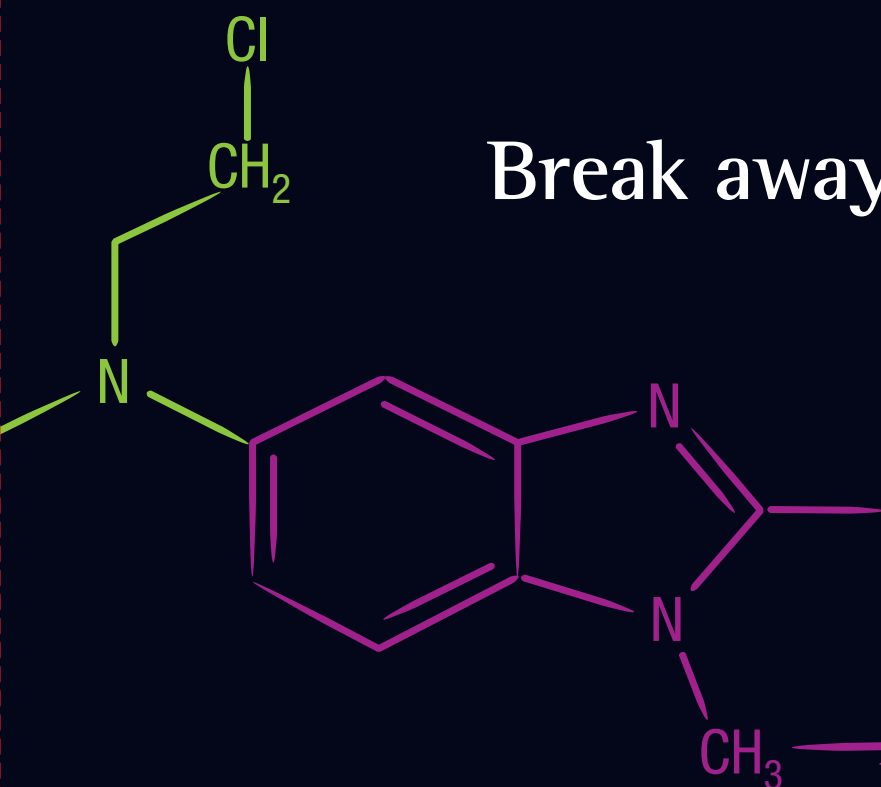


For chronic lymphocytic leukemia (CLL)—
TREANDA®



Break away from expectations



TREANDA is indicated for the treatment of patients with CLL. Efficacy relative to first-line therapies other than chlorambucil has not been established.

Please see accompanying full Prescribing Information.

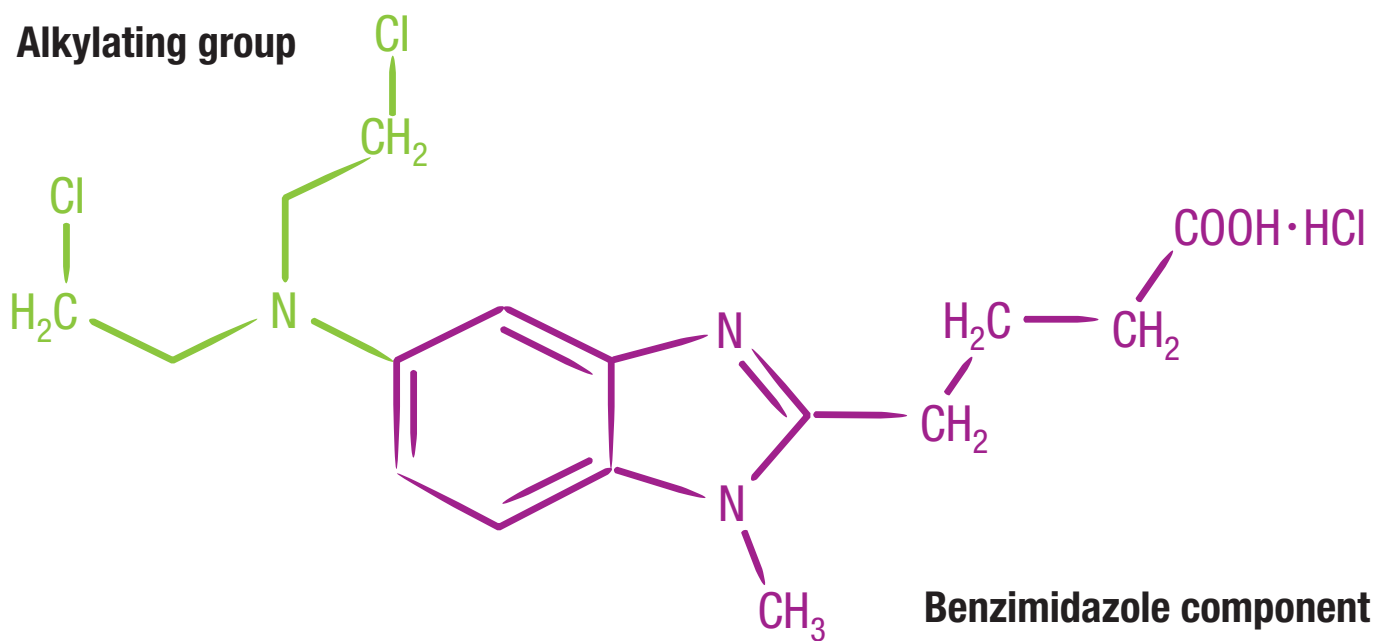
 **TREANDA®**
(bendamustine HCl)
for Injection

Built for Action

www.TREANDA.com

Dual structure

TREANDA is a unique treatment that combines an **alkylating group** with a **purine-like benzimidazole ring**^{1,2}



- The alkylating group contains mechlorethamine, which confers alkylating properties
- The benzimidazole component contains a purine antagonist (a benzimidazole ring)^{3,4}

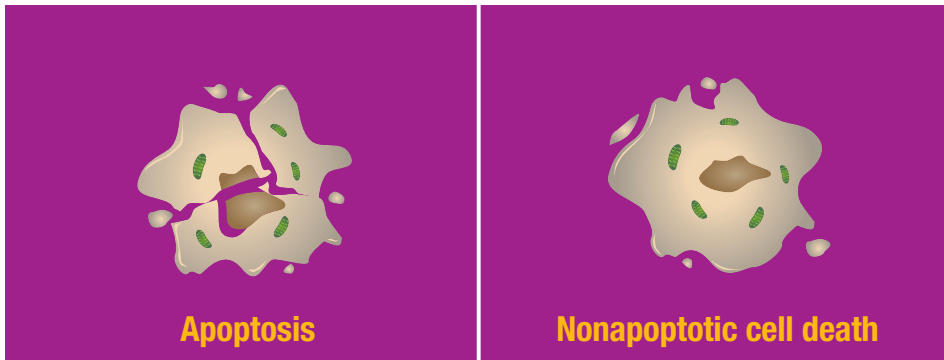
Anti-tumor activity



Cell death via several pathways^{1,5-7}

The exact mechanism of action of TREANDA remains unknown

DUAL CELL-DEATH EFFECTS



TREANDA is active against both quiescent and dividing cells

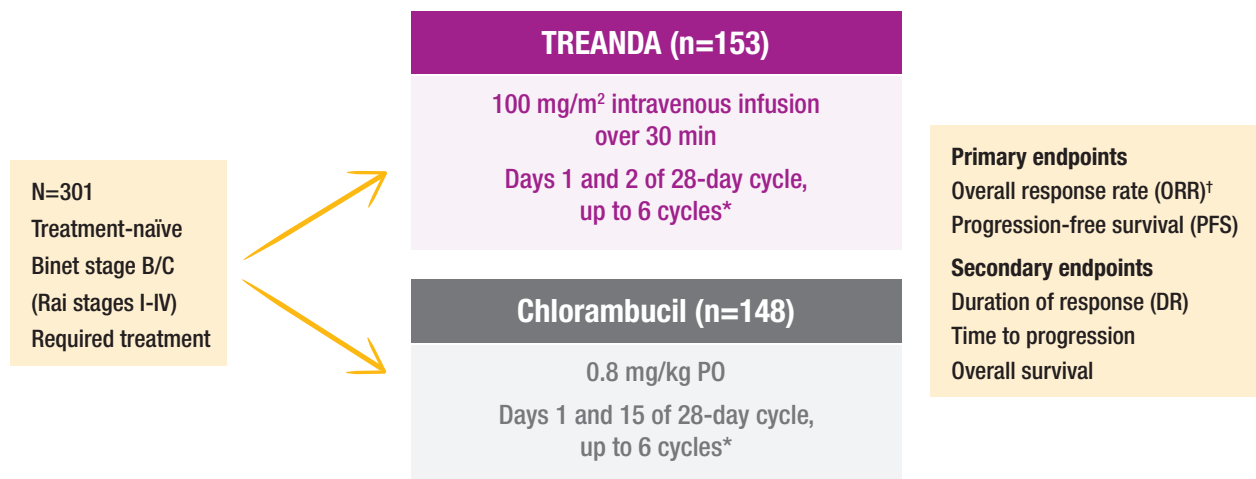
Cephalon Oncology is actively conducting research on the mechanism of action of TREANDA

Preclinical studies suggest that TREANDA may cause both apoptotic and nonapoptotic death of malignant cells by possibly^{1,5-7}:

- Inducing extensive and durable DNA damage^{5,6}
 - Causing both single- and double-strand DNA breaks
- Increasing expression of proapoptotic genes⁵
- Inhibiting mitotic checkpoint control⁵

Pivotal Phase 3 trial design

Randomized, open-label, multicenter trial in treatment-naïve patients



*Duration of treatment depended on response. Patients with complete response (CR), nodular partial response (nPR), or partial response (PR) after 3 cycles could receive 2 consolidation cycles, but no more than 6 cycles. Patients with stable disease had the option to receive up to 6 cycles. Patients with progressive disease discontinued treatment.¹

[†]ORR includes patients with a best response of CR, nPR, and PR (ORR=CR+nPR+PR).

Efficacy was defined according to the National Cancer Institute Working Group (NCI-WG) guidelines.¹



Baseline characteristics were balanced in both treatment groups

Baseline Demographic Information	TREANDA (n=153)	Chlorambucil (n=148)
Median age (years)	63	66
Male (%)	63	61
Lymphadenopathy (%)	79	82
Spleen enlarged (%)	76	80
Liver enlarged (%)	48	46
Hypercellular bone marrow (%)	79	73
B symptoms (%) (fever, night sweats, or weight loss)	51	53
Mean lymphocyte count ($10^9/L$)	65.7	65.1
Binet stage B (%)	71	69
Immunophenotype CD5, CD23, and either CD19 or CD20 or both (%)	90	90
Mean lactate dehydrogenase (U/L)	370.2	388.4

In a
randomized,
open-label,
pivotal
Phase 3 trial

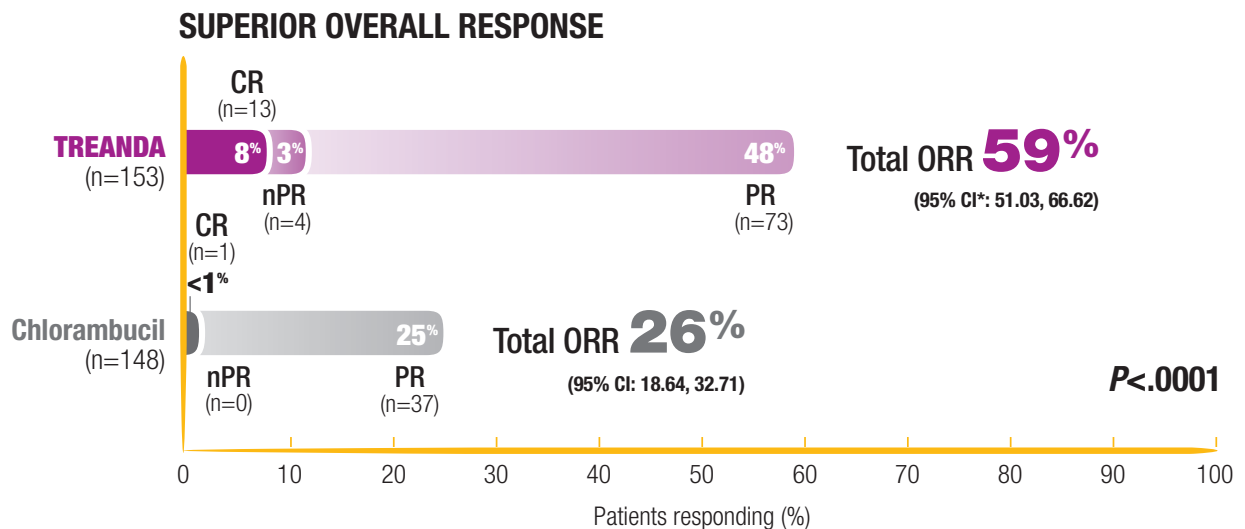
TREANDA

Superior clinical performance

Compared with chlorambucil...

TREANDA more than doubled overall response rate

59% ORR for TREANDA vs 26% with chlorambucil



*CI=confidence interval.

- An additional evaluation by an independent committee for response assessment (ICRA) demonstrated a 27% CR with TREANDA vs 2% with chlorambucil (62% ORR vs 33% [95% CI: TREANDA 54.40, 69.78; chlorambucil 25.53, 40.69; $P<.0001$]; 10% nPR vs 3%; 25% PR vs 28% with TREANDA and chlorambucil, respectively)¹
- Response results from the ICRA analysis could not be fully verified in some patients. Therefore, the assignment of CR, nPR, and PR varied between the ICRA analysis and the results presented in the graph above, which were calculated using a stringent, prespecified algorithm¹

The most common non-hematologic adverse reactions (frequency $\geq 15\%$) were pyrexia (24%), nausea (20%), and vomiting (16%).

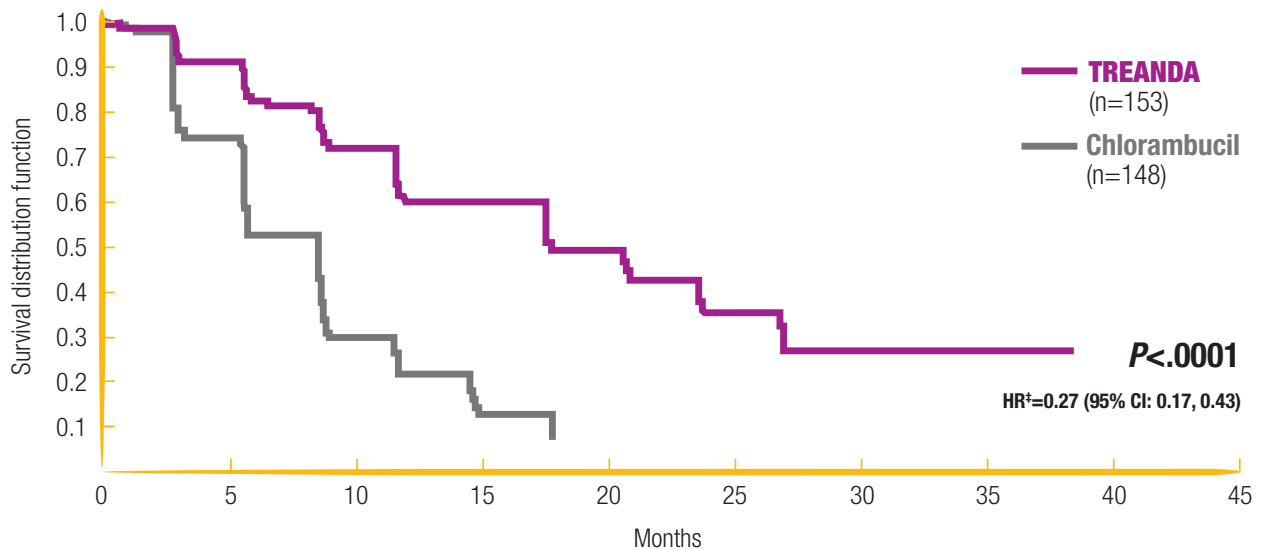
The most common hematologic abnormalities (frequency $\geq 15\%$) were anemia (89%), thrombocytopenia (77%), neutropenia (75%), lymphopenia (68%), and leukopenia (61%).



TREANDA tripled progression-free survival

Median PFS 18 mo for TREANDA vs 6 mo with chlorambucil*

SUPERIOR PFS: 73% RISK REDUCTION WITH TREANDA[†]



*TREANDA (95% CI: 11.7, 23.5) vs chlorambucil (95% CI: 5.6, 8.6); CI=confidence interval.

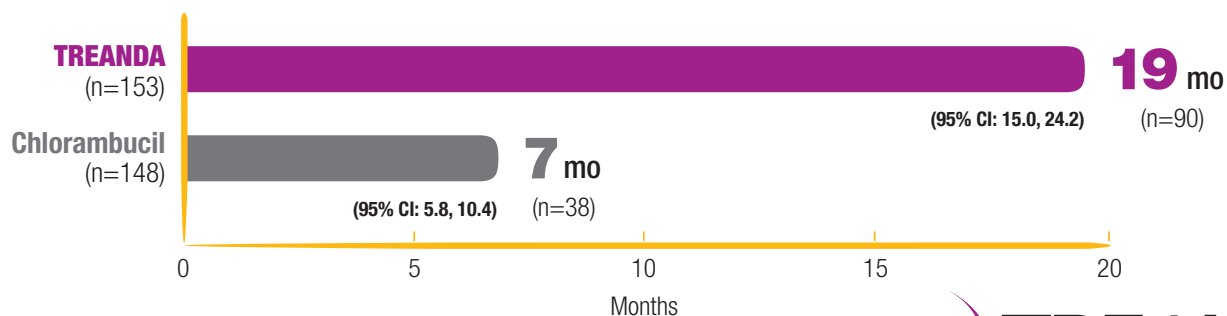
[†]Reduction in risk of progression of disease or death from any cause.

[‡]HR=hazard ratio.

TREANDA sustained therapeutic effect— more than doubled duration of response^{1§}

Over 2 times longer median duration of response for TREANDA vs chlorambucil (median 19 mo vs 7 mo)

MEDIAN DURATION OF RESPONSE IN RESPONDING PATIENTS¹



[§]Duration was defined as the time from response to disease progression or death.

TREANDA[®]
 (bendamustine HCl)
 for Injection
Built for Action

Safety results

TREANDA had a manageable side-effect profile in the pivotal Phase 3 trial

- TREANDA is associated with serious risks, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions, other malignancies, and a warning against use in pregnancy
- Some of these adverse reactions required dose modifications, interruptions, or discontinuation
- Patients receiving TREANDA experienced low incidence of alopecia

NON-HEMATOLOGIC ADVERSE REACTIONS OCCURRING IN ≥5% OF PATIENTS (ALL GRADES)				
Adverse reaction	Number (%) of patients			
	TREANDA (n=153)		Chlorambucil (n=143)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Total number of patients with at least 1 adverse reaction (%)	121 (79)	52 (34)	96 (67)	25 (17)
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Fatigue	14 (9)	2 (1)	8 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
Asthenia	13 (8)	0	6 (4)	0
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Weight decreased	11 (7)	0	5 (3)	0
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Chills	9 (6)	0	1 (<1)	0
Pruritus	8 (5)	0	2 (1)	0
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0

HEMATOLOGIC LABORATORY ABNORMALITIES IN PATIENTS WITH CLL				
Hematology variable	TREANDA (n=150)		Chlorambucil (n=141)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hemoglobin decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils decreased	113 (75)	65 (43)	86 (61)	30 (21)

Safety information

Contraindications

TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol.

Warnings and precautions

Myelosuppression

May warrant treatment delay or dose reduction. Monitor closely and restart treatment based on ANC and platelet count recovery. Complications of myelosuppression may lead to death.

Infections

Monitor for fever and other signs of infection and treat promptly.

Infusion reactions and anaphylaxis

Severe anaphylactic reactions have occurred. Monitor clinically and discontinue drug for severe reactions. Ask patients about reactions after the first cycle. Consider pre-treatment for cycles subsequent to milder reactions.

Tumor lysis syndrome

May lead to acute renal failure and death. Take precautions in patients at high risk.

Skin reactions

Discontinue for severe skin reactions. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes.

Other malignancies

Pre-malignant and malignant diseases have been reported.

Use in pregnancy

Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TREANDA.

Safety information (cont'd)

Post-marketing experience

The following adverse reactions have been identified during post-approval use of TREANDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: anaphylaxis and injection or infusion site reactions, including pruritus, irritation, pain, and swelling.

Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes.

Drug interactions

Patients receiving concomitant CYP1A2 inhibitors/inducers

Inhibitors of CYP1A2 (eg, fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of TREANDA and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (eg, omeprazole, smoking) have potential to decrease plasma concentrations of TREANDA and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered, if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

Use in specific populations

Pregnancy

If TREANDA is used during pregnancy, or if the patient becomes pregnant while taking TREANDA, the patient should be apprised of the potential hazard to the fetus.

Nursing mothers

Advise patients to avoid nursing while taking TREANDA. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for TREANDA in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

The safety and effectiveness of TREANDA in pediatric patients have not been established.

Geriatric use

There were no clinically significant differences in adverse reactions between geriatric (≥ 65 years of age) and younger patients.

Renal impairment

TREANDA should be used with caution in patients with mild or moderate renal impairment. TREANDA should not be used in patients with CrCL < 40 mL/min.

Hepatic impairment

TREANDA should be used with caution in patients with mild hepatic impairment. TREANDA should not be used in patients with moderate (AST or ALT 2.5-10 x ULN and total bilirubin 1.5-3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment.

Effect of gender

No clinically significant differences between genders were seen in the overall incidences of adverse reactions.

Convenient dosing and administration

TREANDA offers the convenience of 30-minute intravenous infusion

- The recommended dose is 100 mg/m² administered daily on Days 1 and 2 of a 28-day cycle, up to 6 cycles
- TREANDA can be administered in an outpatient setting

100 mg/m²
Days 1 and 2



Up to six 28-day cycles

The most common hematologic abnormalities (frequency $\geq 15\%$) were anemia, thrombocytopenia, neutropenia, lymphopenia, and leukopenia.



Dose delays

- TREANDA administration should be delayed in the event of a Grade 4 hematologic toxicity
- TREANDA administration should be delayed in the event of clinically significant \geq Grade 2 non-hematologic toxicity

Dose modifications

Managing hematologic toxicity	
If Grade 3/4 toxicity occurs	50 mg/m ² daily, Days 1 and 2 of 28-day cycle
If Grade 3/4 toxicity recurs	25 mg/m ² daily, Days 1 and 2 of 28-day cycle

Managing non-hematologic toxicity	
If clinically significant Grade 3/4 toxicity occurs	50 mg/m ² daily, Days 1 and 2 of 28-day cycle

- Dose re-escalation in subsequent cycles may be considered

Dose reinitiation

- Once blood counts have improved to ANC $\geq 1 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$; and/or
- Non-hematologic toxicity has recovered to \leq Grade 1, treatment may be reinitiated at the discretion of the treating physician



References: **1.** Data on file. Cephalon, Inc. **2.** Hirschberg E, Gellhorn A, Gump WS. Laboratory evaluation of a new nitrogen mustard, 2-[Di-(2-chloroethyl)aminomethyl]benzimidazole, and of other 2-chloroethyl compounds. *Cancer Res.* 1957;17(9):904-910. **3.** Rummel MJ, Chow KU, Hoelzer D, Mitrou PS, Weidmann E. In vitro studies with bendamustine: enhanced activity in combination with rituximab. *Semin Oncol.* 2002;29:12-14. **4.** Barman Balfour JA, Goa KL. Bendamustine. *Drugs.* 2001;61:631-638. **5.** Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. *Clin Cancer Res.* 2008;14:309-317. **6.** Strumberg D, Harstrick A, Doll K, Hoffmann B, Seeber S. Bendamustine hydrochloride activity against doxorubicin-resistant human breast carcinoma cell lines. *Anti-cancer Drugs.* 1996;7:415-421. **7.** Schwänen C, Hecker T, Hübinger G, et al. In vitro evaluation of bendamustine induced apoptosis in B-chronic lymphocytic leukemia. *Leukemia.* 2002;16:2096-2105.

 **TREANDA**[®]
(bendamustine HCl)
for Injection
Built for Action

Break away from expectations

Dual structure, anti-tumor activity¹⁻⁷

- Combines an alkylating group with a purine-like benzimidazole ring
- Dual cell-death effects via several pathways
- Active against both quiescent and dividing cells
- The exact mechanism of action of TREANDA remains unknown

Superior clinical performance

TREANDA vs chlorambucil

- More than doubled ORR* (**59%** [95% CI: 51.03, 66.62] vs **26%** [95% CI: 18.64, 32.71]) ($P < .0001$)
- Tripled median PFS (**18 mo** [95% CI: 11.7, 23.5] vs **6 mo** [95% CI: 5.6, 8.6]) (HR=0.27 [95% CI: 0.17, 0.43; $P < .0001$])
- More than doubled median DR¹ (**19 mo** [95% CI: 15.0, 24.2] vs **7 mo** [95% CI: 5.8, 10.4])

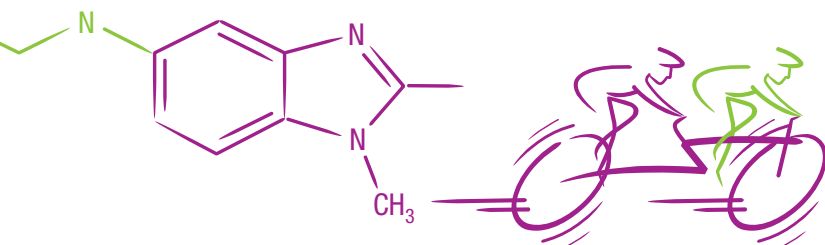
Observed side-effect profile

- The most common non-hematologic adverse reactions (frequency $\geq 15\%$) were pyrexia (24%), nausea (20%), and vomiting (16%)
- The most common hematologic abnormalities (frequency $\geq 15\%$) were anemia (89%), thrombocytopenia (77%), neutropenia (75%), lymphopenia (68%), and leukopenia (61%)

Convenient 30-minute intravenous infusion

- The recommended dose is 100 mg/m² administered daily on Days 1 and 2 of a 28-day cycle, up to 6 cycles
- Can be administered in an outpatient setting

TREANDA is indicated for the treatment of patients with CLL. Efficacy relative to first-line therapies other than chlorambucil has not been established.



*Please see definition of ORR on page 4.

Please see important safety information on pages 9 to 11 and accompanying full Prescribing Information.

TREANDA[®]
(bendamustine HCl)
for Injection

Built for Action

www.TREANDA.com