RESONATE™-2: DELIVERS MORE DATA FOR 1L CLL/SLL PATIENTS, INCLUDING THOSE IN CERTAIN HIGH-RISK SUBGROUPS[1]

LIVING LONGER IN 1L CLL/SLL[2]
RESONATE™-2 PRIMARY ANALYSIS[2,3]*

High-risk patient populations with *TP53* mutation, del11q, and uIGHV were included[2,3]

Overall survival[2,3]

95% (OS) Estimated 2-year OS rate with IMBRUVICA® (95% CI: 89, 97)

VS

84% (OS) with chlorambucil (95% CI: 77, 90)

- Median follow-up of 28.1 months
  - HR=0.44 (95% CI: 0.21, 0.92) (secondary endpoint)
- 41% of chlorambucil-treated patients crossed over to IMBRUVICA® upon disease progression

Progression-free survival[2,3]

90% (PFS) Estimated 18-month PFS rate with IMBRUVICA®

VS

52% (PFS) with chlorambucil

- Median follow-up of 18.4 months
  - HR=0.16 ([95% CI: 0.09, 0.28]; P<0.0001) (IRC-assessed primary endpoint)
- Median PFS with IMBRUVICA® was not estimable vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil

PFS was the primary endpoint, OS was a secondary endpoint[3]

RESONATE™-2 STUDY DESIGN[2,3]

Phase 3, multicenter, open-label trial of 1L CLL/SLL patients (N=269) ≥65 years of age who were randomized 1:1 to IMBRUVICA® 420 mg once daily until disease progression or unacceptable toxicity (n=136) or chlorambucil (n=133) for up to 12 cycles. Patients with del17p were excluded. The primary endpoint was PFS as assessed by an IRC per iwCLL criteria (primary analysis). OS was a secondary endpoint. Patients with IRC-confirmed disease progression were enrolled in an extension study (long-term follow-up), and second-line treatment was investigator's choice (including IMBRUVICA® for patients progressing on chlorambucil).

MOST COMMON ARs REPORTED IN THE PRIMARY ANALYSIS OF RESONATE™-2 (MEDIAN DURATION OF EXPOSURE TO IMBRUVICA®: 17.4 MONTHS, N=135)[2]

- The most common ARs (all grades) occurring in ≥15% of patients receiving IMBRUVICA® were neutrophils decreased (55%), platelets decreased (47%), diarrhea (42%), hemoglobin decreased (36%), musculoskeletal pain† (36%), fatigue (30%), cough (22%), nausea (22%), rash† (21%), bruising† (19%), peripheral edema (19%), dry eye (17%), pyrexia (17%), upper respiratory tract infection (17%), arthralgia (16%), constipation (16%), and skin infection† (15%)
- The most common (≥5%) ARs (grades ≥3) occurring in patients receiving IMBRUVICA® were neutrophils decreased‡ (28%), pneumonia† (8%), and platelets decreased‡ (7%)

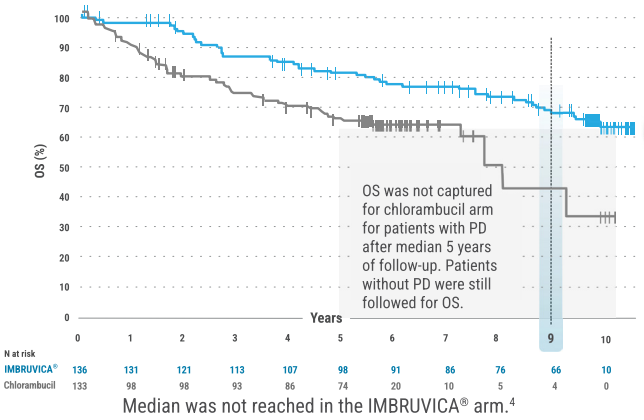
RESONATE™-2 long-term analysis: up to 10 years of follow-up data[1,4]

Long-term PFS analysis[4]

50% (PFS) Estimated PFS was 50% at 9 years with IMBRUVICA® vs 4% with chlorambucil

- Investigator-assessed PFS with IMBRUVICA® vs chlorambucil in 1L CLL/SLL in the intent-to-treat population

Long-term OS analysis[1,4]



Median was not reached in the IMBRUVICA® arm.[4]

68% (OS) ESTIMATED 9-YEAR OS RATE WITH IMBRUVICA®

10-year RESONATE™-2 long-term efficacy results are not included in the Prescribing Information for IMBRUVICA®. The timing for long-term follow-up was not prespecified, and the analysis was descriptive in nature.

Median follow-up for patients in the IMBRUVICA® arm for all efficacy endpoints was 9.6 years (115.0 months [range, 0.1-122.8])[1,4]

MOST COMMON ARs ACROSS 10 YEARS[1]

- The most common ARs (all grades) occurring in ≥20% of patients receiving IMBRUVICA® were diarrhea (52%), fatigue (41%), cough (39%), nausea (32%), arthralgia (31%), peripheral edema (31%), hypertension (30%), pyrexia (30%), upper respiratory tract infection (30%), pneumonia (29%), anemia (27%), urinary tract infection (26%), weight loss (25%), atrial fibrillation (24%), constipation (23%), vomiting (22%), back pain (21%), fall (21%), muscle spasms (21%), and dry eye (20%).
- The most common ARs (grades ≥3) occurring in ≥5% of patients receiving IMBRUVICA® were pneumonia (20%), neutropenia (13%), hypertension (12%), anemia (7%), cataract (7%), hyponatremia (7%), atrial fibrillation (6%), syncope (6%), cardiac failure (5%), and diarrhea (5%).

LONG-TERM SAFETY ANALYSIS[2,5]

- The safety data from long-term treatment with IMBRUVICA® over 5 years of 1,284 patients (including treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646) were analyzed. The median treatment duration was 51 months (range, 0.2 to 97.7 months for CLL/SLL). The cumulative rate of hypertension increased over time. Among the 1,284 patients, the prevalence for grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%.

*Patients on chlorambucil were able to cross over to IMBRUVICA® after IRC-confirmed disease progression. †Includes multiple ADR terms. ‡Grade 3-4 for laboratory abnormalities.
1L=first-line, ADR=adverse drug reaction, AR=adverse reaction, CI=confidence interval, CLL=chronic lymphocytic leukemia, del=deletion, HR=hazard ratio, IGHV=immunoglobulin heavy-chain variable region gene, IRC=independent review committee, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, LTFU=long-term follow-up, OS=overall survival, PD=progressive disease, PFS=progression-free survival, SLL=small lymphocytic lymphoma, *TP53*=tumor protein 53, uIGHV=unmutated immunoglobulin heavy-chain variable region gene.

INDICATIONS

IMBRUVICA® is a kinase inhibitor indicated for the treatment of:

- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).
- Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4.2% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively.

The mechanism for the bleeding events is not well understood.

Please see Important Safety Information continued on page 2 and click here for full Prescribing Information.

Hemorrhage (cont'd): Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients with B-cell malignancies who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

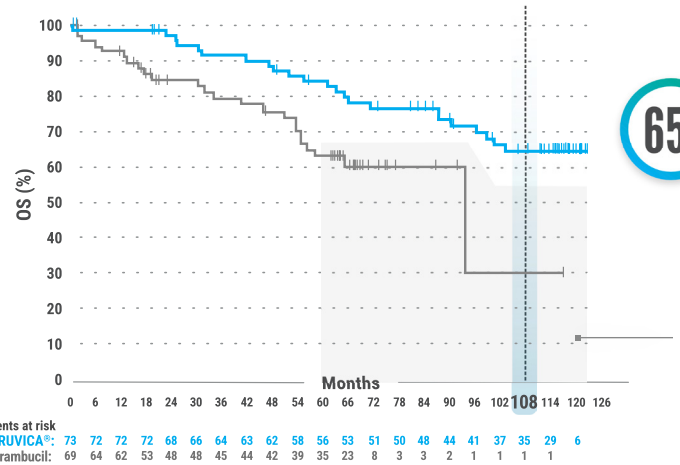
imbruvica® (ibrutinib)
420, 280, 140 mg tablets | 140, 70 mg capsules
70 mg/mL oral suspension

THE ONLY BTKi

WITH UP TO 10 YEARS OF FOLLOW-UP IN 1L CLL/SLL, INCLUDING CERTAIN HIGH-RISK PATIENTS[1,6]

What can the only BTKi with 4 completed 1L CLL phase 3 studies mean for your high-risk patients?

Descriptive subgroup analysis: OS for patients with high-risk mutations, including *TP53* mutation, del11q, and unmutated IGHV[1]



65% OS

ESTIMATED 9-YEAR OS RATE WITH IMBRUVICA®, *TP53* MUTATION, del11q, AND UNMUTATED IGHV

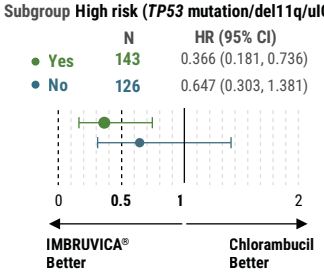
OS was not captured for chlorambucil arm for patients with PD after median 5 years of follow-up. Patients without PD were still followed for OS.

- The RESONATE™-2 long-term subgroup analysis was not prespecified, is descriptive, and is not included in USPI
- RESONATE™-2 was not designed to test treatment effects in subpopulations and was not powered to show statistical differences among these subgroups
- No subgroups were adjusted for multiplicity, and there is no *P* value
- Patients with del17p were excluded from the trial
- RESONATE™-2, all subgroups were prespecified in the protocol, except for IGHV mutation status, which was exploratory
- **10-year RESONATE™-2 long-term efficacy results are not included in the Prescribing Information for IMBRUVICA®. The timing for long-term follow-up was not prespecified, and the analysis was descriptive in nature**

- Median follow-up of high risk group LTFU RESONATE™-2 was 9.6 years (115.0 months; range, 0.1-122.8 months)[1]

Please see previous page for primary analysis, study design, and long-term follow-up.

Primary analysis: forest plot[6]



IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Cardiac Arrhythmias, Cardiac Failure, and Sudden Death: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Deaths due to cardiac causes or sudden deaths occurred in 1% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These adverse reactions occurred in patients with and without preexisting hypertension or cardiac comorbidities. Patients with cardiac comorbidities may be at greater risk of these events.

Grade 3 or greater ventricular tachyarrhythmias were reported in 0.2%, Grade 3 or greater atrial fibrillation and atrial flutter were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These events have occurred particularly in patients with cardiac risk factors including hypertension and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections.

Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines, and consider the risks and benefits of continued IMBRUVICA® treatment.

Hypertension: Hypertension occurred in 19% of 1,476 patients with B-cell malignancies who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from a subset of these patients (N=1,124), the median time to onset was 5.9 months (range, 0 to 24 months). In a long-term safety analysis over 5 years of 1,284 patients with B-cell malignancies treated for a median of 36 months (range, 0 to 98 months), the cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%. Monitor blood pressure in patients treated with IMBRUVICA®, initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate, and follow dosage modification guidelines for Grade 3 or higher hypertension.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8%, and grade 3 or 4 anemia in 2.8%, based on laboratory measurements. Monitor complete blood counts monthly.

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (3.9%), occurred among the 1,476 patients with B-cell malignancies who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Hepatotoxicity, Including Drug-Induced Liver Injury: Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including IMBRUVICA®. Evaluate bilirubin and transaminases at baseline and throughout treatment with IMBRUVICA®. For patients who develop abnormal liver tests after IMBRUVICA®, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold IMBRUVICA®. Upon confirmation of DILI, discontinue IMBRUVICA®.

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS

The most common adverse reactions (≥30%) in adult patients with B-cell malignancies were thrombocytopenia (55%)*, diarrhea (44%), fatigue (39%), musculoskeletal pain (39%), neutropenia (39%)*, rash (36%), anemia (35%)*, bruising (32%), and nausea (30%).

The most common grade ≥3 adverse reactions (≥5%) in adult patients with B-cell malignancies were neutropenia (21%)*, thrombocytopenia (14%)*, pneumonia (8%), and hypertension (8%).

Approximately 9% (CLL/SLL) and 14% (WM) of adult patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL) and 5% (WM) of adult patients discontinued due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Coadministration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA® are recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7days). Avoid grapefruit and Seville oranges during IMBRUVICA® treatment, as these contain strong or moderate inhibitors of CYP3A. See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria)**:** Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please click here for full Prescribing Information.

References: 1. Data on file ABVRRTI77982 **2.** IMBRUVICA® (ibrutinib) Prescribing Information. **3.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437. **4.** Burger JA, Barr PM, Tadeusz R, et al. Final analysis of the resonate-2 study: up to 10 years of follow-up of first-line ibrutinib treatment in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA Library website. Published May 14, 2024. EHA Library. Accessed December 17, 2024. https://library.ehaweb.org/eha/2024/eha2024-congress/420734/jan.burger.final.analysis.of.the.resonate-2.study. up.to.10.years.of.follow-up.html **5.** Data on file ABVRRTI77315 **6.** Data on file ABVRRTI76502

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