Brand Name: Venclexta

Generic Name: Venetoclax

Manufacturer[1]: AbbVie, USA

Drug Class[2]: Signal Transduction Inhibitor

Uses[1]: Chronic lymphoid leukemia, In patients with 17p chromosome deletion, who have received at least 1 prior therapy

Mechanism of Action[1,2,3,4]: selective small-molecule inhibitor of B-cell lymphoma-2 protein, an antiapoptotic protein that prevents chronic lymphocytic leukemia (CLL) cell death and is associated with chemotherapy resistance. Venetoclax mimics the BH3 domain on BCL-2 family proteins and binds with high affinity; the action antagonizes pro-apoptotic proteins like BIM and causes mitochondrial outer membrane permeability and the activation of caspases that kill cells.

Pharmacokinetics[1,2,3,4]:

Absorption

T_{max}	5-8 hours
V_d	256-321 L
$t_{1/2}$	26 hours
Clearance	99.9% feces, 20.8% unchanged
Protein Binding	99%, albumin not reported
Bioavailability	Not reported

Metabolism

Primarily metabolized by CYP3A4/5 to the metabolite M27 which has 58-fold less activity than the parent drug. Also a substrate and inhibitor of P-gp and BCRP.

Elimination

Venetoclax is excreted 99.9% into the feces with 20.8% unchanged. Less than 0.1% in urine.

Efficacy:

Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2016;374(4):311-22. Accessed: Sept 14, 2016.

Study Design: Phase 1, open-label, multi-center, dose-escalation trial

Description of Study: *Methods:* 116 patients with relapsed or refractory CLL, SLL, or non-Hodgkin's lymphoma were enrolled in the trial, 56 in the dose-escalation cohort and 60 in a later expansion cohort with dosing regimens based on data from the former. In the dose-escalation cohort patients were assigned sequentially to dose-escalation groups of 3 patients or more according to a 3+3 design. The week 1 dose was 50mg followed by the week 2 assigned step-up dose for the corresponding target group dose being assessed. Target group doses assessed were 150mg, 200mg, 300mg, 400mg, 600mg, 800mg, and 1200mg/day. Measures of efficacy were overall response rate, progression-free survival, duration of response, time to progression, and overall survival. *Outcome Results*: Tumor lysis syndrome (TLS) occurred in 10/56 (18%) patients in the dose-escalation cohort, 3 of which were clinically evident and the rest laboratory only. 9/10 patients resumed venetoclax after resolution of TLS. One patient in the expansion cohort had laboratory evidence of TLS and none had clinical sequelae. Grade 3 or 4 neutropenia developed in 41% of the study patients. Of the 56 patients in the dose-escalation cohort, the pooled response rate was 77% with 30% having complete response. The median time to first objective response was 6 weeks, and median time to complete response was 6 months (range 3-19 months). In the 400mg expansion cohort, response rate was 82%, and complete response was 10% at time of data cutoff. Across all 116 patients in both cohorts the pooled overall response rate was 76% with complete response in 20% of patients. Of the 23 patients with complete response, 6 had negative results for residual disease (5% of study patients). Median length of progression-free survival in the dose-escalation cohort was 25 months. 15 month progression-free survival was analyzed for dosage groups of <400mg/day, 400mg/day, and >400mg/day as 58%, 69%, and 77%, respectively.

Limitations: The study was funded by AbbVie, the manufacturer of venetoclax. The study protocol was designed by both the study sponsors and investigators. The data was compiled and confirmed by AbbVie, and the final drafts of the manuscript were created with assistance from a medical writer hired by AbbVie. The study authors received grant monies from the manufacturer, were employees of the manufacturer, had equity interest in the manufacturer, or a combination of these. Blinding in this trial was absent, per the open label design. The study was conducted in patients with relapsed or refractory disease who were otherwise healthy individuals (minimal disability on oncology group performance score, normal marrow and organ function, normal blood counts, no active infection, and no history of stem-cell transplant), and thus may not accurately reflect the entire population of patients with relapsed or refractory disease.

Conclusion: Venetoclax induced a 76% response rate across all study patients with 20% achieving complete response and 5% of study patients achieving negative residual disease. There were notably high response rates in patients with 17p deletions, resistance to fludarabine or unmutated IGHV, and bulky disease. Venetoclax shows promise in otherwise healthy patients with relapsed or refractory CLL or SLL, notably in those with mutations known to confer poor prognosis. Further study is needed in patients who do not meet the state of health required for inclusion in this trial. The potential for bias should also be considered given the monetary interactions and interests of both the authors and drug company.

Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicenter, open-label, phase 2 study. Lancet Oncol. 2016;17:768-78. Accessed: Sept 14, 2016.

Study Design: Phase 2, single-arm, multicentre study

Description of Study: *Methods:* 107 patients aged 18 or older were enrolled to receive oral venetoclax once daily continuously until progression or other discontinuation criteria were met. A stepwise weekly dose ramp-up from a starting dose of 20mg to the final 400mg daily dose over 4-5 weeks was used based off of results from phase 1 results. Interruption of venetoclax was required for patients with febrile neutropenia or grade 4 neutropenia for greater than 1 week despide growth factor support, and a lower dose could be reinitiated if ANC >500cells/uL. The primary outcome was activity of venetoclax monotherapy, as measured by the proportion of patients who achieved an overall response (defined as partial remission and higher). Secondary outcomes included proportion of patients with complete remission and partial remission, time to first response, time to 50% reduction in absolute lymphocyte count, duration of overall response, progression-free survival, overall survival, event-free survival, time to progression, proportion of patients proceeding to allogenic stem-cell transplantation, and safety. *Outcome Results*: All patients in the study but 1 had 17p deletion. Median time on treatment was 12.1 months (IQR 10.1-14.2) and 65% of patients were receiving treatment at time of data cutoff. 37 patients discontinued treatment: 22 due to progression, 9 for adverse events, 2 withdrew consent, and 1 for non-compliance. 3 patients proceeded to allogenic stem-cell transplantation. Overall response was achieved in 79.4% (95% CI 70.5-86.6) of the study population. 18 patients had no minimal residual disease detectible in peripheral blood, and 6 of these patients were also minimal residual disease-negative in the bone marrow. Median time to first response was 0.8 months (IQR 0.7-1.7). Median time to complete remission or complete remission with incomplete recovery of blood counts was 8.2 months (IQR 6.7-10.0). Estimated 12-month progression-free survival was 72.0% (95% CI 61.8-79.8) and estimated 12-month overall survival was 86.7% (78.6-91.9). Estimated 12-month event-free survival was 70% (95% CI 67-84). 24 of 107 patients had disease progression, 13 of which had progression of CLL and 11 had Richter's transformation. Median time to progression was 6.3 months (IQR 4.4-9.8) for CLL and 4.7 months (IQR 1.0-10.2) for Richter's transformation. The most common grade 3-4 adverse events were neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%). Serious adverse events were recorded in 55% of patients irrespective of relationship to venetoclax with the most common being pyrexia and autoimmune hemolytic anemia (7% each), pneumonia (6%), and febrile neutropenia (5%). Laboratory TLS was recorded in 5 patients without clinical sequelae.

Limitations: The study was funded by AbbVie, the manufacturer of venetoclax. The funders participated in design, study conduct, analysis, and interpretation of data as well as the writing, review, and approval of the publication. AbbVie confirmed and compiled all data. A professional medical writer hired by AbbVie assisted in writing the manuscript. The study authors received grant monies from the manufacturer, were employees of the manufacturer, had equity interest

in the manufacturer, or a combination of these. The study was conducted in patients with CLL and 17p deletion mutations who were otherwise healthy individuals (minimal disability on oncology group performance score, normal marrow and organ function, normal blood counts, no active infection, and no history of stem-cell transplant), and thus may not accurately reflect the entire population of patients with relapsed or refractory disease. Data analysis of this study only progressed through 36 weeks and as a result some outcomes had to be estimated including: duration of overall response, event-free survival, time to progression, progression-free survival, and overall survival.

Conclusion: Venetoclax induced an overall response rate of 79.4% in patients (95% CI 70.5-86.6) with CLL and 17p deletion – a known poor prognostic factor for which few current treatment options existed. This study was conducted with otherwise healthy individuals and many of the secondary outcomes had to be estimated due to limited time of data collection and analysis. Further study is needed to assess these outcomes as well as to evaluate efficacy of venetoclax in patients with del17p CLL who did not meet the stringent state of health criteria for this study. The potential for bias should also be considered given the monetary interactions and interests of both the authors and drug company.

Salem AH, Agarwal SK, Dunbar M, Enschede SL, Humerickhouse RA, Wong SL. Pharmacokinetics of Venetoclax, a Novel BCL-2 Inhibitor, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Non-Hodgkin's Lymphoma. J Clin Pharmacol. 2016. Accessed: Sept 14, 2016.

Study Design: Pooled dataset cohort for pharmacokinetic analysis

Description of Study: *Methods:* 116 patients with CLL and 106 patients with non-Hodgkin's Lymphoma (NHL) were enrolled in the study. The CLL arm had 8 cohorts with doses escalating from 150mg to 1200mg and a safety expansion cohort at 400mg. The NHL arm had 9 cohorts with doses escalating from 200mg to 1200mg with a safety expansion cohort at the 1200mg dose. Patients received daily doses until disease progression or unacceptable toxicity. Patients were restricted from using steroid therapy, CYP3A4 inhibitors/inducers, additional anticancer therapy, and grapefruit during the study. NHL patients in the dose escalation cohorts up to 400mg received venetoclax following a standard high-fat breakfast (50% total calories from fat) on week 1 day -7, under fasting conditions on week 1 day 1, and following a standard low-fat breakfast (30% total calories from fat) on all other days. There was a 7-day washout period between high-fat and fasting conditions. All other patients received treatment with standard low-fat meals. *Results:* After multiple dose administrations under low-fat conditions, median peak concentrations were observed 5 to 8 hours post-dose across the different venetoclax doses. Terminal phase elimination half-life ranged between 14.1 and 18.2 hours. Venetoclax urine samples were available from 53 CLL and 27 NHL patients. Of these 80 patients only 1 CLL and 6 NHL patients had detectable venetoclax concentrations in urine collected over a 24-hour dosing interval at week 7 day 1. The calculated amount of parent drug excreted unchanged in the urine was <0.01%. High-fat meals increased venetoclax C_{max} and AUC_{∞} by 3.68-fold (90% CI 3.01-4.50) and 4.42-fold (90% CI 3.37-5.79), respectively, relative to fasting conditions.

Similarly, when multiple doses of venetoclax were administered after a low-fat meal , the AUC_{0-24} value increased by 4.27-fold (90% CI 2.98-6.12) compared with the AUC_{∞} observed under fasting conditions. Despite the restriction criteria, data were available from 31 patients who were taking weak or moderate CYP3A4 inhibitors at the time of steady-state sampling. Median dose-normalized C_{max} and AUC_{0-24} values were 40-60% higher in the presence of moderate CYP3A4 inhibitors (ciprofloxacin, diltiazem, and fluconazole).

Limitations: The study was funded by AbbVie, the manufacturer of venetoclax. The funders participated in design, study conduct, analysis, and interpretation of data as well as the writing, review, and approval of the publication. AbbVie confirmed and compiled all data. The study authors received grant monies from the manufacturer, were employees of the manufacturer, had equity interest in the manufacturer, or a combination of these. Only patients with an Eastern Cooperative Oncology Group score of 1 or less were enrolled in this study, so applicability is limited in patients with advanced disease and disability. The effect of food on bioavailability of venetoclax may have been overestimated due to limited terminal-phase concentration-time profile data in the fasting group used for comparison.

Conclusion: Data from the study suggest venetoclax has a higher bioavailability when given with food, irrespective of the fat content, although the authors report the possibility of slight exaggeration of the results. Dose reductions should be considered in patients taking venetoclax concomitantly with moderate CYP3A4 inhibitors, as these were shown to increase plasma levels and drug exposure. No dose reductions are necessary in patients with renal failure, as venetoclax is excreted <0.01% unchanged in the urine.

Contraindications[1,2,3,4]: Concomitant use with strong CYP3A4 inhibitors during initiation and at ramp-up phase.

Precautions[1,2,3,4]:

Tumor Lysis Syndrome: Venetoclax may cause a rapid reduction in tumor volume and therefore a risk of tumor lysis syndrome (TLS) is present during the initial 5-week dose escalation phase of treatment. TLS has occurred with venetoclax in previously treated chronic lymphocytic leukemia (CLL) patients with high tumor burden; renal failure (requiring dialysis) and fatalities have been reported. Changes in blood chemistries consistent with TLS may occur as early as 6 to 8 hours after the first dose and with dose increases, and require prompt management. The risk of TLS is increased with high tumor burden and comorbidities; creatinine clearance less than 80 mL/minute further increases TLS risk. Assess risk of TLS; initiate appropriate TLS prophylactic management (eg, hydration and anti-hyperuricemic therapy); monitor blood chemistries closely and manage abnormalities promptly. May require treatment interruption and dose reduction. The risk of TLS may decrease as tumor burden decreases. Patients at high risk of TLS may require hospitalization at treatment initiation. Concomitant use of CYP3A or P-gp inhibitors at initiation or during dose escalation may increase the risk of TLS.

Bone Marrow Suppression: Neutropenia, thrombocytopenia, and anemia may occur. Grade 3 and 4 neutropenia occurred in almost half of patients receiving venetoclax. Neutropenic fever has been reported. Monitor CBC with differential throughout treatment. May require treatment interruption and/or dose reduction. Consider antimicrobials and WBC growth factor support as clinically indicated

Immunization: Live vaccines should not be administered prior to, during, or after venetoclax treatment until B-cell recovery occurs. Vaccines may be less effective.

Appropriate Use: Patients should be selected for treatment based on the presence of a 17p deletion. Patients without a 17p deletion at diagnosis should be re-tested at relapse as acquisition of 17p deletion may occur.

Renal Function Impairment: Patients with decreased renal function (CrCl < 80 mL/min) may be at increased risk of developing tumor lysis syndrome (TLS) with venetoclax therapy. Increased monitoring and more intensive TLS propylaxis may be necessary during initiation and dose escalation.

Hepatic Function Impairment: Adverse events may be more prevalent in patients with hepatic impairment. Monitor closely for toxicity.

Concomitant use:

- Avoid use with grapefruit products, Seville oranges, starfruit.
- Avoid use with P-gp inhibitors (eg, amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor), or moderate CYP3A inhibitors (eg, ciprofloxacin, diltiazem, dronedarone, erythromycin, fluconazole, verapamil); reduction of dose required and monitoring recommended
- Avoid use with moderate CYP3A inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin) or strong CYP3A inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort)
- Avoid use with P-gp substrates with a narrow therapeutic index (eg, digoxin, everolimus, sirolimus); dosage adjustment required

Breast Feeding: Women should avoid breast feeding due to potential for serious adverse effects in breastfed infants.

Pregnancy: Based on the mechanism of action and data from animal reproduction studies, venetoclax is expected to cause fetal harm if administered during pregnancy. Females of reproductive potential should have a pregnancy test prior to therapy, and use effective contraception during treatment and for at least 30 days after the final dose. Based on animal data, venetoclax may compromise fertility in males.

Adverse effects[1,2,3,4]:

Occuring in >10%

Cardiovascular:
Peripheral edema (11%; grades 3/4: <1%)

Central nervous system:
Fatigue (21%; grades 3/4: 2%), headache (15%; grades 3/4: <1%)

Endocrine & metabolic:
Hyperkalemia (20%; ≥ grade 3: 2%), hyperphosphatemia (15%; ≥ grade 3: 3%), hypokalemia (12%; grades 3/4: 4%)

Gastrointestinal:
Diarrhea (35%; grades 3/4: <1%), nausea (33%; grades 3/4: <1%), vomiting (15%; grades 3/4: <1%), constipation (14%)

Hematologic & oncologic:
Neutropenia (45%; grades 3/4: 41%), anemia (29%; grades 3/4: 18%), thrombocytopenia (22%; grades 3/4: 15%)

Respiratory:
Upper respiratory tract infection (22%; grades 3/4: 1%), cough (13%)

Miscellaneous:
Fever (16%; grades 3/4: <1%)

Occuring in 1% to 10%

Endocrine & metabolic:
Hypocalcemia (9%; ≥ grade 3: 3%), hyperuricemia (6%; ≥ grade 3: 2%)

Hematologic & oncologic:
Tumor lysis syndrome (2 to 3 week ramp-up phase: 12%; 5 week ramp-up phase: 6%; ≥ grade 3: 6%), febrile neutropenia (5%; grades 3/4: 5%)

Neuromuscular & skeletal:
Back pain (10%; grades 3/4: <1%)

Respiratory:
Pneumonia (8%; grades 3/4: 5%)

Drug Interactions[1,2,3,4,8]:

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination.*

Bitter Orange: May increase the serum concentration of Venetoclax. *Risk X: Avoid combination.*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy.*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination.*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of Venetoclax. *Risk X: Avoid combination.*

- Deferasirox, siltuximab, tocilizumab, bosentan, efavirenz, etravirine, and modafinil

CYP3A4 Inducers (Strong): May decrease the serum concentration of Venetoclax. *Risk X: Avoid combination.*

- Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Venetoclax. Management: Reduce the venetoclax dose by at least 50% in patients requiring these combinations. *Risk D: Consider therapy modification.*

- Dasatinib, aprepitant, fosaprepitant, luliconazole, palbociclib, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Venetoclax. Management: These combinations are contraindicated during venetoclax initiation and ramp-up. In patients receiving steady venetoclax doses after completing ramp-up, reduce the venetoclax by at least 75% if strong CYP3A4 inhibitor use cannot be avoided. *Risk D: Consider therapy modification.*

- Fusidic acid, grapefruit juice, idelalisib, mifepristone, stiripentol, boceprevir, cobicistat, conivaptan, danoprevir, ritonavir, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telapravir, tipranavir, troleandomycin, and voriconazole

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination.*

Digoxin: Venetoclax may increase the serum concentration of Digoxin. Management: Administer digoxin at least 6 hours before venetoclax when concomitant therapy is required. *Risk D: Consider therapy modification.*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination.*

Everolimus: Venetoclax may increase the serum concentration of Everolimus. Management: Administer everolimus at least 6 hours before venetoclax when concomitant therapy is

required. *Risk D: Consider therapy modification.*

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy.*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of Venetoclax. Management: Reduce the venetoclax dose by at least 50% in patients requiring these combinations. *Risk D: Consider therapy modification.*

Sirolimus: Venetoclax may increase the serum concentration of Sirolimus. Management: Administer sirolimus at least 6 hours before venetoclax when concomitant therapy is required. *Risk D: Consider therapy modification.*

Star Fruit: May increase the serum concentration of Venetoclax. *Risk X: Avoid combination.*

Vaccines (Inactivated): Venetoclax may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy.*

Vaccines (Live): Venetoclax may enhance the adverse/toxic effect of Vaccines (Live). Venetoclax may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live, attenuated vaccines before, during, or after (prior to B-cell recovery) venetoclax treatment. *Risk X: Avoid combination.*

Warfarin: Venetoclax may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Dosing/Administration[1,2,3,4]:

Adult Dosing:
Week 1: 20 mg once daily
Week 2: 50 mg once daily
Week 3: 100 mg once daily
Week 4: 200 mg once daily
Week 5 and thereafter: 400 mg once daily; continue until disease progression or unacceptable toxicity.

Premedications: Hydration and antihyperuricemic therapy based on TLS risk:

Low tumor burden (all lymph nodes <5 cm and absolute lymphocyte count [ALC] <25,000/mm^3): Outpatient: Hydrate with 1.5 to 2 L of oral hydration and administer allopurinol (beginning 2 to 3 days prior to venetoclax initiation). Administer IV hydration for patients unable to tolerate oral hydration.

Medium tumor burden (any lymph node 5 to <10 cm or ALC ≥25,000/mm^3): Outpatient: Hydrate with 1.5 to 2 L of oral hydration (administer IV hydration for patients unable to tolerate oral hydration; consider additional IV hydration) and administer allopurinol (beginning 2 to 3 days prior to venetoclax initiation).

High tumor burden (any lymph node ≥10 cm OR ALC ≥25,000/mm^3 and any lymph node ≥5 cm): Inpatient: Hydrate with 1.5 to 2 L of oral hydration (administer IV hydration for patients unable to tolerate oral hydration) and 150 to 200 mL/hour IV hydration as tolerated; administer allopurinol (beginning 2 to 3 days prior to venetoclax initiation); consider rasburicase if baseline uric acid is elevated.

Pediatric Dosing:
Safety and efficacy have not been established in the pediatric population.

Geriatric Dosing:
Refer to adult dosing.

Renal Impairment Dosing:
There are no recommendations for dosage adjustments in renal impairment. Dialysis is unlikely to remove venetoclax.

Hepatic Impairment Dosing:
No dosage adjustments are necessary in hepatic impairment.

Conclusion:

Venetoclax appears to be an effective agent for the treatment of chronic lymphocytic leukemia (CLL) in patients with 17p chromosome deletion. Its effectiveness in eliciting overall response shows promise in patients with minimal disability who are otherwise healthy individuals. Further study is needed to determine its efficacy in patients with disease that has progressed to the point of significant disability. Venetoclax has well understood pharmacokinetic and side effect profiles, and seems to be acceptably tolerated for an anti-cancer therapy. Further research is needed to better assess secondary outcomes of therapy with venetoclax, but for now it is a viable option for relapsed or refractory CLL with 17p chromosome deletion.

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