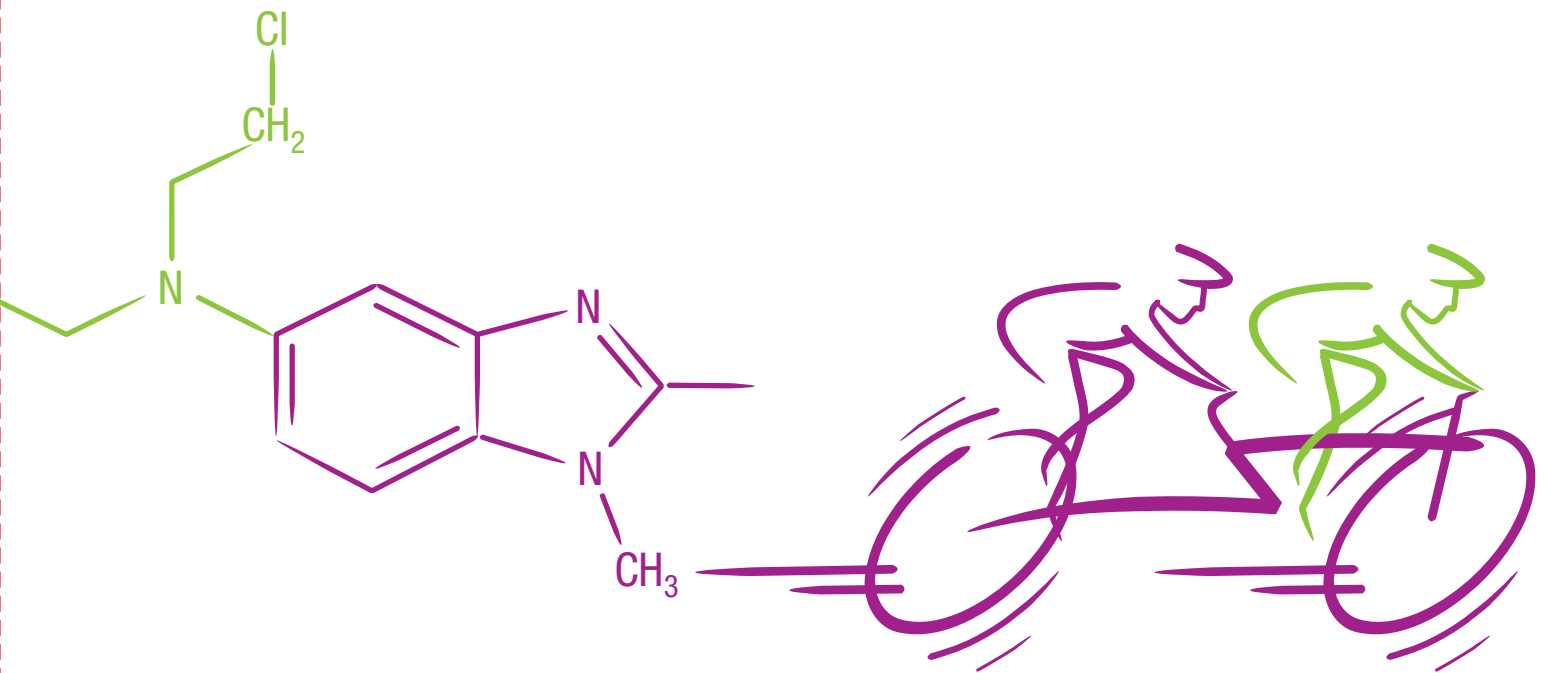


For indolent B-cell non-Hodgkin's lymphoma (NHL)—
TREANDA[®]

When patients progress past their first-line indolent B-cell NHL therapy...

Redefine expectations



TREANDA is indicated for the treatment of patients with indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

Please see accompanying full Prescribing Information.

 **TREANDA[®]**
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Proven in a pivotal trial

TREANDA is indicated for the treatment of patients with indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen*

STUDY DESIGN

	Pivotal trial
Principal investigator	Kahl BS ¹
Design	Multicenter, single-arm (N=100)
Dosing	120 mg/m ² on Days 1 and 2 of a 21-day treatment cycle, up to 8 cycles
Primary endpoints	Overall response rate (ORR) [†] and duration of response (DR)
Method of analysis	Powered to detect difference between treatment response vs null hypothesis (ORR ≤40%) ^{1,2}

*Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.

[†]ORR was defined as a best response of a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study (ORR=CR+CRu+PR).

BASELINE CHARACTERISTICS

Pivotal trial (N=100)	
Median age (years)	60
Male (%)	65
Baseline WHO performance status (%) 0 or 1	95
Major tumor subtypes (%)	
Follicular lymphoma	62
Diffuse small lymphocytic lymphoma	21
Marginal zone lymphoma	16



The efficacy and safety of TREANDA were evaluated in previously treated patients²

PRIOR TREATMENT HISTORY

	(N=100)
Rituximab-containing regimens (%)	100
Chemotherapy (%)	99
Alkylator therapy (%)	91
Purine-analog treatment (%)	44

PERCENTAGE OF PATIENTS RESISTANT TO PREVIOUS REGIMENS*

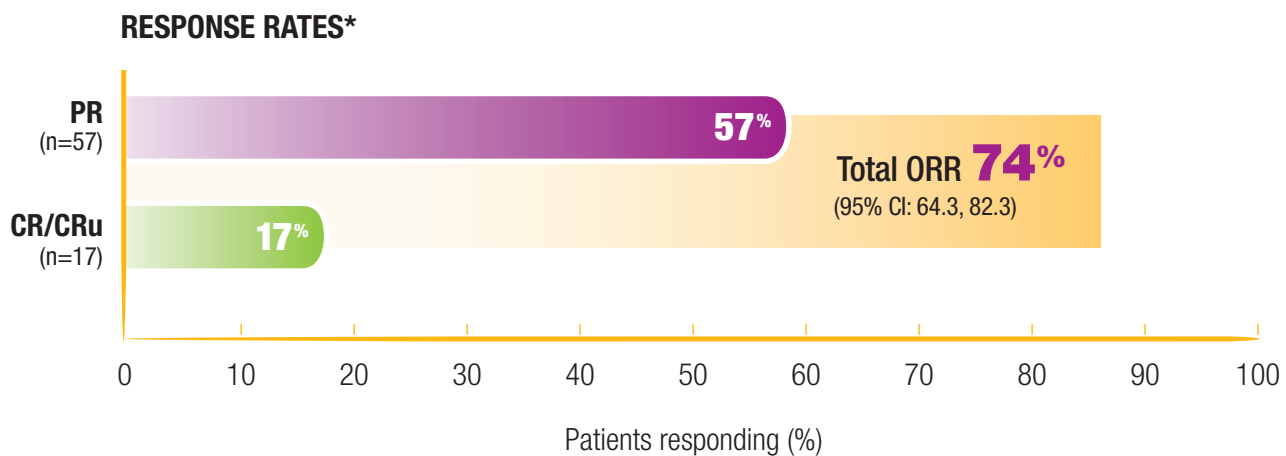
	(N=100)
Resistant to rituximab-based therapies (%)	97
Rituximab plus chemotherapy	26
Rituximab monotherapy/maintenance	58
Rituximab alone and combination therapy	13
Chemotherapy (%)	
Resistant to most recent chemotherapy-containing regimen	36
Resistant to most recent alkylator-containing therapy	30

*Resistant is defined as a best response of no objective response or progressive disease.

High rates of durable response

In the pivotal trial

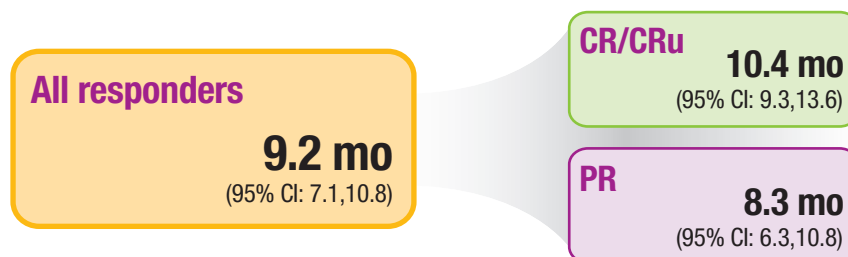
TREANDA produced a *robust* response in patients with indolent B-cell NHL that progressed during or within 6 months of a rituximab-containing regimen



- ✦ The ORR was significantly >40%, which was the protocol-defined measure of minimal meaningful efficacy ($P < .0001$)²
- ✦ The DR was significantly >4 months, which was the protocol-defined measure of minimal meaningful efficacy ($P < .0001$)²

TREANDA provided *durable* responses that lasted 9 months²

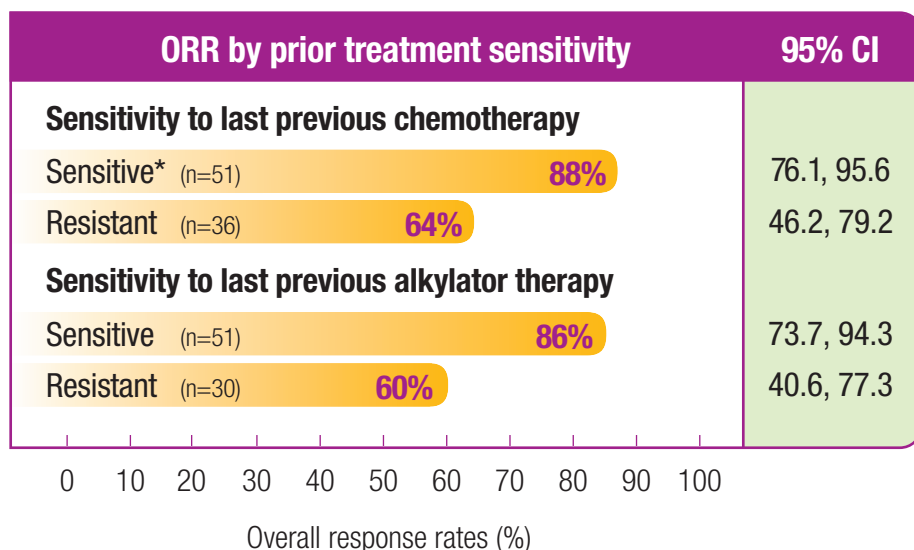
MEDIAN DURATION OF RESPONSE*




*Independent Review Committee (IRC) assessment was based on modified International Working Group response criteria (IWG-RC). Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥ 20 mm.



TREANDA produced *meaningful* responses in the majority of patients with disease resistant to prior chemotherapy²



*Sensitive is defined as a best response of complete response or partial response to treatment.

 The majority of patients who were resistant to previous alkylator therapy responded to treatment with TREANDA

The most common non-hematologic adverse reactions (frequency $\geq 30\%$) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), and pyrexia (34%).

The most common hematologic abnormalities (frequency $\geq 15\%$) were lymphopenia (99%), leukopenia (94%), anemia (88%), neutropenia (86%), and thrombocytopenia (86%).

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Safety results

TREANDA had a manageable side-effect profile in 2 single-arm studies of patients with indolent B-cell NHL (N=176)

- ▶ 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 alopecia²

HEMATOLOGIC ABNORMALITIES IN PATIENTS WITH INDOLENT B-CELL NHL TREATED WITH TREANDA

Hematology variable	% of patients	
	All Grades	Grade 3/4
Lymphocytes decreased	99	94
Leukocytes decreased	94	56
Hemoglobin decreased	88	11
Neutrophils decreased	86	60
Platelets decreased	86	25

- ▶ Prophylactic use of growth factors was allowed in conjunction with the study drug; use was discouraged during the first treatment cycle. Investigators were advised to follow the American Society of Clinical Oncology (ASCO) guidelines²



Please see important safety information on pages 8 and 9 and accompanying full Prescribing Information.

NON-HEMATOLOGIC ADVERSE REACTIONS OCCURRING IN ≥5% OF INDOLENT B-CELL NHL PATIENTS TREATED WITH TREANDA

Adverse reaction	% of patients*		Adverse reaction	% of patients*	
	All Grades	Grade 3/4		All Grades	Grade 3/4
<i>Total % of patients with at least 1 adverse reaction</i>	100	53			
Cardiac disorders			Metabolism and nutrition disorders		
Tachycardia	7	0	Anorexia	23	2
Gastrointestinal disorders			Dehydration	14	5
Nausea	75	4	Decreased appetite	13	<1
Vomiting	40	3	Hypokalemia	9	5
Diarrhea	37	3	Musculoskeletal and connective tissue disorders		
Constipation	29	<1	Back pain	14	3
Stomatitis	15	<1	Arthralgia	6	0
Abdominal pain	13	1	Pain in extremity	5	1
Dyspepsia	11	0	Bone pain	5	0
Gastroesophageal reflux disease	10	0	Nervous system disorders		
Dry mouth	9	<1	Headache	21	0
Abdominal pain upper	5	0	Dizziness	14	0
Abdominal distension	5	0	Dysgeusia	7	0
General disorders and administration site conditions			Psychiatric disorders		
Fatigue	57	11	Insomnia	13	0
Pyrexia	34	2	Anxiety	8	<1
Chills	14	0	Depression	6	0
Edema peripheral	13	<1	Respiratory, thoracic, and mediastinal disorders		
Asthenia	11	2	Cough	22	<1
Chest pain	6	<1	Dyspnea	16	2
Infusion site pain	6	0	Pharyngolaryngeal pain	8	<1
Pain	6	0	Wheezing	5	0
Catheter site pain	5	0	Nasal congestion	5	0
Infections and infestations			Skin and subcutaneous tissue disorders		
Herpes zoster	10	3	Rash	16	<1
Upper respiratory tract infection	10	0	Pruritus	6	0
Urinary tract infection	10	2	Dry skin	5	0
Sinusitis	9	0	Night sweats	5	0
Pneumonia	8	5	Hyperhidrosis	5	0
Febrile neutropenia	6	6	Vascular disorders		
Oral candidiasis	6	1	Hypotension	6	1
Nasopharyngitis	6	0			
Investigations					
Weight decreased	18	2			

*Patients may have reported more than 1 adverse reaction.

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.

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.



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Convenient dosing and administration

The recommended dose is 120 mg/m² administered daily on Days 1 and 2 of a 21-day cycle, up to 8 cycles

- 60-minute intravenous infusion
- TREANDA can be administered in an outpatient setting

120 mg/m² daily on Days 1 and 2



Up to eight 21-day cycles

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



Dose delays

- Dose administration should be delayed in the event of 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 4 toxicity occurs	90 mg/m ² daily, Days 1 and 2 of 21-day cycle
If Grade 4 toxicity recurs	60 mg/m ² daily, Days 1 and 2 of 21-day cycle

Managing non-hematologic toxicity	
If Grade 3/4 toxicity occurs	90 mg/m ² daily, Days 1 and 2 of 21-day cycle
If Grade 3/4 toxicity recurs	60 mg/m ² daily, Days 1 and 2 of 21-day cycle

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

ANC=absolute neutrophil count.

References: 1. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory indolent B-cell non-Hodgkin's lymphoma: results from a multicenter study. Submitted for publication. 2. Data on file. Cephalon, Inc.

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Redefine expectations

TREANDA is a unique treatment that is synthesized to combine an alkylating group and a purine-like benzimidazole ring

TREANDA produced robust and durable responses

In the pivotal trial

- TREANDA achieved a **74% total ORR*** (95% CI: 64.3, 82.3)
- TREANDA maintained a **9.2-month median DR** (95% CI: 7.1, 10.8)

Observed side-effect profile

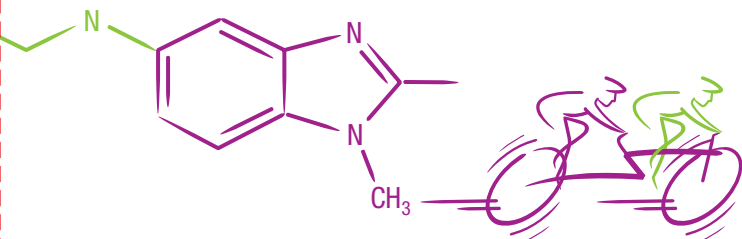
In 2 indolent B-cell NHL studies including the pivotal trial (N=176)

- The most common non-hematologic adverse reactions (frequency $\geq 30\%$) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), and pyrexia (34%)
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Convenient 60-minute intravenous infusion

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- TREANDA can be administered in an outpatient setting

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*Please see definition of ORR on page 2.

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