cytarabine cytotoxic agents has remained the standard of treatment with little improvement in survival with the additions of novel agents. Though the manipulation of intensity and duration of treatment modestly improved survival in certain patient subsets, a consolidation chemotherapy often including stem cell transplant remains necessary (Fernandez et al. 2009). Venetoclax demonstrated high efficiency in preclinical AML models as well as synergy with anthracyclines (Teh et al. 2017).

Venetoclax achieved remarkable results in early clinical trials in AML. The M13-387 phase Ib trial evaluated the safety and the maximum tolerable dose of venetoclax in treatment naïve elderly AML patients not eligible for standard induction chemotherapy. Patients were treated in two arms, a ramp-up of venetoclax with decitabine or 5-azacitidine. Nineteen of 22 patients completed the first 28-day cycle with venetoclax. The response to treatment was 75% in the decitabine and 70% in the 5-azacitidine arms (DiNardo et al. 2015). Also, venetoclax as a

single agent in heavily pretreated AML patients resulted in an overall response rate of 19% (Konopleva et al. 2016). Based on these results, further clinical trials were initiated for the treatment of AML. A phase III study was initiated to assess treatment with Venetoclax in combination with azacitidine, where patients not eligible for intensive therapy were randomized to venetoclax with azacitidine or placebo with azacitidine arms. Interim results present an impressive overall response rate of 69% with a complete response (CR) of 60% in high-risk AML patients (NCT03236857; DiNardo et al. 2015).

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## 5 Venetoclax in Solid Tumors

As various cancers show dependency on anti-apoptotic BCL2 family members for their survival, the use of venetoclax extends beyond that of hematologic malignancies.

BCL2 is overexpressed in 85% of estrogen receptor-positive (ER) breast cancers. ER was found to bind two estrogen response elements (EREs) in the coding regions of BCL2, thereby enhancing BCL2 expression in these tumors (Perillo et al. 2000). Preclinical data generated in ER-positive breast cancer xenografts showed venetoclax to be highly efficacious. Also, venetoclax was found to synergize with PI3K and mTOR inhibitors enhancing its apoptotic effect (Vaillant et al. 2013). To explore more effective therapeutic strategies, safety and efficiency of venetoclax were tested in a phase Ib study in ER<sup>+</sup> BCL2<sup>+</sup> breast cancer patients. The results were heterogeneous, as four patients had a partial response and five has a stable disease with a clinical benefit rate of 69%. Venetoclax treatment of ER+ breast cancers is further being validated in phase II clinical trials which are ongoing (NCT02391480).

Small-cell lung cancer (SCLC) is a high proliferating cancer with a low doubling time, rapid metastasis, and quick relapse after treatment. First-line chemotherapy with platinum-based agents and etoposide remains without long-term success, and multiple-targeted approaches using receptor tyrosine kinase (RTK) inhibitors are being investigated. Though the RTK inhibitors were of therapeutic relevance, the curative potential was minimal (Niederst et al. 2013). Assessment of the efficacy of venetoclax in SCLC treatment is still in the pre-clinical phase. The expression of BCL2 was comprehensively assessed in different lung cancer cell lines, and BCL2 inhibitors were found to synergize with anthracyclines providing a promising strategy for treatment (Inoue-Yamauchi et al. 2017). Venetoclax was also addressed in combination with BET inhibitor ABBV-075, since BET is known to regulate key oncogenes as MYC, CCND2, and BCL2L1 and enhance complex formation of pro-apoptotic BIM and BCL2 (Lam et al. 2017). The combination treatment proved to be highly synergistic and therefore might be a possible rationale for treatment of SCLC patients with high BCL2 expression.

## 6 Toxicity and Adverse Effects Associated with BCL2 Inhibitor Treatments

### 6.1 Thrombocytopenia

BH3 mimetics such as ABT-767 and ABT-263 inhibit BCL2, as well as BCL-x<sub>L</sub> and BCL-W. Since thrombocytes depend on BCL-x<sub>L</sub> for survival, treatment with these inhibitors leads to reduction in platelets and dose-dependent thrombocytopenia due to direct toxic anti-platelet effects. Assessment of safety and tolerability of navitoclax documented the prevalence of thrombocytopenia in different tumor entities. In a clinical trial on 39 SCLC patients, 41% developed grade III–VI thrombocytopenia upon treatment with navitoclax (Rudin et al. 2012). In a phase II study of CLL patients, 36% of patients suffered from grad III–IV thrombocytopenia (Kipps et al. 2015). This mode of action of these drugs on platelets was clarified to be mediated by apoptosis cell death, as well as decreased calcium flux, reducing the activation of platelets (Vogler et al. 2013). To circumvent severe thrombocytopenia, the initial dose of navitoclax was kept low within the first seven days of treatment. However, these side effects limited the clinical development of navitoclax. Venetoclax being a highly specific for BCL2 with lower affinity toward BCL-x<sub>L</sub> did not induce dose-dependent thrombocytopenia.

### 6.2 Tumor Lysis Syndrome (TLS)

The tumor lysis syndrome is one of the major risk issues in venetoclax treatment, owing to the very high potency of the drug. Due to the rapid response, with abrupt onset at 6–8 h following dosing, venetoclax is prone to induce tumor lysis syndrome, depending on tumor mass, comorbidities (in particular renal function), and treatment dose (Cheson et al. 2017). TLS results from rapid cell death, wherein tumor cells release their metabolites, nucleic acids, and intracellular ions into the blood stream, thereby potentially inducing metabolic dysfunction. The efflux of cellular metabolites leads to a disbalance of the blood homeostasis with an increase in uric acid, potassium, and phosphoric acid and decrease in calcium levels. If the renal excretion is affected or delayed, an accumulation of these metabolites occurs in blood. The incidence of TLS is increased in tumors with a high tumor burden or high cell turnover (Cheson et al. 2017; Crombie and Davids 2017). The most common criteria for subdivision into clinical and laboratory TLS were defined in 2004 by Cairo et al. (2004). Laboratory TLS includes at least two or more biochemical variables being increased or reduced by a factor of more than 25%; furthermore, TLS appears within three days prior or seven days after initiation of therapy. TLS causes hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia and can lead to acute renal failure and cardiac events of life-threatening potential. If laboratory TLS is accompanied by clinically relevant events such as creatinine increase, seizures, or cardiac dysfunction, a clinical TLS is

diagnosed. Prophylaxis and treatment of TLS includes hydration, diuresis, monitoring of electrolytes, and prevention of hypouricemia with allopurinol or rasburicase (Howard et al. 2011).

For treatment with venetoclax, a treatment risk stratification is implemented where patients are grouped according to their TLS risk. Low risk for TLS is defined by small nodal disease, a low ALS  $< 25 \times 10^9/L$ . Medium risk includes an ALS  $> 25 \times 10^9/L$  or a lymph node with more than 5 cm diameter. The high-risk group for TLS is a radiological tumor  $> 10$  cm in diameter and a ALS  $> 25 \times 10^9/L$  (Roberts et al. 2016). Therapy with venetoclax is initiated with a low starting dose, and patients pass through a weekly dose ramp-up from 20 to 50, 100, 200, and 400 mg to ensure safety and tolerability. Laboratory monitoring of blood counts and clinical chemistry is mandatory during treatment initiation, and immediate action is required in case of relevant abnormalities. Detailed information and guidance on TLS management are beyond the scope of this article and are available in the prescription information of venetoclax. Meticulous adherence to the guidelines is required to deliver venetoclax therapy safely.

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## 7 Venetoclax Drug Interactions

### 7.1 Interaction with CYP3A4 Inhibitors

The routes of elimination of venetoclax were tested by administration of a 200 mg single dose of  $^{14}C$  (100  $\mu Ci$ ) venetoclax to four healthy volunteers. The recovery of total radioactive dose ( $100\% \pm 5\%$ ) was through feces as the major route of drug elimination. The major metabolite M27 was formed by oxidation cytochrome P450 isoform 3A4 (CYP3A4) (Choo et al. 2014; Li et al. 2016). Since various drugs such as protease inhibitors, anti-fungal agents, macrolide antibiotics, and anti-depressants are described to be inhibitors of CYP3A4, possibility of drug interactions was tested using ketoconazole as a representative agent. Twelve NHL patients were enrolled for a phase I, open-label study, where patients received venetoclax and ketoconazole, the strong CYP3A4 inhibitor. Inhibition of CYP3A4 led to a significant increase in the mean maximum observed plasma concentration  $C_{max}$  and area under the plasma concentration-time curve ( $AUC_{\infty}$ ) by 2.3-fold and 6.4-fold, respectively.

Similarly, also, simultaneous treatment with venetoclax and CYP3A4 inducers such as Rifampin led to an increase in the AUC and  $C_{max}$  of venetoclax (Agarwal et al. 2016). These studies suggest the need to avoid concomitant use of strong and moderate inhibitors or inducers of CYP3A4 during the venetoclax ramp-up phase in patients (Agarwal et al. 2017). Also, venetoclax dosage should be reduced by 25–50% when co-administering the CYP3A4 modulators after dose escalation.

## 7.2 Interaction with P-Glycoprotein Inhibitors

Venetoclax has been described to be a substrate of P-glycoproteins (P-gp) based on *in vitro* studies. Also, venetoclax was shown to inhibit P-glycoprotein at the transcriptional and protein levels (Weiss et al. 2016). In a clinical trial in healthy volunteers, the effect of venetoclax on the pharmacokinetics of digoxin, a P-gp inhibitor was evaluated. Co-administration of digoxin and venetoclax increased digoxin maximum observed plasma concentration (C<sub>max</sub>) by 35% and area under the plasma concentration-time curve (AUC<sub>0-∞</sub>) by 9%. The study indicated that venetoclax can increase the concentrations of P-gp substrates. The study suggested administration of narrow therapeutic index P-gp substrates, six hours prior to venetoclax to minimize the potential interaction.

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## 8 Biomarkers of Resistance to Venetoclax Treatment

Biomarkers are important to predict the response and efficacy to venetoclax therapy and for early assignment of combination or alternative treatments for effective therapy.

Due to the high specificity of venetoclax, upregulation of alternative anti-apoptotic is described to confer resistance to therapy. Several preclinical and *ex vivo* studies analyzed the ratio between BCL2 and MCL1 which was of clinical importance to predict venetoclax treatment response. Studies of multiple myeloma xenografts showed that the overexpression of BCL2 and MCL1 led to resistance toward BCL2 inhibitors treatment (Punnoose et al. 2016). Upregulation of BCL-x<sub>L</sub> or MCL1 or both is also contributing to venetoclax resistance in lymphoma cell lines (Tahir et al. 2017).

Functional analysis of the cell's response to venetoclax using BH3 profiling of primary CLL cells showed a significant association between apoptotic priming by venetoclax *ex vivo* to clinical response to venetoclax. Precisely, the extent of mitochondrial depolarization by a BIM BH3 peptide *in vitro* correlated with percentage reduction of CLL in the blood following venetoclax treatment suggesting its use as a potential biomarker for early risk stratification (Anderson et al. 2016).

Furthermore, acquired missense mutations in the BH3 binding groove of resistant cell lines were detected to interfere with drug binding capacity. Also, acquired mutations in the pro-apoptotic BAX gene limiting its anchoring to the mitochondria were also described to interfere with apoptosis induction by venetoclax (Fresquet et al. 2014).

## 9 Summary and Future Perspectives

The EMA and FDA approval of venetoclax, a novel, and highly specific BCL2 inhibitor already indicates its high therapeutic potential in CLL and potentially also in various other malignancies. Venetoclax demonstrated tremendous success in treatment of poor risk, relapsed/refractory CLL, and in the future may be revolutionizing treatment of various other hematological malignancies. With precision medicine evolving to a real-world paradigm, there is an absolute need for novel and specific targeted therapies. The use of targeted combination therapies will further improve the landscape of treatment options for patients who are refractory to conventional therapies and may eventually lead to novel approaches en route toward the cure of cancer.

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