J-C Health Care Ltd.

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פברואר 2023

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: **Imbruvica Capsules, Imbruvica 140, 280, 420, 560mg Tablets**

חברת ג'יי סי הלת'קר בע"מ (J-C Health Care Ltd.) מבקשת להודיעכם כי העלון של התכשירים הבאים התעדכן ב-12/2022:

Imbruvica Capsules 140mg, ibrutinib 140mg 151-98-34062-01/02

Imbruvica 140mg Tablets, ibrutinib 140mg 167-61-36458-99

Imbruvica 280mg Tablets, ibrutinib 280mg 167-62-36459-99

Imbruvica 420mg Tablets, ibrutinib 420mg 167-63-36460-99

Imbruvica 560mg Tablets, ibrutinib 560mg 167-64-36461-99

העדכון נובע מאישור השינויים הבאים:

1. שילוב תרופתי של Venclexta+Imbruvica לחולי Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma
2. שינוי משטר מינון עקב תופעות לוואי לבביות

ההתוויות העדכניות המאושרות לתכשיר בישראל:

• Mantle Cell Lymphoma:
Imbruvica is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
• Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma :
Imbruvica is indicated for the treatment of adult patients, with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
• Chronic Lymphocytic Leukemia (CLL) /Small Lymphocytic Lymphoma (SLL) with 17p deletion:
Imbruvica is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) /Small Lymphocytic Lymphoma (SLL) with 17p deletion.
• Waldenström's Macroglobulinemia
Imbruvica is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).
• Marginal Zone Lymphoma
IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.
• Chronic Graft versus Host Disease
IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

מרכיב פעיל:
ibrutinib

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העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug.

כמו כן, מצורפים לפרסום זה וניתן לקבל העתק מודפס של באמצעות פנייה לבעל הרישום: יאנסן ישראל בע"מ , קיבוץ שפיים, 6099000, טל': 09-9591111.

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט כחול עם קו חוצה, טקסט המהווה החמרה מודגש ברקע צהוב), אך קיימים עדכונים נוספים.

בברכה,
דנית ראובני

רוקחת ממונה
ג'יי סי הלת'קר בע"מ

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העדכונים העיקריים בעלון לרופא הינם:

4 INDICATIONS AND USAGE

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 4.2

IMBRUVICA is indicated for the ~~first line~~ treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

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5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenström's Macroglobulinemia

The recommended dosage of IMBRUVICA for CLL/SLL and WM is 420 mg orally once daily until disease progression or unacceptable toxicity.

For CLL/SLL, IMBRUVICA can be administered as a single agent, in combination with rituximab or Obinutuzumab (BR), or in combination with bendamustine and rituximab (BR), or in combination with venetoclax. In the co-morbid and elderly population the combination should be used with more caution~~.~~

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.

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5.2 DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS

~~Interrupt IMBRUVICA therapy for any Grade 3 or 4 non-hematological toxicities, Grade 3 or 4 neutropenia with infection or fever, or .Grade 4 hematological toxicities. Once the adverse reaction has improved to Grade 1 or baseline (recovery), IMBRUVICA may be reinitiated at the starting dose. If the adverse reaction reoccurs, reduce dose by 140 mg per day. Consider a second reduction of dose by 140 mg as needed. If these adverse reactions persist or recur following two dose reductions, discontinue IMBRUVICA.~~

For adverse reactions listed in Table 1, interrupt IMBRUVICA therapy. Once the adverse reaction has improved to Grade 1 or baseline (recovery), follow the recommended dosage modifications (see Table 1).

~~Recommended dose modifications are described below:~~

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Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction[a,b]	~~Toxicity~~ Occurrence	Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg	Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg
Grade 2 cardiac failure	First	Restart at ~~560~~420 mg ~~daily~~ daily[c]	Restart at ~~420~~280 mg ~~daily~~ daily[c]
	Second	Restart at 280 mg daily[c]	Restart at 140 mg daily[c]
	Third	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]
	Second	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Other Grade 3 or 4 non-hematological toxicities[d] Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First	Restart at ~~560~~ 420 mg daily	Restart at ~~420~~ 280 mg daily
	Second	Restart at ~~420~~ 280 mg daily	Restart at ~~280~~ 140 mg daily
	Third	~~Restart at 280 mg daily~~ Discontinue IMBRUVICA	~~Restart at 140 mg daily~~ Discontinue IMBRUVICA
	~~Forth~~	~~Discontinue IMBRUVICA~~	~~Discontinue IMBRUVICA~~

[a] See *Warnings and Precautions (5)*.

[b] Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematologic toxicities in CLL/SLL.

[d] For Grade 4 non-hematologic toxicities, evaluate the benefit-risk before resuming treatment.

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8WARNINGS AND PRECAUTIONS

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~~8.3 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 3%, based on laboratory measurements.~~

~~Monitor complete blood counts monthly.~~

~~8.4~~8.3 Cardiac Arrhythmias, Cardiac Failure, and Sudden Death

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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 ~~occurred~~were reported in 0.2~~% of patients and~~%, Grade 3 or greater atrial fibrillation and atrial flutter ~~occurred in 4~~were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of ~~1,476~~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~~, acute infections,~~ and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections *[see Adverse Reactions (9.1)]*.

~~Periodically~~Evaluate cardiac history and function at baseline, and monitor patients ~~clinically~~ for cardiac arrhythmias and cardiac function. Obtain ~~an~~ further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop ~~arrhythmic~~ symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain~~) or~~), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, ~~and if it persists, consider the risks and benefits of IMBRUVICA treatment and~~ follow dose modification guidelines *[see Dosage and Administration (5.2)]*, ~~)~~], and consider the risks and benefits of continued IMBRUVICA treatment.

8.4 Hypertension

Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients *[see Adverse Reactions (9.1)]*. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA ~~and~~, initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate~~.~~, and follow dosage modification guidelines for Grade 3 or higher hypertension *[see Dosage and Administration (5.2)]*.

8.5 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 *[see Adverse Reactions (9.1)]*.

Monitor complete blood counts monthly.

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9 ADVERSE REACTIONS

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PCYC-1142-CA

Adverse reactions and laboratory abnormalities described below in Tables 15 and 16 reflect exposure to IMBRUVICA in combination with venetoclax with a median duration of 14.1 months in patients with previously untreated CLL/SLL who were 70 years or younger in Study PCYC-1142-CA.[a]

Table 15: Adverse reactions reported in at least 15% patient previously untreated with CLL/SLL in Study PCYC-1142-CA[b]

System Organ Class Adverse Reaction Term	IMBRUVICA + Venetoclax (N=323) (%)	
	All Grades	Grade 3 or 4
Gastrointestinal disorders		
Diarrhea	67	4
Nausea	44	1
Stomatitis*	30	1
Abdominal pain*	24	1
Vomiting	22	1
Dyspepsia	18	0
Constipation	16	0
General disorders and administration site conditions		
Fatigue	26	2
Infections and infestations		
Upper respiratory tract infection	26	0
Skin infection*	20	2
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	41	1
Arthralgia	34	2
Muscle spasms	24	0
Nervous system disorders		
Headache	27	1
Dizziness	16	0
Respiratory, thoracic and mediastinal disorders		
Cough	17	0
Skin and subcutaneous tissue disorders		
Bruising*	47	0
Rash*	38	3
Vascular disorders		
Hemorrhage*	33	1
Hypertension*	16	7

Pooled safety data is from the Fixed Duration (FD) cohort and first 16 cycles of the Minimal Residual Disease (MRD) cohort.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple adverse reaction terms

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Table 16: Select Laboratory Abnormalities (≥20% Any Grade), New or Worsening from Baseline in patients with CLL/SLL treated with IMBRUVICA in combination with venetoclax in Study PCYC-1142-CA[c,d]

	IMBRUVICA + venetoclax (N=323) (%)	
	All Grades	Grade 3 or 4
Hematology abnormalities*		
Neutrophils decreased	72	37
Platelets decreased	60	11
Hemoglobin decreased	22	<1
Chemistry abnormalities		
Hypernatremia	43	0
Hypocalcemia	38	<1
Hypomagnesemia	32	1
Bilirubin increased	28	3
Hyperkalemia	26	2
Hyperuricemia	26	26
AST increased	23	2
ALP increased	22	<1
ALT increased	20	2
Creatinine increased	20	0

* Based on laboratory measurements per iwCLL criteria grade (iwCLL: International Workshop on Chronic Lymphocytic. Leukemia)
<1 used for frequency above 0 and below 0.5%

CLL3011

Adverse reactions and laboratory abnormalities described below in Tables 17 and 18 reflect exposure to IMBRUVICA + venetoclax with a median duration of 13.8 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in Study CLL3011 in patients with previously untreated CLL/SLL who were 65 years or older, or adult patients <65 years of age with a CIRS score >6 or CrCL <70 mL/min. [e]

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Table 17: Adverse reactions reported in at least 15% of Patients in the IMBRUVICA arm in Patients with CLL/SLL in Study CLL3011[f]

System Organ Class Adverse Reaction Term	IMBRUVICA + Venetoclax (N=106) (%)		Chlorambucil + Obinutuzumab (N=105) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Diarrhea	51	10	12	1
Nausea	26	0	26	0
Stomatitis*	15	0	3	0
Skin and subcutaneous tissue disorders				
Rash*	28	7	14	1
Bruising*	23	1	3	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	24	3	17	0
Vascular disorders				
Hemorrhage*	23	4	5	1
Infections and infestations				
Urinary tract infection	16	2	5	2
General disorders and administration site conditions				
Peripheral edema	15	0	3	0
Fatigue	15	1	10	0

* Includes multiple adverse reaction terms

Table 18: Select Laboratory Abnormalities (≥20% Any Grade), New or Worsening from Baseline in previously untreated patients with CLL/SLL in Study CLL3011[g,h]

	IMBRUVICA + venetoclax (N=106) (%)		Chlorambucil + Obinutuzumab (N=105) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematology abnormalities*				
Neutrophils decreased	76	42	90	54
Platelets decreased	49	13	74	31
Hemoglobin decreased	36	0	40	0
Chemistry abnormalities				
Hypocalcemia	25	0	29	0
Bilirubin increased	34	2	24	1
Hyperkalemia	29	2	21	1
Hyperuricemia	35	8	18	5
AST increased	22	2	29	3
ALT increased	21	3	25	3
Creatinine increased	31	1	16	0

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Creatinine clearance decreased	38	5	16	1
Hypoalbuminemia	34	0	19	2
Hypokalemia	24	3	9	0
Hyponatremia	24	8	25	1

* Based on laboratory measurements per iwCLL criteria grade (iwCLL: International Workshop on Chronic Lymphocytic. Leukemia)

…

16 CLINICAL STUDIES

16.2 CHRONIC LYMPHOCYTIC LEUKEMIA / SMALL LYMPHOCYTIC LYMPHOMA

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Fixed duration combination therapy

The safety and efficacy of fixed duration therapy with IMBRUVICA in combination with venetoclax versus chlorambucil in combination with obinutuzumab in patients with previously untreated CLL were evaluated in a randomised, open-label, phase 3 (CLL3011) study. The study enrolled patients with previously untreated CLL who were 65 years or older, and adult patients <65 years of age with a CIRS score >6 or CrCL ≥30 to <70 mL/min. Patients with del 17p or known TP53 mutations were excluded. Patients (n=211) were randomised 1:1 to receive either IMBRUVICA in combination with venetoclax or chlorambucil in combination with obinutuzumab. Patients in the IMBRUVICA plus venetoclax arm received single agent IMBRUVICA for 3 cycles followed by IMBRUVICA in combination with venetoclax for 12 cycles (including 5-week dose-titration schedule). Each cycle was 28 days. IMBRUVICA was administered at a dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg. Patients randomised to the chlorambucil plus obinutuzumab arm received treatment for 6 cycles. Obinutuzumab was administered at a dose of 1,000 mg on Days 1, 8 and 15 in Cycle 1. In Cycles 2 to 6, 1,000 mg obinutuzumab was given on Day 1. Chlorambucil was administered at a dose of 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 to 6. Patients with confirmed progression by IWCLL criteria after completion of either fixed duration regimen could be treated with single-agent IMBRUVICA.

The median age was 71 years (range, 47 to 93 years), 58% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (35%), 1 (53%), or 2 (12%). At baseline, 18% of patients presented with CLL with del 11q and 52% with unmutated IGHV.

At baseline assessment for risk of tumor lysis syndrome, 25% of patients had high tumor burden. After 3 cycles of single-agent IMBRUVICA lead-in therapy, 2% of patients had high tumor burden. High tumor burden was defined as any lymph node ≥10 cm; or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/L.

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With a median follow-up time on study of 28 months, efficacy results for Study CLL3011 assessed by an IRC according to IWCLL criteria are shown in Table 28, the Kaplan-Meier curve for PFS is shown in Figure 7, and rates of minimal residual disease (MRD) negativity are shown in Table 33.

Table 33: Efficacy Results in Study CLL3011

Endpoint[a]	**IMBRUVICA + Venetoclax N=106**	**Chlorambucil + Obinutuzumab N=105**
Progression Free Survival		
Number of events (%)	22 (20.8)	67 (63.8)
Median (95% CI), months	NE (31.2, NE)	21.0 (16.6, 24.7)
HR (95% CI)	0.22 (0.13, 0.36)	
P-value[b]	<0.0001	
Complete Response Rate (%)[c]	38.7	11.4
95% CI	(29.4, 48.0)	(5.3, 17.5)
P-value[d]	<0.0001	
Overall Response Rate (%)[e]	86.8	84.8
95% CI	(80.3, 93.2)	(77.9, 91.6)

[a] Based on IRC assessment
[b] P-value is from stratified log-rank test
[c] Includes 3 patients in the IMBRUVICA + venetoclax arm with a complete response with incomplete marrow recovery (CRi)
[d] P-value is from Cochran-Mantel-Haenszel chi-square test
[e] Overall response = CR+CRi+nPR+PR

CR = complete response; CRi = complete response with incomplete marrow recovery; HR = hazard ratio; NE = not evaluable; nPR = nodular partial response; PR = partial response

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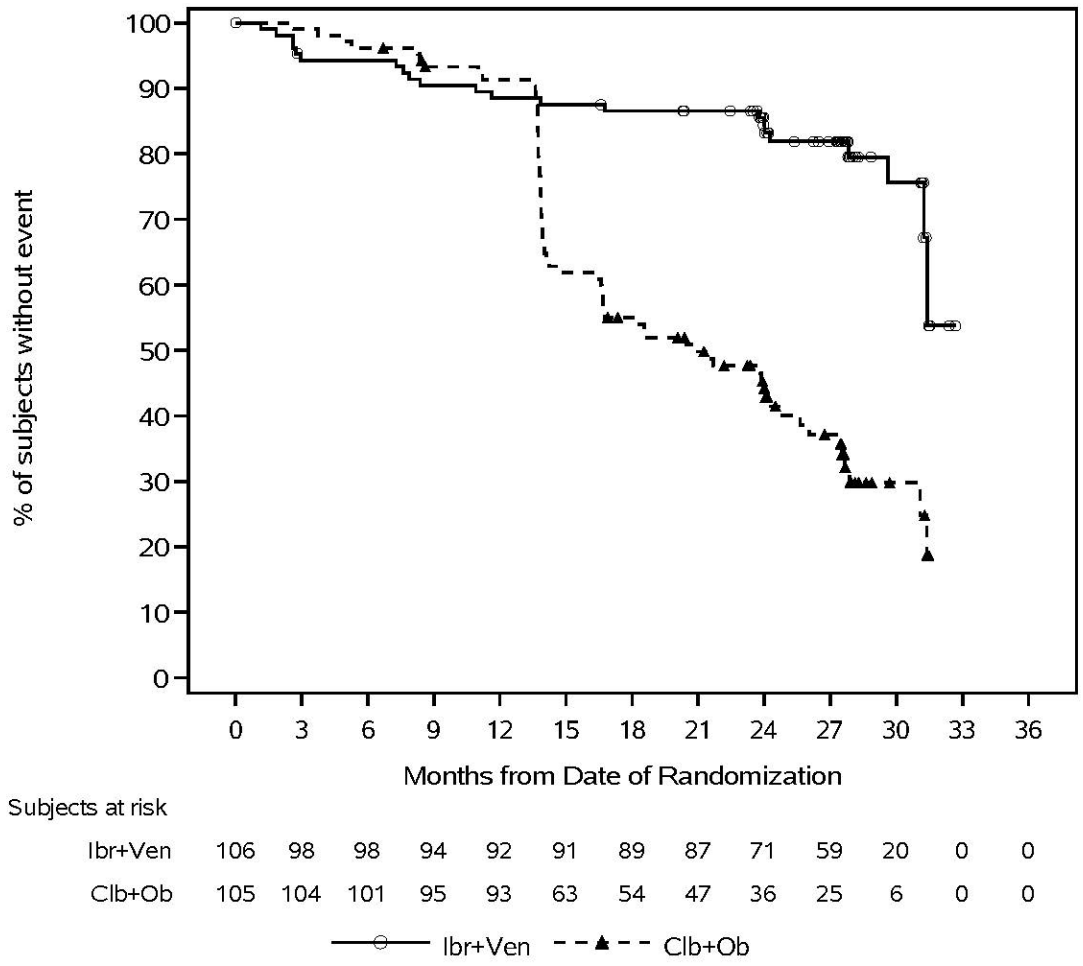
Figure 7: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL in Study CLL3011



The treatment effect of IMBRUVICA plus venetoclax was consistent across the high-risk CLL population (TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.41)].

Overall survival data were not mature. With a median follow-up of 28 months, there was no significant difference between treatment arms with a total of 23 deaths: 11 (10.4%) in the IMBRUVICA plus venetoclax arm and 12 (11.4%) in the chlorambucil plus obinutuzumab arm with a OS HR of 1.048 [95% CI (0.454, 2.419)]. After 6 months additional follow-up, 11 (10.4%) and 16 (15.2%) deaths were reported in the IMBRUVICA plus venetoclax arm and the chlorambucil plus obinutuzumab arm, respectively with OS HR estimated at 0.760 [95% CI (0.352, 1.642]).

Table 34: Minimal Residual Disease Negativity Rates in Study CLL3011

	NGS Assay[a]		Flow cytometry[b]	
	IMBRUVICA +	Chlorambucil +	IMBRUVICA +	Chlorambucil +

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	Venetoclax N=106	Obinutuzumab N=105	Venetoclax N=106	Obinutuzumab N=105
MRD Negativity Rate				
Bone marrow, n (%)	59 (55.7)	22 (21.0)	72 (67.9)	24 (22.9)
95% CI	(46.2, 65.1)	(13.2, 28.7)	(59.0, 76.8)	(14.8, 30.9)
P-value	<0.0001			
Peripheral Blood, n (%)	63 (59.4)	42 (40.0)	85 (80.2)	49 (46.7)
95% CI	(50.1, 68.8)	(30.6, 49.4)	(72.6, 87.8)	(37.1, 56.2)
MRD Negativity Rate at Three Months After Completion of Treatment				
Bone marrow, n (%)	55 (51.9)	18 (17.1)	60 (56.6)	17 (16.2)
95% CI	(42.4, 61.4)	(9.9, 24.4)	(47.2, 66.0)	(9.1, 23.2)
Peripheral Blood, n (%)	58 (54.7)	41 (39.0)	65 (61.3)	43 (41.0)
95% CI	(45.2, 64.2)	(29.7, 48.4)	(52.0, 70.6)	(31.5, 50.4)

P-values are from Cochran-Mantel-Haenszel chi-square test. P-value for MRD negativity rate in bone marrow by NGS was the primary MRD analysis.

[a] Based on threshold of 10^{-4} using a next-generation sequencing assay (clonoSEQ)

[b] MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The definition of negative status was <1 CLL cell per 10,000 leukocytes ($<1\times10^4$).

CI = confidence interval; NGS = next-generation sequencing

Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 49.1% (52/106) by NGS assay and 54.7% (58/106) by flow cytometry in patients treated with IMBRUVICA plus venetoclax and, at the corresponding time point, was 12.4% (13/105) by NGS assay and 16.2% (17/105) by flow cytometry in patients treated with chlorambucil plus obinutuzumab.

TLS was reported in 6 patients treated with chlorambucil plus obinutuzumab and no TLS was reported in IMBRUVICA in combination with venetoclax.

The safety and efficacy of fixed duration therapy with IMBRUVICA in combination with venetoclax in patients with previously untreated CLL were further evaluated in a cohort of the phase 2, multi-center, 2-cohort study (PCYC-1142-CA). The study enrolled previously untreated patients with CLL who were 70 years or younger. The study enrolled 323 patients, of these, 159 patients were enrolled to fixed duration therapy consisting of 3 cycles of single agent IMBRUVICA followed by IMBRUVICA in combination with venetoclax for 12 cycles (including 5-week dose titration schedule). Each cycle was 28 days. IMBRUVICA was administered at a dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg. Patients with confirmed progression by IWCLL criteria after completion of the fixed duration regimen could be retreated with single-agent IMBRUVICA.

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The median age was 60 years (range, 33 to 71 years), 67% were male, and 92% were Caucasian. All patients had a baseline ECOG performance status of 0 (69%) or 1 (31%). At baseline, 13% of patients had del 17p, 18% with del 11q, 17% with del 17p/TP53 mutation, 56% with unmutated IGHV and 19% with complex karyotype. At baseline assessment for risk of tumor lysis syndrome, 21% of patients had high tumor burden.

After 3 cycles of single-agent IMBRUVICA lead-in therapy, 1% of patients had high tumor burden. High tumor burden was defined as any lymph node ≥10 cm, or any lymph node ≥5 cm and absolute lymphocyte count ≥25×10^9/L.

With a median follow-up time on study of 28 months, efficacy results for PCYC-1142-CA assessed by an IRC according to IWCLL criteria are shown in Table 35, and rates of minimal residual disease (MRD) negativity are shown in Table 36.

Table 35: Efficacy Results in Study PCYC-1142-CA (Fixed Duration Cohort)

Endpoint[a]	IMBRUVICA + Venetoclax	
	Without Del 17p (N=136)	All (N=159)
Overall Response Rate, n (%)[b]	130 (95.6)	153 (96.2)
95% CI (%)	(92.1, 99.0)	(93.3, 99.2)
Complete Response Rate, n (%)[c]	83 (61.0)	95 (59.7)
95% CI (%)	(52.8, 69.2)	(52.1, 67.4)
Median duration of CR, months (range)[d]	NE (0.03+, 24.9+)	NE (0.03+, 24.9+)

[a] Based on IRC assessment
[b] Overall response = CR + CRi + nPR + PR
[c] Includes 3 patients with a complete response with incomplete marrow recovery (CRi)
[d] A '+' sign indicates a censored observation
CR = complete response; CRi = complete response with incomplete marrow recovery; nPR = nodular partial response; PR = partial response; NE = not evaluable

Table 36: Minimal Residual Disease Negativity Rates in Study PCYC-1142-CA (Fixed Duration Cohort)

Endpoint	IMBRUVICA + Venetoclax	
	Without Del 17p (N=136)	All (N=159)
MRD Negativity Rate		
Bone marrow, n (%)	84 (61.8)	95 (59.7)
95% CI	(53.6, 69.9)	(52.1, 67.4)
Peripheral Blood, n (%)	104 (76.5)	122 (76.7)
95% CI	(69.3, 83.6)	(70.2, 83.3)

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MRD Negativity Rate at Three Months After Completion of Treatment		
Bone marrow, n (%)	74 (54.4)	83 (52.2)
95% CI	(46.0, 62.8)	(44.4, 60.0)
Peripheral Blood, n (%)	78 (57.4)	90 (56.6)
95% CI	(49.0, 65.7)	(48.9, 64.3)

MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The definition of negative status was <1 CLL cell per 10,000 leukocytes ($<1\times10^4$).
CI = confidence interval

In patients with del 17p/TP53 mutation (n=27) in PCYC-1142-CA the overall response rate based on IRC assessment was 96.3%; complete response rate was 55.6% and the median duration of complete response was not reached (range, 4.3 to 22.6 months). The MRD negativity rate in patients with del 17p/TP53 mutation 3 months after completion of treatment in bone marrow and peripheral blood was 40.7% and 59.3%, respectively.

No TLS was reported in patients treated with IMBRUVICA in combination with venetoclax.

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העדכונים העיקריים בעלון לצרכן הינם:

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1. למה מיועדת התרופה?

- התרופה מיועדת לטיפול במחלת Mantle Cell Lymphoma) MCL) במבוגרים שקיבלו לפחות טיפול קודם אחד.
- התרופה מיועדת לטיפול במחלת Small Lymphocytic Lymphoma)/Chronic Lymphocytic) CLL (Leukemia) במבוגרים ~~שקיבלו לפחות טיפול קודם אחד~~.
- ~~התרופה מיועדת לטיפול בקו ראשון במחלת Chronic Lymphocytic) CLL/(Small Lymphocytic Lymphoma) SLL Leukemia) במבוגרים מגיל 65 ומעלה.~~

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3. כיצד תשתמש בתרופה:

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המינון המקובל הוא:

Chronic Lymphocytic Leukemia (CLL) ו- Small Lymphocytic Lymphoma (SLL) ו- Waldenström's Macroglobulinemia (WM) – 420 מ״ג, פעם ביום עד התקדמות מחלה או תופעות לוואי שאינן נסבלות.
עבור CLL/SLL, ניתן ליטול אימברוביקה כתרופה יחידה, בשילוב עם ריטוקסימאב או אובינוטוזומאב, או בשילוב של ~~ריבוטיניב~~איברוטיניב עם בנדמוסטין וריטוקסימאב, או בשילוב של איברוטיניב עם ונטוקלקס. באוכלוסיה מבוגרת או מטופלים בעלי מחלות נלוות רבות, יש לנקוט במשנה זהירות בשילוב של איברוטיניב עם ונטוקלקס.
בשילוב של איברוטיניב עם ונטוקלקס לטיפול ב- CLL, יש ליטול אימברוביקה כתרופה יחידה למשך 3 מחזורים (מחזור אחד הינו 28 ימים), ולאחריו 12 מחזורים של אימברוביקה בשילוב עם ונטוקלקס. יש לעיין בעלון של ונטוקלקס למידע מלא על מינון התכשיר.

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4. תופעות לוואי

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- **זיהומים** – עלולים להתרחש במהלך הטיפול באימברוביקה. הזיהומים עלולים להיות חמורים ולהוביל למוות. יש

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ליידע את הרופא באופן מיידי אם אתה סובל מחום, צמרמורות, חולשה, בלבול או כל סימן או תסמין אחר לזיהום במהלך הטיפול באימברוביקה.

- ~~**ירידה בספירת דם** – ירידה בספירת דם (תאי דם לבנים, טסיות ותאי דם אדומים) הינה תופעה שכיחה בטיפול באימברוביקה אך עלולה להיות גם חמורה. הרופא המטפל צריך להפנות אותך לבצע ספירת דם כל חודש.~~
- **בעיות לב** – בעיות חמורות בקצב הלב (פרפור חדרים, פרפור פרוזדורים ורפרוף פרוזדורים), כשל לבבי ואף מוות התרחשו באנשים המטופלים באימברוביקה, בייחוד ~~אנשים בעלי~~בקרב מטופלים עם זיהומים, ~~-~~מטופלים בעלי סיכון מוגבר למחלות לב, ~~אנשים עם זיהומים~~ או אנשים שסבלו מבעיות בקצב הלב בעבר. תפקוד הלב שלך ייבדק לפני ובמהלך הטיפול עם אימברוביקה. יש ליידע את הרופא אם אתה סובל מתסמינים של בעיות בלב, כגון התחושה שהלב פועם בקצב מהיר ולא סדיר, סחרחורת, קוצר נשימה, נפיחות בכפות הרגליים, בקרסוליים או ברגליים, אי-נוחות בחזה או עילפון. אם הינך מפתח אחד מתסמינים אלו, ייתכן שהרופא יפנה אותך לבדיק~~ה~~ות לב ~~(אק"ג)~~ ו~~עשוי לשנות ישנה~~ את מינון התרופה.
- **יתר לחץ דם (יל"ד)** – הופעה או החמרה של יתר לחץ דם התרחשו באנשים המטופלים באימברוביקה. ייתכן והרופא המטפל יחליט לתת לך טיפול תרופתי חדש להורדת לחץ הדם או ישנה טיפול קיים.
- **ירידה בספירת הדם** – ירידה בספירת דם (תאי דם לבנים, טסיות ותאי דם אדומים) הינה תופעה שכיחה בטיפול באימברוביקה אך גם עלולה להיות חמורה. הרופא המטפל צריך להפנות אותך לבצע בדיקות לספירת דם בכל חודש.

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תופעות לוואי נוספות הקשורות ב- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) אשר ניצפו בשילוב של אימברוביקה עם ונטוקלקס:**

מערכת בגוף	תופעת הלוואי
הפרעות בקיבה ובמעיים	שלשול בחילות דלקת בפה כאבי בטן הקאות קשיי עיכול עצירות
הפרעות כלליות ותנאי אזור המתן	עייפות בצקת היקפית
זיהומים ונגעים	זיהום בדרכי נשימה עליונות זיהומים בעור זיהום בדרכי השתן
הפרעות בשרירי השלד וברקמות חיבור	כאבי שרירים ושלד כאבי מפרקים התכווציות שרירים
הפרעות במערכת העצבים	כאב ראש סחרחורת
הפרעות נשימה וחלל בית חזה	שיעול
הפרעות בעור וברקמות התת עוריות	חבלות פריחה
הפרעות בכלי הדם	דימום

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	יתר לחץ דם
חריגות בתוצאות בדיקות המטולוגיות	ירידה ברמת הנויטרופילים ירידה ברמת הטסיות ירידה ברמת ההמוגלובין
חריגות בתוצאות מעבדה כימיות	רמת נתרן גבוהה/נמוכה בדם רמת סידן נמוכה בדם רמת מגנזיום נמוכה בדם עליה ברמת בילירובין רמת אשלגן גבוהה/נמוכה בדם רמת גבוהה של חומצה אורית בדם עליה ברמת אנזימי כבד עלייה ברמת קריאטנין ירידה בפינוי קריאטנין רמת אלבומין נמוכה בדם