Indirect comparison of IMBRUVICA® + venetoclax and venetoclax + obinutuzumab[1]

Your previously untreated patients with comorbidities may have a greater chance of survival with I+V vs V+G[1]

imbruvica® (ibrutinib) + venetoclax

LIVING AHEAD OF THE CURVE

with IMBRUVICA® + venetoclax[2–5]

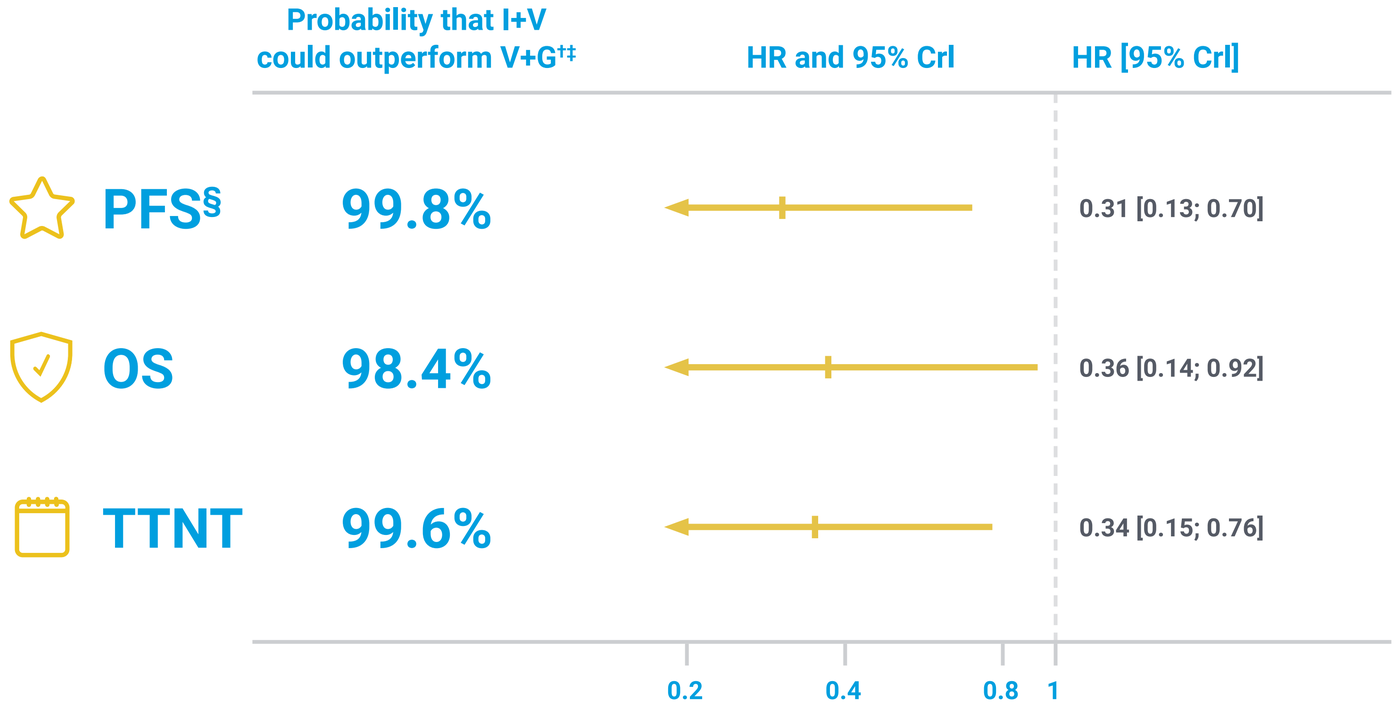
START NOW ›

Because life is the ultimate endpoint[6–9]

PI

1. Rivas J, *et al.* Cross-Study Comparison of Ibrutinib in Combination with Venetoclax (I+V) versus Venetoclax in Combination with Obinutuzumab (V+G) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL) with Comorbidities. Presented at 11º Tendiendo Puentes Congreso de Oncología, Hematología y Farmacia Oncohematológica; November 22-25, 2023; Madrid, Spain.
2. IMBRUVICA® Summary of Product Characteristics. September 2023.
3. Niemann CU, *et al.* Fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial [published online ahead of print, 2023 Nov 6]. *Lancet Oncol.* 2023;S1470-2045(23)00452-7.
4. Kater AP, *et al.* Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evid.* 2022;1(7).
5. Tam CS, *et al.* Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. *Blood.* 2022;139(22):3278–3289.
6. Eichhorst B, *et al.* Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021;32(1):23–33.
7. Delgado A, Guddati AK. Clinical endpoints in oncology-a primer. *Am J Cancer Res.* 2021;11(4):1121.
8. Driscoll JJ, Rixe O. Overall survival: still the gold standard: why overall survival remains the definitive end point in cancer clinical trials. *The Cancer J.* 2009;15(5):401–405.
9. Le H, *et al.* Oncologist and patient preferences for novel agents in first-line treatment for chronic lymphocytic leukemia: commonalities and disconnects. *Patient Prefer Adherence.* 2021;15:99–110.

A matching-adjusted indirect comparison (MAIC) suggests that **I+V could outperform V+G** across several efficacy metrics for 1L CLL[1]*



>98%

probability that I+V could improve PFS, TTNT and OS vs V+G,†‡ as suggested by indirect comparison of GLOW¶ and CLL14[1]**

MAIC details and caveats +

*The anchored matching-adjusted indirect treatment comparison was performed following the guidelines from the National Institute for Health and Care Excellence.[1] †Based on a comparison of GLOW (46-month median follow-up) and CLL14 (52.4-month median follow-up), N=158, ESS=89.[1] Results were consistent with comparison against CAPTIVATE 39.6 month median follow-up with probability of I+V outperfoming V+G (HR [95% CrI]) being: 97.04% (0.49 [0.24; 1.03]) for PFS; 99.2% (0.30 [0.11; 0.79]) for OS; 99.8% (0.31 [0.13, 0.70]) for TTNT.[1] ‡Data were adjusted by applying CLL14 exclusion criteria and matching age, ECOG performance status, CIRS score, TP53 mutation status, IGHV mutation status, creatinine clearance, gender β-2 macroglobulin level and time from initial diagnoses.[1] §Assessed by investigator.[1] ¶GLOW is a Phase III trial evaluating the efficacy and safety of I+V in older patients and/or those with comorbidities with previously untreated CLL. The study enrolled 211 patients, who were randomly assigned (1:1) to treatment with either I+V (n=106) or Clb+O (n=105).[2] **CLL14 is a multicentre, randomised, open-label, Phase III trial that compared the long-term efficacy of fixed-duration V+G (n=216) treatment with Clb+O (n=216) in patients with previously untreated CLL.[3]

1L=first-line; CrI=credible interval; CIRS=Cumulative Illness Rating Scale; Clb+O=chlorambucil+obinituzumab; CLL=chronic lymphocytic leukaemia; ECOG=Eastern Cooperative Oncology Group; ESS=effective sample size; HR=hazard ratio; I+V=IMBRUVICA® + venetoclax; IGHV=immunoglobulin heavy-chain variable region; MAIC=matching-adjusted indirect comparison; OS=overall survival; PFS=progression-free survival; TTNT=time to next treatment or death; V+G=venetoclax + obinutuzumab

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Matching-adjusted indirect comparison of GLOW* vs CLL14†[1]

There are no current head-to-head clinical trials investigating I+V and V+G, hence this MAIC compared data from the GLOW and CLL14, which respectively evaluated the efficacy of I+V and V+G against Clb+O in patients with CLL.[1]

The methodology‡ attempts to account for the differences in patient baseline characteristics and inclusion/exclusion criteria between the 2 studies.[1] Due to a lack of matching data cuts between studies, median follow-ups of both 39.6 months and 52.4 months from CLL14 were compared against a median follow-up of 46 months from GLOW.[1]

There are potential sources of bias that cannot be accounted for in this MAIC which may influence results: The key factors are:[1]

- **Study could not adjust for exclusion of del17p patients from GLOW**
- **CLL14 had longer chlorambucil treatment period, which may have impacted relative treatment effect**
- **Measurement of progression was stricter in GLOW, requiring computer or magnetic imaging regardless of suspected progression**
- **There may be unreported treatment-effect modifying baseline characteristics, which are unaccounted for**

*GLOW is a Phase III trial evaluating the efficacy and safety of IMBRUVICA® + venetoclax in older patients and/or those with comorbidities with previously untreated CLL. The study enrolled 211 patients, who were randomly assigned (1:1) to treatment with either I=V (n=106) or Clb+O (n=105).[2] †CLL14 is a multicentre, randomised, open-label, Phase III trial that compared the long-term efficacy of fixed-duration venetoclax plus obinutuzumab (n=216) treatment with chlorambucil plus obinutuzumab (n=216) in patients with previously untreated chronic lymphocytic leukaemia.[3] ‡Follows the guidelines from the National Institute for Health and Care Excellence. Data were adjusted by applying CLL14 exclusion criteria and matching age, ECOG performance status, CIRS score, TP53 mutation status, IGHV mutation status, creatinine clearance, gender β-2 macroglobulin level and time from initial diagnoses.[1]
CIRS=Cumulative Illness Rating Scale; Clb+O=chlorambucil + obinutuzumab; CLL=chronic lymphocytic leukaemia; ECOG=Eastern Cooperative Oncology Group; I+V=IMBRUVICA® + venetoclax; IGHV=immunoglobulin heavy-chain variable region; MAIC=matching-adjusted indirect comparison; V+G=venetoclax + obinutuzumab.

1. Rivas J, *et al.* Cross-Study Comparison of Ibrutinib in Combination with Venetoclax (I+V) versus Venetoclax in Combination with Obinutuzumab (V+G) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL) with Comorbidities. Presented at 11º Tendiendo Puentes Congreso de Oncología, Hematología y Farmacia Oncohematológica; November 22-25, 2023; Madrid, Spain.
2. Kater AP, *et al.* Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evid.* 2022;1(7).
3. Al Sawaf O, *et al.* Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188–1200.

Prescribing Information

IMBRUVICA® 140 mg Hard Capsules

IMBRUVICA® 140 mg, 280 mg, 420 mg, 560 mg Film-Coated Tablets

ABBREVIATED PRESCRIBING INFORMATION BASED ON THE EU SUMMARY OF PRODUCT CHARACTERISTICS

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

ACTIVE INGREDIENT: Each hard capsule contains 140 mg of ibrutinib.
Each film-coated tablet contains either 140 mg, 280 mg, 420 mg or 560 mg ibrutinib.

INDICATIONS: IMBRUVICA is indicated for treatment of adult patients: as a single agent for relapsed/refractory mantle cell lymphoma (MCL); as a single agent or in combination with rituximab or obinutuzumab or venetoclax for previously untreated chronic lymphocytic leukaemia (CLL); as a single agent or in combination with bendamustine and rituximab (BR) in CLL after at least one prior therapy; as a single agent for Waldenström's macroglobulinaemia (WM) after at least one prior therapy, or in first line treatment for patients unsuitable for chemo immunotherapy; in combination with rituximab for WM. **DOSAGE & ADMINISTRATION: Adults:** Orally, once daily, swallowed whole with water. MCL - 560 mg once daily; CLL and WM as single agent or in combination - 420 mg once daily. In combination with venetoclax for the treatment of CLL, IMBRUVICA should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax. See the venetoclax Summary of Product Characteristics (SmPC) for full venetoclax dosing information. In combination with anti-CD20 therapy - administer IMBRUVICA prior to anti-CD20 therapy when given on the same day. Concomitant strong CYP3A4 inhibitors - reduce IMBRUVICA dose to 140 mg once daily or withhold for up to 7 days. Concomitant moderate CYP3A4 inhibitors - reduce IMBRUVICA dose to 280 mg once daily. Withhold IMBRUVICA therapy for any new onset/worsening grade 2 cardiac failure, grade 3 cardiac arrhythmias, grade ≥ 3 non haematological toxicity, grade ≥ 3 neutropenia with infection or fever, or grade 4 haematological toxicities. Once symptoms of the toxicity have resolved to grade 1 or baseline, follow the dose modification tables for cardiac and non-cardiac events provided in Summary of Product Characteristics (SmPC). **Children:** It is not recommended for use as efficacy not established <18 years old. For currently available data in patients with mature B-cell non-Hodgkin lymphoma, please refer to SmPC. **Elderly:** No dose adjustment required. **Renal impairment:** Mild/moderate no dose adjustment. Severe no data; consider benefit/risk and monitor closely. No data with dialysis. **Hepatic impairment:** Mild (Child Pugh class A) 280 mg daily; moderate (Child Pugh class B) 140 mg daily; monitor for toxicities. Severe (Child Pugh class C) not recommended. **Severe cardiac disease:** No clinical data.**CONTRAINDICATIONS:** Hypersensitivity to active substance/excipients. St. John's Wort preparations. **SPECIAL WARNINGS & PRECAUTIONS:** Bleeding related events: Minor and major bleeding events reported, some fatal; caution with anticoagulant therapy do not use concomitantly with warfarin or other vitamin K antagonists. Benefit risk balance of anticoagulant or antiplatelet therapy should be evaluated when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding. Avoid fish oil and vitamin E preparations. Withhold IMBRUVICA ≥ 3 to 7 days pre /post surgery. Leukostasis: Cases reported; consider temporary withhold of IMBRUVICA; monitor closely, give supportive care.Splenic rupture: Cases of splenic rupture reported following discontinuation of IMBRUVICA treatment. Carefully monitor (e.g. clinical examination, ultrasound) disease status and spleen size when IMBRUVICA treatment is interrupted or ceased. Patients who develop left upper abdominal or shoulder tip pain should be evaluated and a diagnosis of splenic rupture should be considered. Infections: Infections seen, some resulting in hospitalisation and death; monitor for fever, abnormal liver function tests, neutropenia and infections and give anti infective therapy. Consider prophylaxis in patients at increased risk for opportunistic infections. Invasive fungal infections, including Aspergillosis, Cryptococcosis and Pneumocystis jiroveci reported, some with fatal outcomes. Cases of Progressive Multifocal Leukoencephalopathy (PML) including fatal ones reported following ibrutinib use with prior or concomitant immunosuppressive therapy. Consider PML diagnosis in patients with new/worsening neurological/cognitive/behavioral signs/symptoms. If suspected, evaluate and suspend treatment until PML is excluded. If in doubt, refer to a neurologist and consider appropriate diagnostic measures for PML. Hepatic events: Cases of hepatotoxicity, hepatitis B reactivation, and cases of hepatitis E, which may be chronic, have occurred in patients treated with IMBRUVICA. Hepatic failure, including fatal events, has occurred in patients treated with IMBRUVICA. Liver function and viral hepatitis status should be assessed before initiating treatment with IMBRUVICA. Patients should be periodically monitored for changes in liver function parameters during treatment. As clinically indicated, viral load and serological testing for infectious hepatitis should be performed per local medical guidelines. For patients diagnosed with hepatic events, consider consulting a liver disease expert for management. Cytopenias: Treatment emergent grade 3/4 cytopenias reported; monitor complete blood counts monthly. Interstitial Lung Disease (ILD): Cases reported; monitor for pulmonary symptoms indicative of ILD; interrupt IMBRUVICA and manage ILD if symptoms develop. If symptoms persist, consider IMBRUVICA risks and benefits; follow dose modification guidelines. Cardiac arrhythmias and cardiac failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with IMBRUVICA. Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia and cardiac failure have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating IMBRUVICA. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment with IMBRUVICA; alternative treatment may be considered. Temporarily discontinue IMBRUVICA in patients who develop signs and/or symptoms of ventricular tachyarrhythmia; consider alternative to IMBRUVICA when pre existing atrial fibrillation requiring anticoagulant therapy or high risk of thromboembolic disease; where no suitable alternatives to IMBRUVICA, consider tightly controlled treatment with anticoagulants. Monitor patients for signs and symptoms of cardiac failure during IMBRUVICA treatment. In some of these cases cardiac failure resolved or improved after IMBRUVICA withdrawal or dose reduction. Cerebrovascular accidents: Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported in patients treated with IMBRUVICA, with and without concomitant atrial fibrillation and/or hypertension. Monitor regularly, due to long latency in onset of ischaemic central nervous vascular conditions. Tumour lysis syndrome: Cases reported; patients with high tumour burden at risk; monitor closely, take precautions. Non melanoma skin cancer: Reported more frequently in IMBRUVICA treated patients than in comparator treated patients in pooled comparative randomised phase 3 studies. Monitor patients for appearance of non melanoma skin cancer. Hypertension: Cases reported; regularly monitor blood pressure and initiate or adjust antihypertensive medication throughout treatment as appropriate. Haemophagocytic lymphohistiocytosis (HLH): Cases (including fatal) of HLH reported. HLH is a life threatening syndrome of pathologic immune activation characterised by fever, hepatosplenomegaly, hypertriglyceridaemia, high serum ferritin and cytopenias. Patients should be informed about symptoms of HLH. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. Drug drug interactions: Strong/moderate CYP3A4 inhibitors may increase ibrutinib exposure; CYP3A4 inducers may decrease IMBRUVICA exposure. Avoid use of strong CYP3A4 inhibitors and strong/moderate CYP3A4 inducers where possible, if not monitor closely for toxicities/lack of efficacy. Excipients with known effect: IMBRUVICA film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product. IMBRUVICA capsules and film-coated tablets contains less than 1 mmol sodium (23 mg),and is essentially sodium free. **SIDE EFFECTS: Very common:** Pneumonia#, upper respiratory tract infection, skin infection, neutropenia, thrombocytopenia, lymphocytosis, dizziness, headache, haemorrhage#, bruising, hypertension, diarrhoea, vomiting, stomatitis, nausea, constipation, dyspepsia, rash, arthralgia, muscle spasms, musculoskeletal pain, pyrexia, oedema peripheral, blood creatinine increased. **Common:** sepsis#, urinary tract infection, sinusitis, non melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma, febrile neutropenia, leukocytosis, interstitial lung disease#, hyperuricaemia, peripheral neuropathy, vision blurred, cardiac failure#, atrial fibrillation, epistaxis, petechiae, urticaria, erythema, onychoclasis, acute kidney injury#. **Uncommon:** cryptococcal infections, pneumocystis infections#, aspergillus infections, hepatitis B reactivation#, tumour lysis syndrome, cerebrovascular accident#, transient ischaemic attack, ischaemic stroke#, eye haemorrhage including some cases associated with loss of vision, ventricular tachyarrhythmia#, cardiac arrest#, subdural haematoma#, hepatic failure#, angioedema, panniculitis, neutrophilic dermatoses, pyogenic granuloma. **Rare:** leukostasis syndrome, Stevens Johnson syndrome. (# includes events with fatal outcome) The overall known safety profile of IMBRUVICA remained consistent with the addition of long-term safety data over 5 years from 1284 patients. No new safety concerns other than an increased prevalence of hypertension. **Refer to the SmPC for other side effects.** Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system to allow for continued monitoring of the benefit/risk balance of the medicinal product.**PREGNANCY:** Not to be used during pregnancy. Women of child bearing potential must use highly effective contraceptive measures during and for 3 months after stopping treatment. **LACTATION:** Discontinue breast feeding during treatment. **INTERACTIONS:** CYP3A4 inhibitors: Strong: Avoid strong CYP3A4 inhibitors where possible or reduce dose of IMBRUVICA to 140 mg for duration of inhibitor use (or withhold IMBRUVICA for ≤ 7 days and monitor closely; e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, voriconazole and posaconazole. Moderate: Reduce dose of IMBRUVICA to 280 mg for duration of inhibitor use and monitor closely; e.g., erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone. Avoid grapefruit and Seville oranges. Mild: No dose adjustment required; monitor closely. CYP3A4 inducers: Strong/moderate: Avoid or monitor closely for lack of efficacy; carbamazepine, rifampin, phenytoin. Mild: may be used; monitor for lack of efficacy. Medicines that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical studies. Potential interactions: Narrow therapeutic range oral P gp or BCRP substrates (e.g., digoxin or methotrexate) should be taken ≥ 6 h before/after IMBRUVICA. Exposure of drugs that undergo BCRP mediated hepatic efflux (e.g., rosuvastatin) may be increased. In studies of ibrutinib (420 mg) in combination with venetoclax (400 mg) in CLL patients, an increase in venetoclax exposure (approximately 1.8-fold based on AUC) was observed compared with monotherapy data for venetoclax.Refer to SmPC for full details of interactions.

LEGAL CLASSIFICATION: Medicinal product subject to restricted medical prescription

MARKETING AUTHORISATION NUMBERS:
140 mg capsule: EU/1/14/945/001 (90 hard capsules) and EU/1/14/945/002 (120 hard capsules)
140 mg tablet: EU/1/14/945/007 (28 tablets) and EU/1/14/945/008 (30 tablets)
280 mg tablet: EU/1/14/945/009 (28 tablets) and EU/1/14/945/010 (30 tablets)
420 mg tablet: EU/1/14/945/011 (28 tablets) and EU/1/14/945/005 (30 tablets)
560 mg tablet: EU/1/14/945/012 (28 tablets) and EU/1/14/945/006 (30 tablets)

MARKETING AUTHORISATION HOLDER: Janssen-Cilag International NV, Turnhoutseweg 30, B 2340 Beerse, Belgium

Products mentioned in this document may not be registered in all countries. Prescribing Information may vary per country. Health Care Providers must refer to their country prescribing information.

Prescribing information generation date or last revised: 29 Sep 2023

Based on 15 Sep 2023 EU Summary of Product Characteristics

Adverse events and product quality complaints should be reported. Healthcare professionals must refer to their country-specific prescribing information for company contact details.

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