Find out more about the analysis of THE OPEN-LABEL, PHASE 3 RESONATE™-2 TRIAL with up to 10 YEARS OF FOLLOW-UP[1]

LIVE FOR MORE WINNING SONGS

IMBRUVICA® gives patients with 1L CLL/SLL an **OPPORTUNITY TO LIVE LONGER** and continue to experience the things they love[2,3]

PRIMARY ANALYSIS:

- Estimated 18-month PFS was 90% with IMBRUVICA® vs 52% with chlorambucil, HR=0.16 (95% CI: 0.09, 0.28; *P*<0.0001; PFS was the primary endpoint)
- Estimated 2-year OS was 95% with IMBRUVICA® (95% CI: 89, 97) vs 84% with chlorambucil (95% CI: 77, 90), HR=0.44 (95% CI: 0.21, 0.92; OS was the secondary endpoint)

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.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage; infections; cardiac arrhythmias, cardiac failure, and sudden death; hypertension; cytopenias; second primary malignancies; hepatotoxicity, including drug-induced liver injury (DILI); tumor lysis syndrome; and embryo-fetal toxicity.

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%).

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

Please see complete Important Safety Information on pages 10-11 and click here full Prescribing Information.

BTKi=Bruton's tyrosine kinase inhibitor, CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

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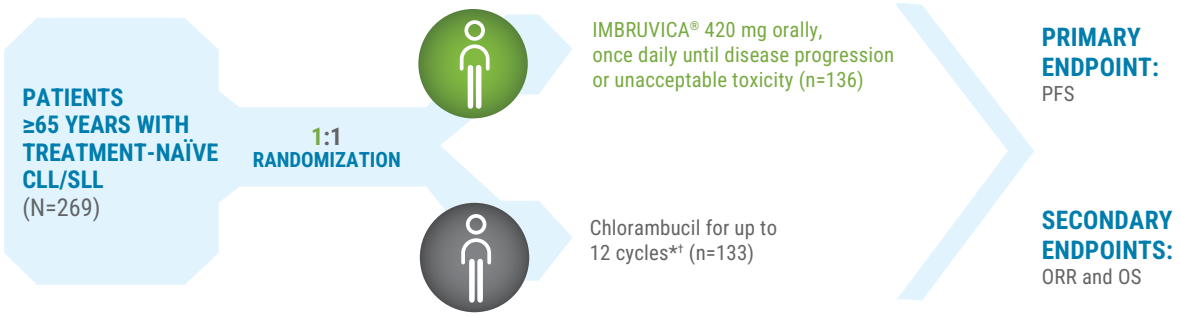
RESONATE™-2: IMBRUVICA® FOR FRONTLINE CLL/SLL[1–5]

Study design

Randomized, multicenter, open-label, phase 3 RESONATE™-2 trial (N=269)[2,3]

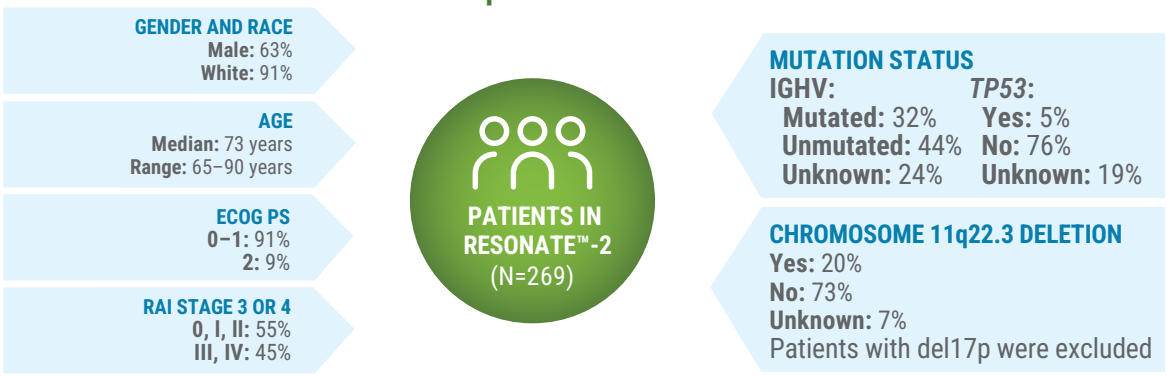


PFS was assessed by an IRC per iwCLL criteria (primary analysis)[2]

- Median follow-up for 10-year update of RESONATE™-2 was 9.6 years (115.0 months [range: 0.1–122.8 months]) for patients in the IMBRUVICA® arm for all efficacy endpoints[1,4]
- 27% of patients (37/136) continued IMBRUVICA® treatment at the median follow-up of 9.6 years (115.0 months, range: 0.1–122.8 months)[1,4]
- The median duration of IMBRUVICA® treatment was 6.2 years (range, 0.06–10.2)[1]

RESONATE™-2 included patients with select high-risk characteristics[2,3,5]

Select patient characteristics



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.

*Patients on chlorambucil were able to cross over to IMBRUVICA® after IRC-confirmed disease progression.
†Patients with IRC-confirmed progressive disease were enrolled in an extension study for follow-up and collection of long-term safety and efficacy data and to allow for second-line treatment per investigator's choice (including IMBRUVICA® for patients progressing on chlorambucil per iwCLL criteria).

CLL=chronic lymphocytic leukemia, del=deletion, ECOG=Eastern Cooperative Oncology Group, IGHV=immunoglobulin heavy-chain variable region gene, IRC=independent review committee, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, PS=performance status, SLL=small lymphocytic lymphoma, *TP53*=tumor protein 53.

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LIVING LONGER IN 1L CLL[2,3]

RESONATE™-2 primary analysis*†

OS (secondary endpoint)[2]

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)
- 41% of chlorambucil-treated patients crossed over to IMBRUVICA® upon disease progression

PFS (IRC-assessed primary endpoint)[2]

90% PFS — Estimated 18-month PFS rate with IMBRUVICA®

VS

52% PFS — with chlorambucil

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

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%), platelets decreased§ (7%)

*Patients on chlorambucil were able to cross over to IMBRUVICA® after IRC-confirmed disease progression.
†Patients with IRC-confirmed progressive disease were enrolled in an extension study for follow-up and collection of long-term safety and efficacy data and to allow for second-line treatment per investigator's choice (including IMBRUVICA® for patients progressing on chlorambucil per iwCLL criteria).
‡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, HR=hazard ratio, IRC=Independent Review Committee, OS=overall survival, PFS=progression-free survival.

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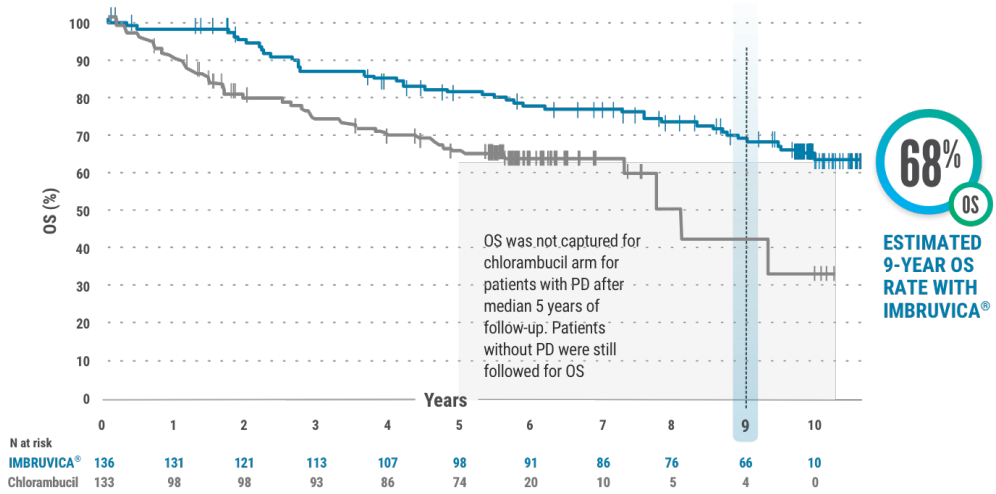
THE ONLY BTKi WITH UP TO 10 YEARS OF FOLLOW-UP DATA[1,4]

Estimated OS was 68% at 9 years with IMBRUVICA®[1,4]

Long-term OS analysis



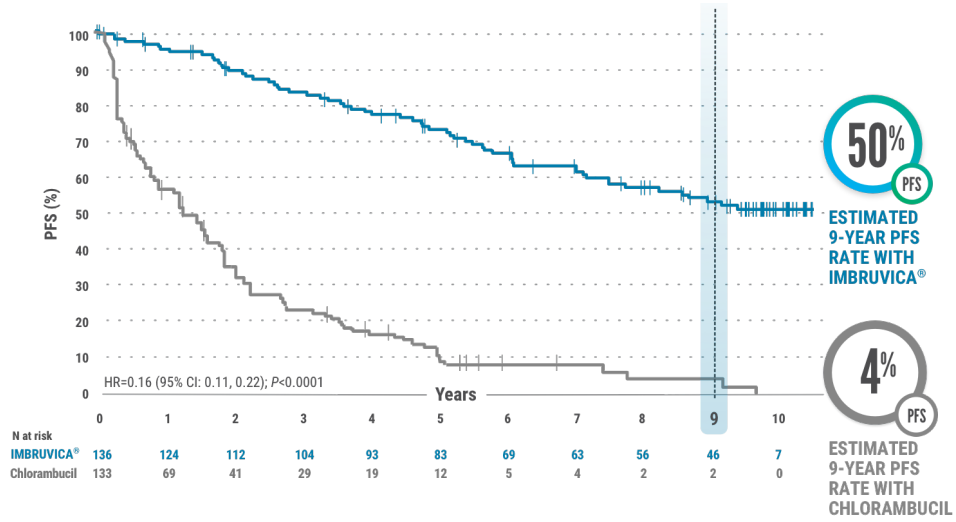
68% OS

ESTIMATED 9-YEAR OS RATE WITH IMBRUVICA®

- Median OS was not reached in the IMBRUVICA® arm[1]
- 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]

Estimated PFS was 50% at 9 years with IMBRUVICA® vs 4% with chlorambucil[1,4]

Long-term PFS analysis (investigator assessed)



50% PFS

ESTIMATED 9-YEAR PFS RATE WITH IMBRUVICA®

4% PFS

ESTIMATED 9-YEAR PFS RATE WITH CHLORAMBUCIL

- With up to 10 years of follow-up, median PFS for IMBRUVICA® was 8.9 years (95% CI: 7.0, NE) vs 1.3 years (95% CI: 0.9–1.6) with chlorambucil[1]
- For patients in the chlorambucil arm, median follow-up was 5.6 years (66.7 months [range 0.1–118.4 months])[1,4]
- 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]

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.

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BTKi=Bruton's tyrosine kinase inhibitor, CI=confidence interval, HR=hazard ratio, NE=not evaluable, OS=overall survival, PD=progressive disease, PFS=progression-free survival.

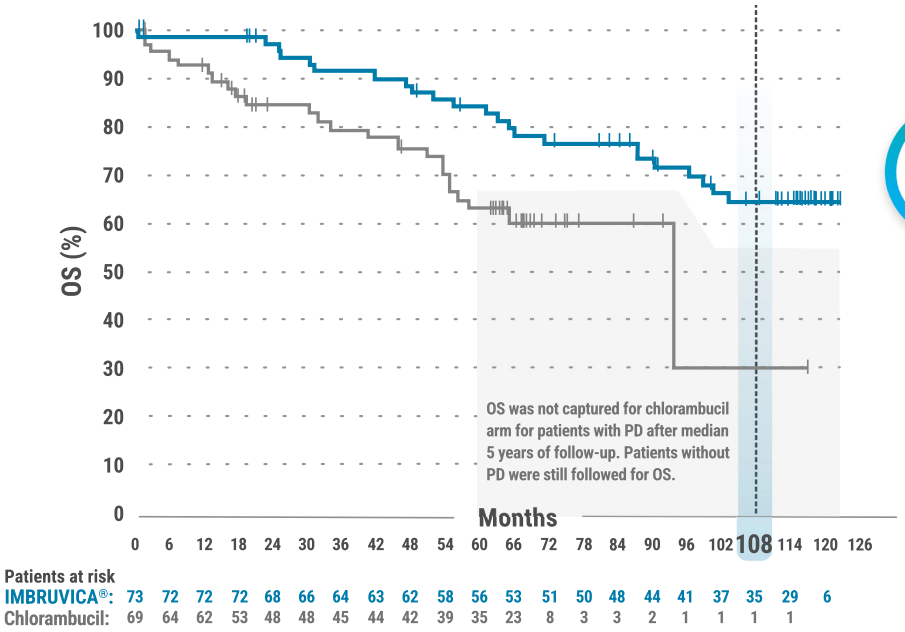
Please see complete Important Safety Information on pages 10-11 and click here for full Prescribing Information.

UP TO 10 YEARS OF FOLLOW-UP INCLUDING IN PATIENTS WITH CERTAIN HIGH-RISK MUTATIONS[4,6]

Discover the long-term OS data for your patients with high-risk mutations, including *TP53* mutation, del11q, and unmutated IGHV[4]

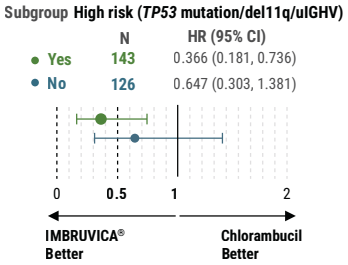
- RESONATE™-2 was not designed to test treatment effect in subpopulations and was not powered to show statistical differences among these subgroups
- Subgroup analysis was not prespecified, is descriptive, and is not included in the USPI
- No subgroups were adjusted for multiplicity, and there is no P value
- Patients with del17p were excluded from the trial

Descriptive subgroup OS analysis in high-risk groups[4]



ESTIMATED 9-YEAR OS RATE WITH IMBRUVICA®, *TP53* MUTATION, DEL11q, AND UNMUTATED IGHV

Primary analysis: forest plot[6]



- Median follow-up of high-risk group LTFU RESONATE™-2 was 9.6 years (115.0 months; range, 0.1–122.8 months)[4]

Most common treatment-emergent ARs across 10 years at the long-term analysis reported in RESONATE™-2 for the overall population (n=135)[4]

- 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 (grade ≥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%), diarrhea (5%), and cardiac failure (5%).

10-year RESONATE™-2 long-term data 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.

AR=adverse reaction, CI=confidence interval, del=deletion, HR=hazard ratio, IGHV=immunoglobulin heavy-chain variable region gene, LTFU=long-term follow-up, OS=overall survival, PD=progressive disease, uIGHV=unmutated immunoglobulin heavy-chain variable region gene, USPI=United States Prescribing Information, *TP53*=tumor protein 53.

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POOLED 5-YEAR LONG-TERM SAFETY DATA[2,7,8]

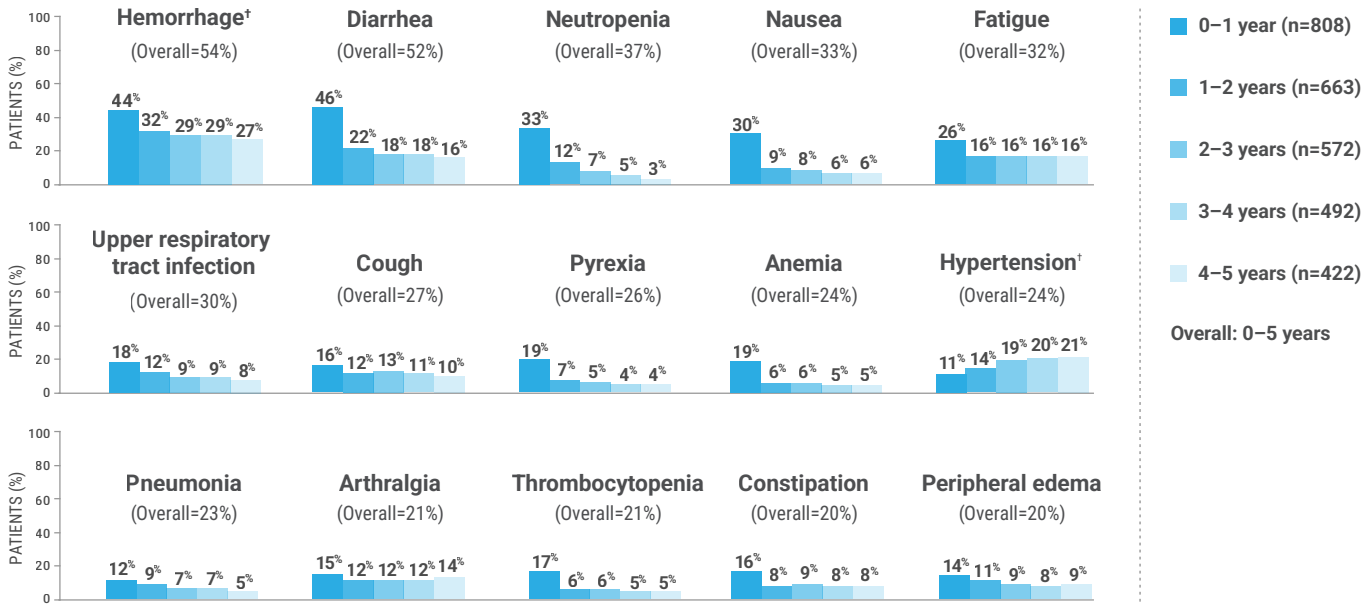
Long-term safety[2]

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%.

5-year, long-term safety from CLL/SLL studies[7*]

In pooled data from multiple open-label rollover and follow-up studies in both treatment-naïve and R/R CLL/SLL patients (N=808), the median treatment duration was 51 months (range, 0.2 to 98 months). Due to types of events collected and less frequent clinic visits, limited data were collected from 1 follow-up study.

Most common treatment-emergent ARs (any grade) in ≥20% of patients with CLL/SLL (N=808)[7,8]



*Additional safety analysis conducted pursuant to FDA postmarketing requirements.
†Includes multiple preferred terms.

Data suggest AR rates generally decreased or remained stable over time, except for hypertension

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Hemorrhage (cont'd): The mechanism for the bleeding events is not well understood.

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.

AR=adverse reaction, CLL=chronic lymphocytic leukemia, CNS=central nervous system, FDA=United States Food and Drug Administration, R/R=relapsed/refractory, SLL=small lymphocytic lymphoma.

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DOSE MODIFICATIONS CAN HELP OPTIMIZE PATIENT MANAGEMENT TO ENABLE CONTINUED IMBRUVICA® TREATMENT WHERE APPROPRIATE[2]

IF AN AR LISTED BELOW OCCURS, INTERRUPT IMBRUVICA® THERAPY AT EACH OCCURRENCE OF THE SAME AR. ONCE THE AR HAS IMPROVED TO GRADE 1 OR BASELINE, FOLLOW THE RECOMMENDED DOSE MODIFICATIONS BELOW[2]

START AT APPROVED DOSE 420 mg
Once daily until disease progression or unacceptable toxicity

ADVERSE REACTION*†	1ST OCCURRENCE	2ND OCCURRENCE	3RD OCCURRENCE
NON-CARDIAC			
GRADE 3 or 4: other non-hematological toxicities‡ GRADE 3 or 4: neutropenia with infection or fever GRADE 4: hematological toxicities	RESTART AT 280 mg§ DAILY	RESTART AT 140 mg§ DAILY	DISCONTINUE
CARDIAC			
GRADE 2: cardiac failure	RESTART AT 280 mg§ DAILY	RESTART AT 140 mg§ DAILY	DISCONTINUE
GRADE 3: cardiac arrhythmias		DISCONTINUE	
GRADE 3 or 4: cardiac failure GRADE 4: cardiac arrhythmias	DISCONTINUE		

*See full Prescribing Information for Warnings and Precautions (Section 5).
†Grading based on NCI-CTCAE criteria, or iwCLL criteria for hematological toxicities in CLL/SLL.
‡For Grade 4 non-hematological toxicities, evaluate the benefit-risk before resuming treatment.
§Evaluate the benefit-risk before resuming treatment.

IMBRUVICA® monotherapy is dosed at 420 mg once daily until disease progression or unacceptable toxicity.[2]

Dose should be taken at approximately the same time each day. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets.[2]

Modify dose or avoid IMBRUVICA® use with CYP3A inhibitors and avoid coadministration with strong CYP3A inducers.[2] For further information on use with CYP3A inhibitors and inducers, and in patients with hepatic impairment, please see the full Prescribing Information.

Consider the risks and benefits of anticoagulant or antiplatelet therapy when coadministered 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.[2]

Please see full Prescribing Information for complete dosage and administration details.

AR=adverse reaction, CLL=chronic lymphocytic leukemia, CYP3A=cytochrome P450, family 3, subfamily A, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, SLL=small lymphocytic lymphoma.

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DOSE MODIFICATIONS FOR ARs: TREATMENT DURATION[5]

8-year dose modification[5]

Median overall duration of treatment

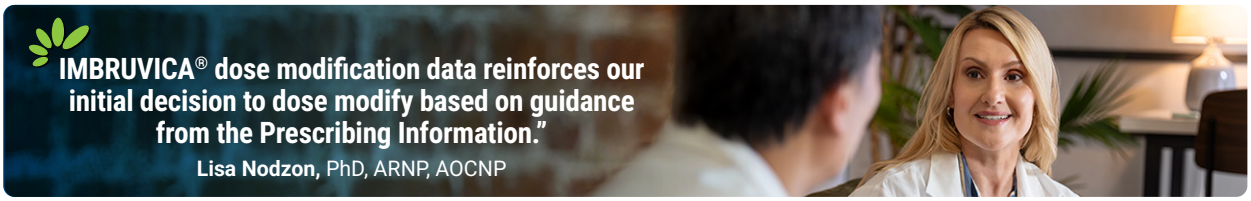
The median duration of IMBRUVICA® treatment was 74 months (range, 0.7-96.6 months; n=135)[5]

Duration of treatment following dose modification*

In a subset of patients who had dose reductions due to ARs (n=31), the median duration of treatment with IMBRUVICA® after the dose modification was 36.1 months (range, 0.0-84+ months)[9]

8-year RESONATE™-2 long-term dosing results are not included in the Prescribing Information for IMBRUVICA®.

- These data are descriptive in nature only and have no implications regarding efficacy or safety
- Dose modifications were defined in the study protocol; patients may not have been dose modified according to current recommendations



IMBRUVICA® discontinuations across CLL/SLL registration studies[2]

The data below are pooled from 5 randomized controlled clinical trials (RESONATE™, RESONATE™-2, HELIOS, iLLUMINATE™, and E1912) and 1 single-arm, open-label clinical trial (Study 1102) in patients with CLL/SLL (N=2,016 total and n=1,133 patients exposed to IMBRUVICA®).

- 4% to 10% of patients receiving IMBRUVICA® discontinued treatment due to ARs
  - These included pneumonia, hemorrhage, atrial fibrillation, neutropenia, arthralgia, rash, and thrombocytopenia
  - ARs leading to dose reduction occurred in approximately 9% of patients

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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.

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*Duration of dose reduction to study drug discontinuation was calculated from first date of the earliest dose reduction to study drug discontinuation.

AR=adverse reaction, CLL=chronic lymphocytic leukemia, SLL=small lymphocytic lymphoma.

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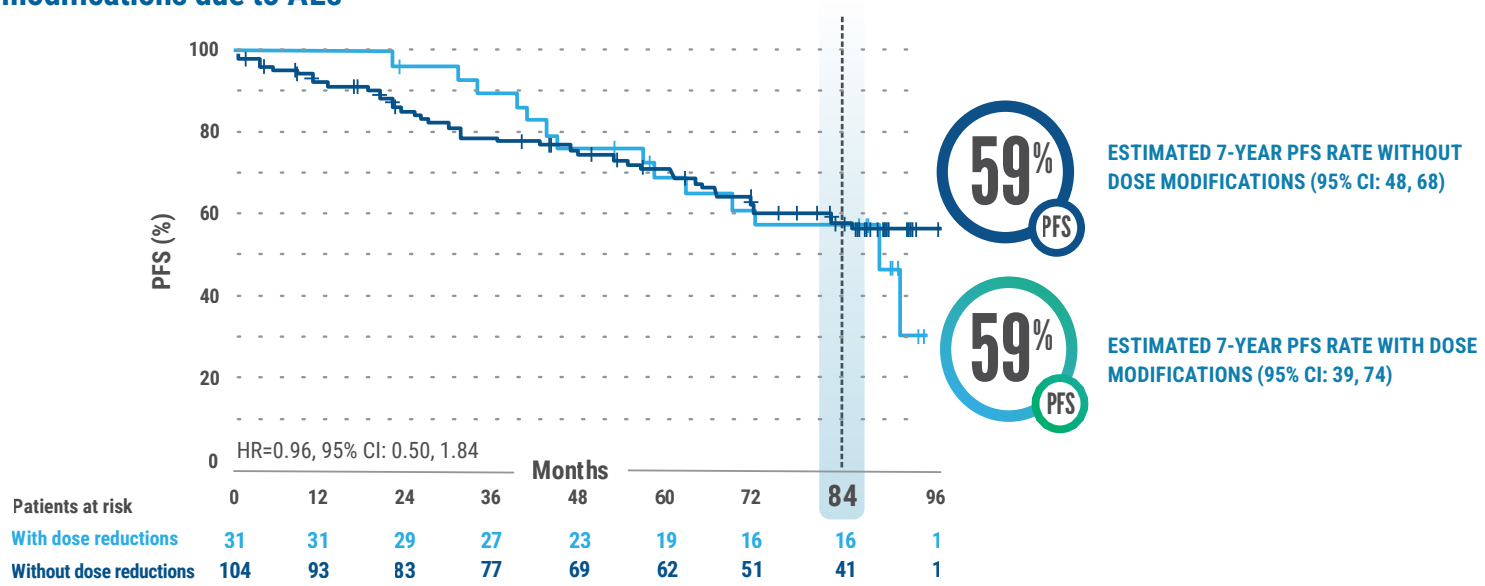
IMBRUVICA® HAS LONG-TERM OUTCOME DATA AFTER DOSE MODIFICATION[9,10]

RESONATE™-2: Long-term analysis

Exploratory post hoc analysis: PFS in IMBRUVICA®-treated patients with or without dose modifications due to AEs[9]



Patients at risk	0	12	24	36	48	60	72	84	96
With dose reductions	31	31	29	27	23	19	16	16	1
Without dose reductions	104	93	83	77	69	62	51	41	1

This exploratory analysis evaluated baseline demographics and clinical outcomes (PFS) in subgroups of patients with and without dose reductions due to AEs from the overall population of IMBRUVICA®-treated CLL patients.[9]

- **The median time to first dose reduction was 23.7 months (range, 1.6–78.4 months)[10]**
- Median PFS for IMBRUVICA®-treated patients with dose reductions was 87.7 months (95% CI: 56.9–NE) and was not reached (95% CI: 81.9–NE) for those without dose reductions[9]
- Median follow-up was 82.7 months (range, 0.1–96.6 months)[9]
- AEs led to dose reductions in 23% (31/135) of all patients treated with IMBRUVICA®[9]

- **Results are based on a starting dosage of IMBRUVICA® 420 mg once daily.** Kaplan-Meier curves ≥7.5 years have a limited sample size, potentially impacting PFS estimates[9]
- Subgroups of patients with and without dose modifications were not stratified for any baseline characteristics. Imbalances in baseline characteristics may exist between these groups[9]
- Outcomes in the subgroup of patients with and without dose reductions in the overall population of all IMBRUVICA®-treated patients from RESONATE™-2 are from exploratory post hoc analyses and were not powered for significance; comparative statistics are provided for descriptive purposes only[9]
- Dose modifications for any reason were per protocol based on the discretion of the physician[9]

8-year RESONATE™-2 long-term dosing results are not included in the Prescribing Information for IMBRUVICA®

AE=adverse event, CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, NE=not estimable, PFS=progression-free survival.

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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.

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.

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.

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

Please see complete Important Safety Information on pages 10-11 and click here for full Prescribing Information.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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. Burger J, Barr PM, Robak T, 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 **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. doi:10.1056/NEJMoa1509388 **4.** Data on file ABVRRTI77982 **5.** Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv.* 2022;6(11):3440-3450. doi:10.1182/bloodadvances.2021006434 **6.** Data on file ABVRRTI76502 **7.** Data on file ABVRRTI77315 **8.** Data on file ABVRRTI78305 **9.** Woyach JA, Barr PM, Kipps TJ, et al. Characteristics and clinical outcomes of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma receiving ibrutinib for ≥5 years in the RESONATE-2 study. *Cancers (Basel)*. 2023;15(2):507. doi:10.3390/cancers15020507 **10.** Data on file ABVRRTI76430

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START AND STAY ON IMBRUVICA® FOR YOUR APPROPRIATE PATIENTS[1-4]

Give your patients an OPPORTUNITY TO LIVE LONGER and continue to experience the things they love[2,3]

RESONATE™-2: primary analysis[2,3]

95% OS **Estimated 2-year OS rate with IMBRUVICA®** (95% CI: 89, 97) **VS** **84% OS** Estimated OS rate with **chlorambucil** (95% CI: 77, 90)

SECONDARY ENDPOINT HR=0.44 (95% CI: 0.21, 0.92); median follow-up of 28.1 months

90% PFS **Estimated PFS rate at 18 months with IMBRUVICA®** **VS** **52% PFS** Estimated PFS rate with **chlorambucil**

PRIMARY ENDPOINT HR=0.16 (95% CI: 0.09, 0.28; *P*<0.0001); median follow-up of 18.4 months (IRC assessed)

The only BTKi with the longest follow-up data in 1L CLL/SLL[1]

RESONATE™-2: 10-year long-term analysis[1,4]

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 after 10 years: 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%).[4]

Up to 10 years of follow-up[1,4]

68% OS **Estimated 9-year OS rate with IMBRUVICA®[1]**

VS

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

Median OS was not reached in the IMBRUVICA® arm[1]

50% PFS **Estimated 9-year PFS rate with IMBRUVICA®[1]** **VS** **4% PFS** with **chlorambucil[1]**

- HR=0.16 (95% CI: 0.11, 0.22) *P*<0.00011
- For patients in the chlorambucil arm, median follow-up was 5.6 years (66.7 months [range 0.1–118.4 months])[1,5]
- **With up to 10 years of follow-up**, median PFS of IMBRUVICA® was 8.9 years (95% CI: 7.0, NE) vs 1.3 years (95% CI: 0.9–1.6) with chlorambucil[1]

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.

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.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage; infections; cardiac arrhythmias, cardiac failure, and sudden death; hypertension; cytopenias; second primary malignancies; hepatotoxicity, including drug-induced liver injury (DILI); tumor lysis syndrome; and embryo-fetal toxicity.

ADVERSE REACTIONS

The most common adverse reactions (≥30%) in 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%).

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

Please see complete Important Safety Information on pages 12-13 and click here for full Prescribing Information.

1L=first-line, AR=adverse reaction, BTKi=Bruton's tyrosine kinase inhibitor, CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=independent review committee, NE=not estimable, OS=overall survival, PD=progressive disease, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

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