BESPONSA®

inotuzumab ozogamicin INJECTION FOR IV INFUSION

0.9 mg single-dose vial

AN OVERVIEW OF

CLINICAL DATA, PRODUCT INFORMATION, AND PATIENT MONITORING & COUNSELING

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INDICATION

BESPONSA is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).[1]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend inotuzumab ozogamicin (BESPONSA®) as a Category 1 treatment option for adults with Ph- relapsed or refractory B-cell precursor ALL.[2]

Ph–=Philadelphia chromosome negative.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia v2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed June 3, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. The NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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IMPORTANT SAFETY INFORMATION (1 of 3)

WARNING: HEPATOTOXICITY, INCLUDING HEPATIC VENO-OCCLUSIVE DISEASE (VOD) (ALSO KNOWN AS SINUSOIDAL OBSTRUCTION SYNDROME) and INCREASED RISK OF POST–HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) NON-RELAPSE MORTALITY (NRM):

- **Hepatotoxicity, including fatal and life-threatening VOD, occurred in patients who received BESPONSA. The risk of VOD was greater in patients who underwent HSCT after BESPONSA treatment. The use of HSCT conditioning regimens containing 2 alkylating agents and last total bilirubin ≥ upper limit of normal (ULN) before HSCT were significantly associated with an increased risk of VOD**
- **Other risk factors for VOD in patients treated with BESPONSA included ongoing or prior liver disease, prior HSCT, increased age, later salvage lines, and a greater number of BESPONSA treatment cycles**
- **Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA. Permanently discontinue treatment if VOD occurs. If severe VOD occurs, treat according to standard medical practice**
- **There was a higher post-HSCT non-relapse mortality rate in patients receiving BESPONSA, resulting in a higher Day 100 post-HSCT mortality rate**

Hepatotoxicity, Including Hepatic VOD: Hepatotoxicity, including fatal and life-threatening VOD, occurred in 23/164 patients (14%) during or following treatment with BESPONSA or following subsequent HSCT. VOD was reported up to 56 days after the last dose during treatment or follow-up without an intervening HSCT. The median time from HSCT to onset of VOD was 15 days.

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IMPORTANT SAFETY INFORMATION (2 of 3)

Patients with prior VOD or serious ongoing liver disease are at an increased risk of worsening liver disease, including development of VOD, following treatment with BESPONSA. Monitor closely for signs and symptoms of VOD; these may include elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites. For patients proceeding to HSCT, the recommended duration of treatment with BESPONSA is 2 cycles. A third cycle may be considered for patients who do not achieve a CR or CRi and MRD-negativity after 2 cycles. Monitor liver tests closely during the first month post HSCT, then less frequently thereafter, according to standard medical practice.

Grade 3/4 increases in aspartate aminotransferase, alanine aminotransferase, and total bilirubin occurred in 7/160 (4%), 7/161 (4%), and 8/161 (5%) patients, respectively.

Increased Risk of Post-HSCT Non-Relapse Mortality (NRM): There was a higher post-HSCT NRM rate in patients receiving BESPONSA, resulting in a higher Day 100 post-HSCT mortality rate. The rate of post-HSCT NRM was 31/79 (39%) with BESPONSA and 8/35 (23%) with investigator's choice of chemotherapy. In the BESPONSA arm, the most common causes of post-HSCT NRM included VOD and infections. Monitor closely for toxicities post HSCT, including signs and symptoms of infection and VOD.

Myelosuppression: Myelosuppression, and severe, life-threatening, and fatal complications of myelosuppression, including hemorrhagic events and infections, have occurred with BESPONSA. Thrombocytopenia and neutropenia were reported in 83/164 patients (51%) and 81/164 patients (49%), respectively. Febrile neutropenia was reported in 43/164 patients (26%).

Monitor complete blood counts prior to each dose of BESPONSA and monitor for signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression during treatment and provide appropriate management. As appropriate, administer prophylactic anti-infectives during and after treatment with BESPONSA. Dose interruption, dose reduction, or permanent discontinuation may be required.

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IMPORTANT SAFETY INFORMATION (3 of 3)

Infusion-Related Reactions: Infusion-related reactions (all Grade 2) were reported in 4/164 patients (2%). Premedicate with a corticosteroid, antipyretic, and antihistamine prior to dosing. Monitor patients closely during and for at least 1 hour after the end of the infusion for the potential onset of infusion-related reactions including symptoms such as fever, chills, rash, or breathing problems. Interrupt the infusion and institute appropriate medical management if an infusion-related reaction occurs. Depending on the severity, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue BESPONSA.

QT Interval Prolongation: Increases in QT interval corrected for heart rate using Fridericia's formula of ≥60 msec from baseline were measured in 4/162 patients (3%). Administer BESPONSA with caution in patients who have a history of or predisposition to QTc prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances. Obtain electrocardiograms and electrolytes prior to treatment and after initiation of any drug known to prolong QTc, and periodically monitor as clinically indicated during treatment.

Embryo-Fetal Toxicity: BESPONSA can cause embryo-fetal harm. Apprise pregnant women of the potential risk to the fetus. Advise males and females of reproductive potential to use effective contraception during BESPONSA treatment and for at least 5 and 8 months after the last dose, respectively. Advise women to contact their healthcare provider if they become pregnant or if pregnancy is suspected during treatment with BESPONSA.

Adverse Reactions: The most common (≥20%) adverse reactions observed with BESPONSA were thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinemia. The most common (≥2%) serious adverse reactions were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, VOD, and fatigue.

Nursing Mothers: Advise women against breastfeeding while receiving BESPONSA and for 2 months after the last dose.

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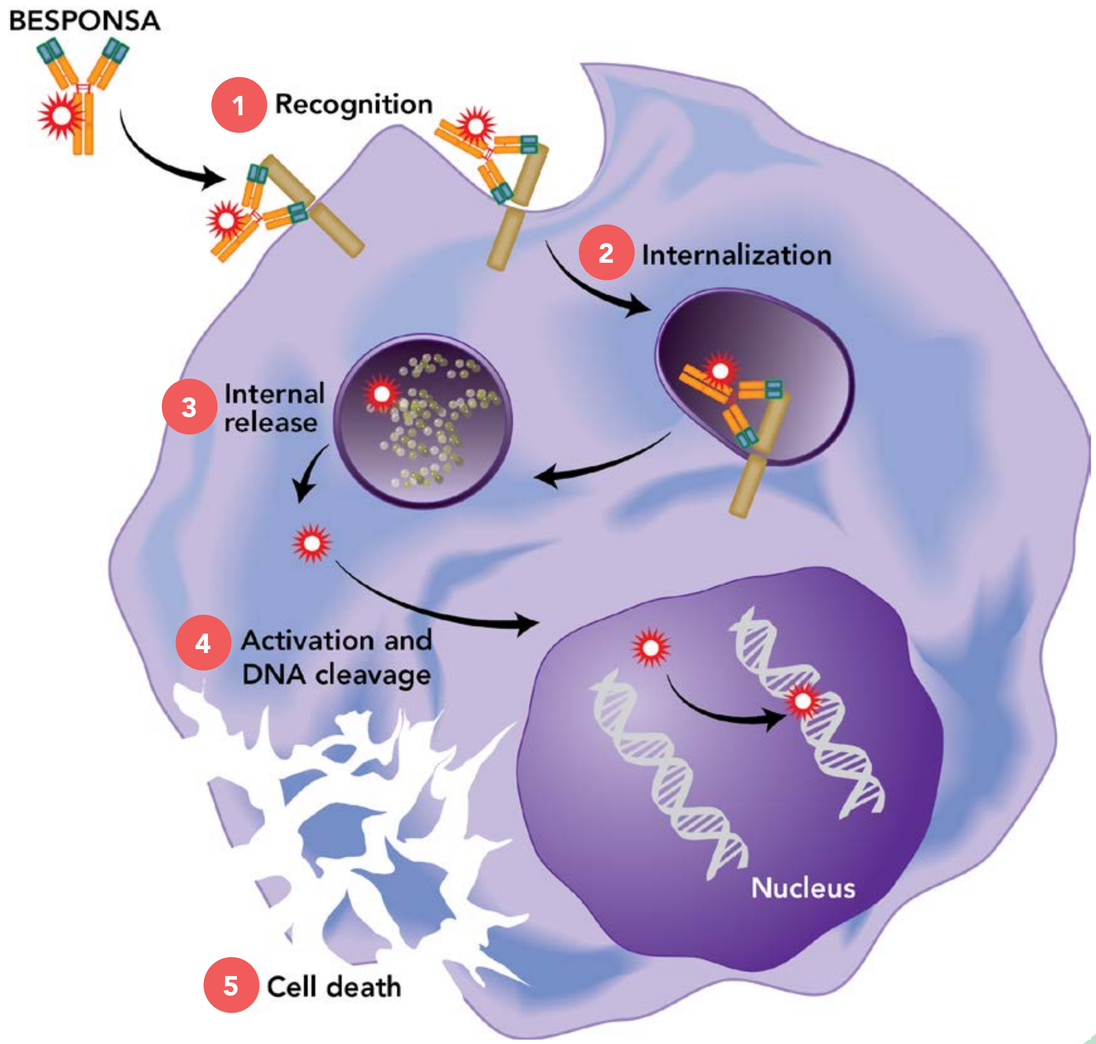
MECHANISM OF ACTION

BESPONSA is a CD22-directed antibody-drug conjugate (ADC)[1,2]

1. BESPONSA recognizes CD22 on the surface of leukemic blasts
2. Upon binding to CD22, the complex is internalized
3. Cleavage of the linker results in the internal release of calicheamicin
4. Calicheamicin is activated and binds to DNA inside the malignant cell
5. The double-stranded DNA breaks caused by calicheamicin induce cell-cycle arrest and apoptotic cell death

The correlation between nonclinical data and clinical outcomes is unknown.



References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Okeley NM, et al. *Hematol Oncol Clin N Am*. 2014;28(1):13-25.

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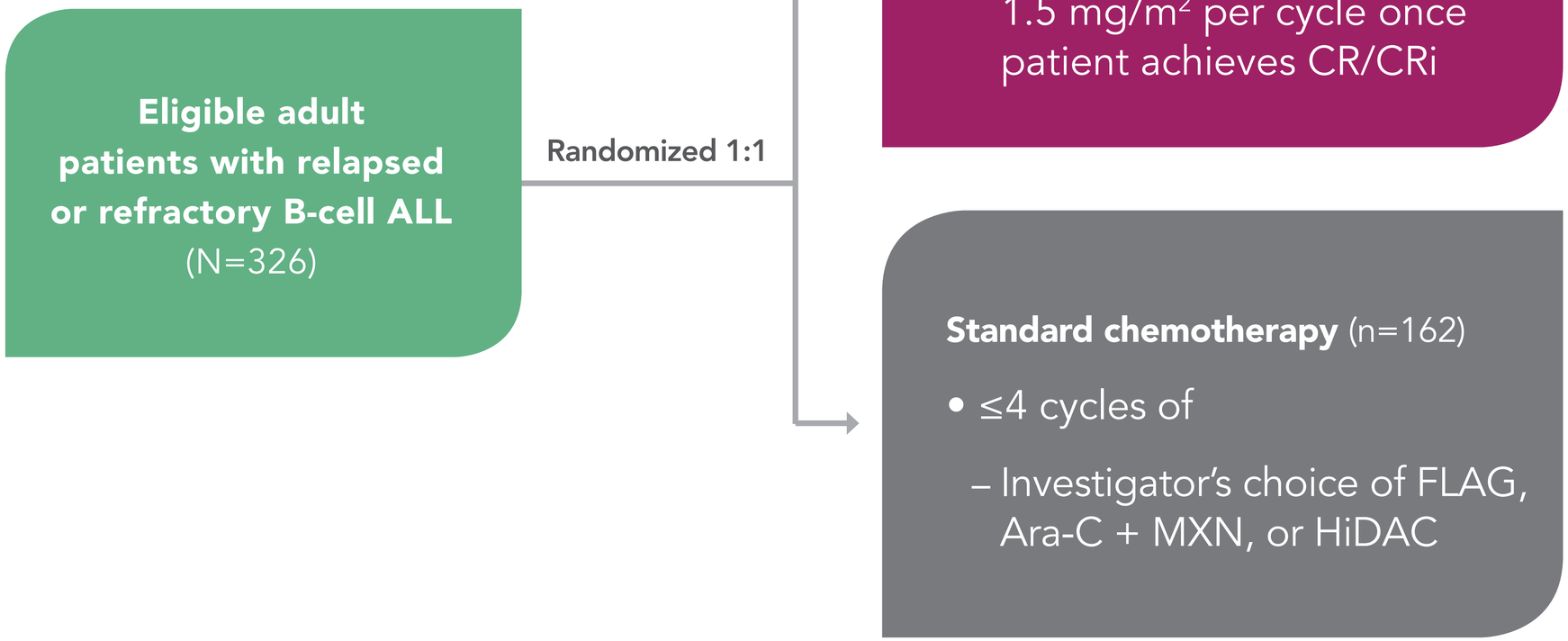
INO-VATE ALL STUDY: DESIGN

BESPONSA was evaluated in the INO-VATE ALL study: a Phase 3, open-label, randomized trial[1-3]



Primary endpoints

- CR/CRi rate
- OS

Secondary endpoints

- MRD-negativity rate
- HSCT rate
- DoR

Inference regarding statistical significance of secondary endpoints cannot be made.

The efficacy of BESPONSA was established on the basis of CR, duration of CR, and proportion of MRD-negative CR in the first 218 patients randomized.

ALL=acute lymphoblastic leukemia; Ara-C=cytarabine; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DoR=duration of remission; FLAG=fludarabine+cytarabine+granulocyte colony-stimulating factor (G-CSF); HiDAC=high-dose Ara-C; HSCT=hematopoietic stem cell transplant; MRD=minimal residual disease; MXN=mitoxantrone; OS=overall survival.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY. **3.** Kantarjian HM, et al. *Cancer*. 2019. doi:10.1002/cncr.32116 [Epub ahead of print].

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INO-VATE ALL STUDY: PATIENT CHARACTERISTICS[1,2]

	BESPONSA (n=164)	SC (n=162)	Total (N=326)
Age			
Median (range)	46.5 (18-78)	47.5 (18-79)	47.0 (18-79)
<55 years, n (%)	104 (63.4)	103 (63.6)	207 (63.5)
≥55 years, n (%)	60 (36.6)	59 (36.4)	119 (36.5)
ECOG performance status, n (%)			
0	62 (37.8)	61 (37.7)	123 (37.7)
1	81 (49.4)	80 (49.4)	161 (49.4)
2	21 (12.8)	20 (12.3)	41 (12.6)
Baseline bone marrow blasts, n (%)[a]			
<50%	53 (32.3)	48 (29.6)	101 (31.0)
≥50%	109 (66.5)	113 (69.8)	222 (68.1)
Salvage status, n (%)			
First salvage	111 (67.7)	102 (63.0)	213 (65.3)
Second salvage	51 (31.1)	59 (36.4)	110 (33.7)
Prior HSCT, n (%)			
Yes	29 (17.7)	32 (19.8)	61 (18.7)
Baseline cytogenetics, n (%)			
Normal	46 (28.0)	42 (25.9)	88 (27.0)
Ph+	22 (13.4)	27 (16.7)	49 (15.0)
t(4;11)	6 (3.7)	8 (4.9)	14 (4.3)
Complex	28 (17.1)	22 (13.6)	50 (15.3)
Other	29 (17.7)	29 (17.9)	58 (17.8)
Duration of first remission, n (%)			
<12 months	96 (58.5)	106 (65.4)	202 (62.0)
≥12 months	68 (41.5)	56 (34.6)	124 (38.0)

ALL=acute lymphoblastic leukemia; HSCT=hematopoietic stem cell transplant; Ph+=Philadelphia chromosome–positive; SC=standard chemotherapy.

[a]As assessed by flow cytometry performed at a central laboratory.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY.

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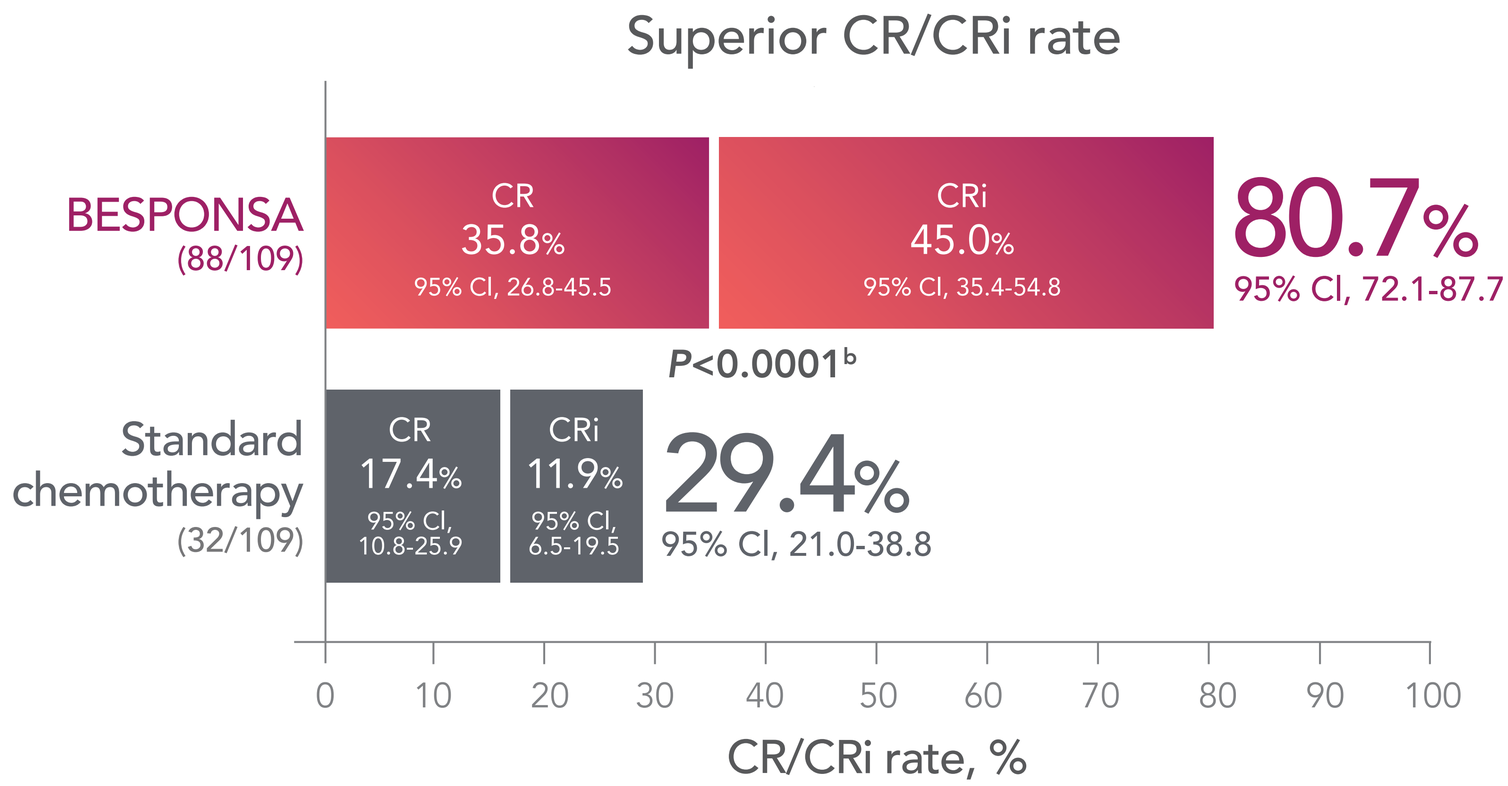
EFFICACY: CR/CRi

BESPONSA more than doubled the rate of CR/CRi[a] compared with SC[1,2]



Among patients in CR/CRi

- 64/88 (73%) responded in Cycle 1 and 21/88 (24%) responded in Cycle 2 in the BESPONSA arm
- 29/32 (91%) responded in Cycle 1 and 1/32 (3%) responded in Cycle 2 in the SC arm

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; SC=standard chemotherapy.

[a]CR, per the Endpoint Adjudication Committee (EAC), was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 × 10^9/L and absolute neutrophil counts [ANC] ≥1 × 10^9/L), and resolution of any extramedullary disease. CRi, per the EAC, was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets <100 × 10^9/L and/or ANC <1 × 10^9/L), and resolution of any extramedullary disease.

[b]1-sided *P* value using chi-square test.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY.

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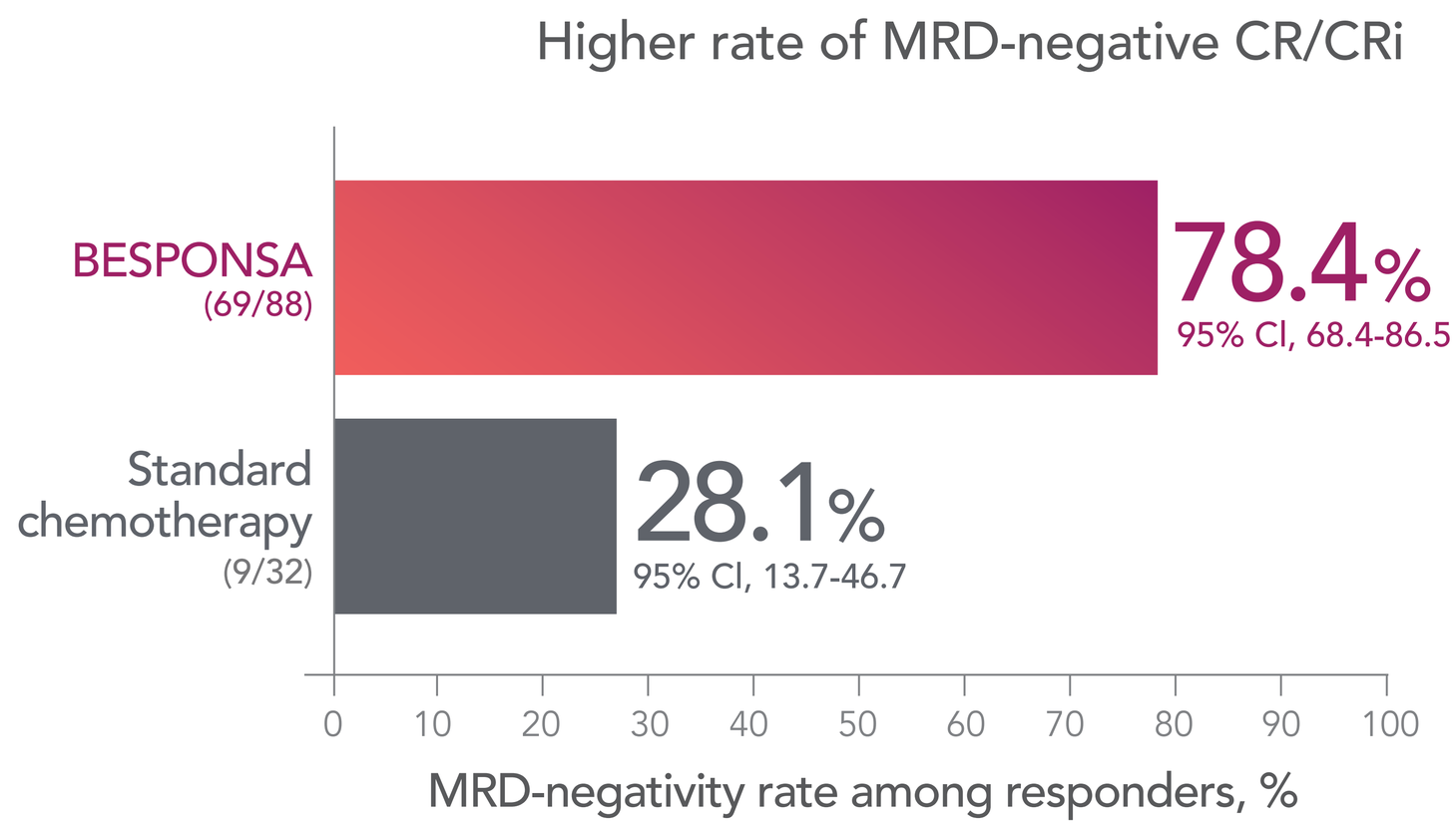
EFFICACY: MRD NEGATIVITY

MRD-negativity[a] rate among responding patients was more than double in patients receiving BESPONSA vs SC



- MRD-negative CR rate was 89.7% (35/39; 95% CI, 75.8-97.1) with BESPONSA vs 31.6% (6/19; 95% CI, 12.6-56.6) with SC
- MRD-negative CRi rate was 69.4% (34/49; 95% CI, 54.6- 81.7) with BESPONSA vs 23.1% (3/13; 95% CI, 5.0-53.8) with SC

- The median duration of remission[b] with BESPONSA was 5.4 months (95% CI, 4.2-8.0) compared with 3.5 months (95% CI, 2.9-6.6) with SC

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DoR=duration of remission; MRD=minimal residual disease; SC=standard chemotherapy.

[a]Patients were considered MRD negative when leukemic cells comprised $<1 \times 10^{-4}$ of bone marrow nucleated cells, as measured by flow cytometry.

[b]DoR, based on a later cutoff date than CR/CRi, was defined for patients who achieved CR/CRi per investigator's assessment as time since first response of CR/CRi per investigator's assessment to the date of a progression-free survival (PFS) event or censoring date if no PFS event was documented.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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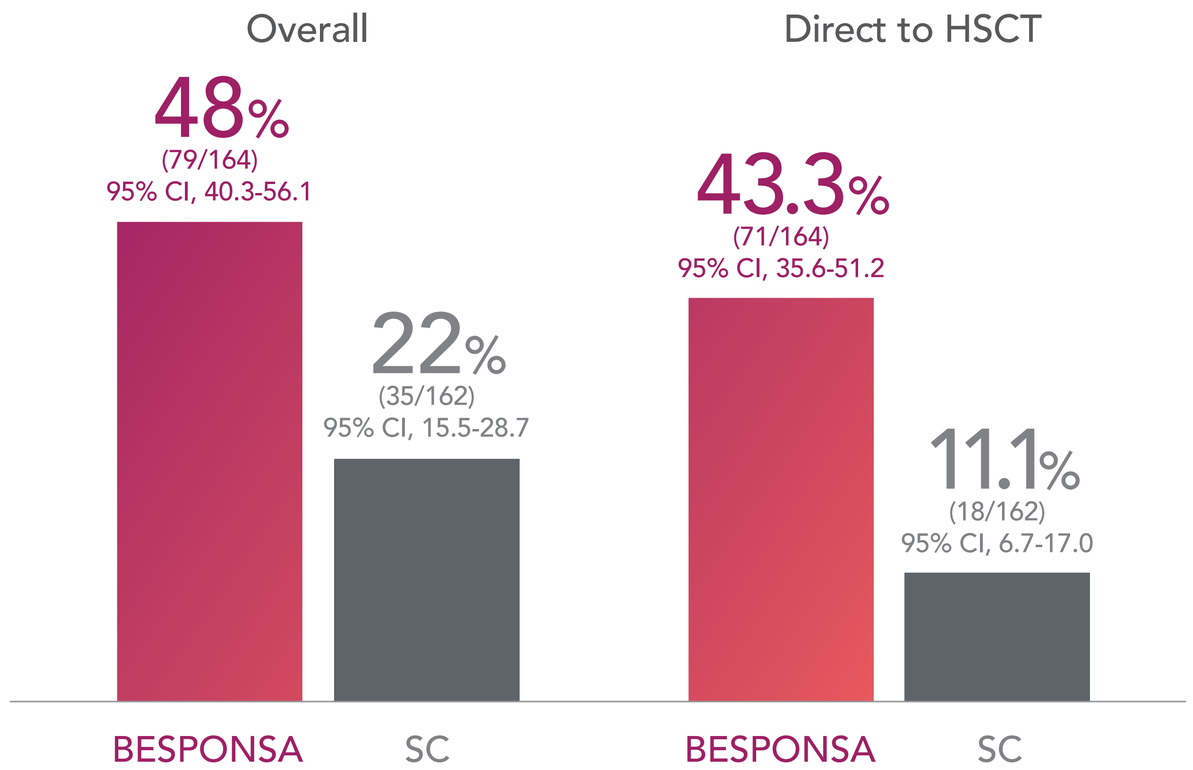
EFFICACY: HSCT

More patients proceeded to HSCT with BESPONSA

Rates of HSCT were more than double with BESPONSA vs SC[1,2]



- The median time from the last dose of BESPONSA to HSCT was 4.9 weeks (n=71; range, 1-19 weeks)

Consider involving the transplant team early in treatment planning, particularly when assessing a patient receiving BESPONSA for HSCT eligibility.

HSCT=hematopoietic stem cell transplant; SC=standard chemotherapy.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY.

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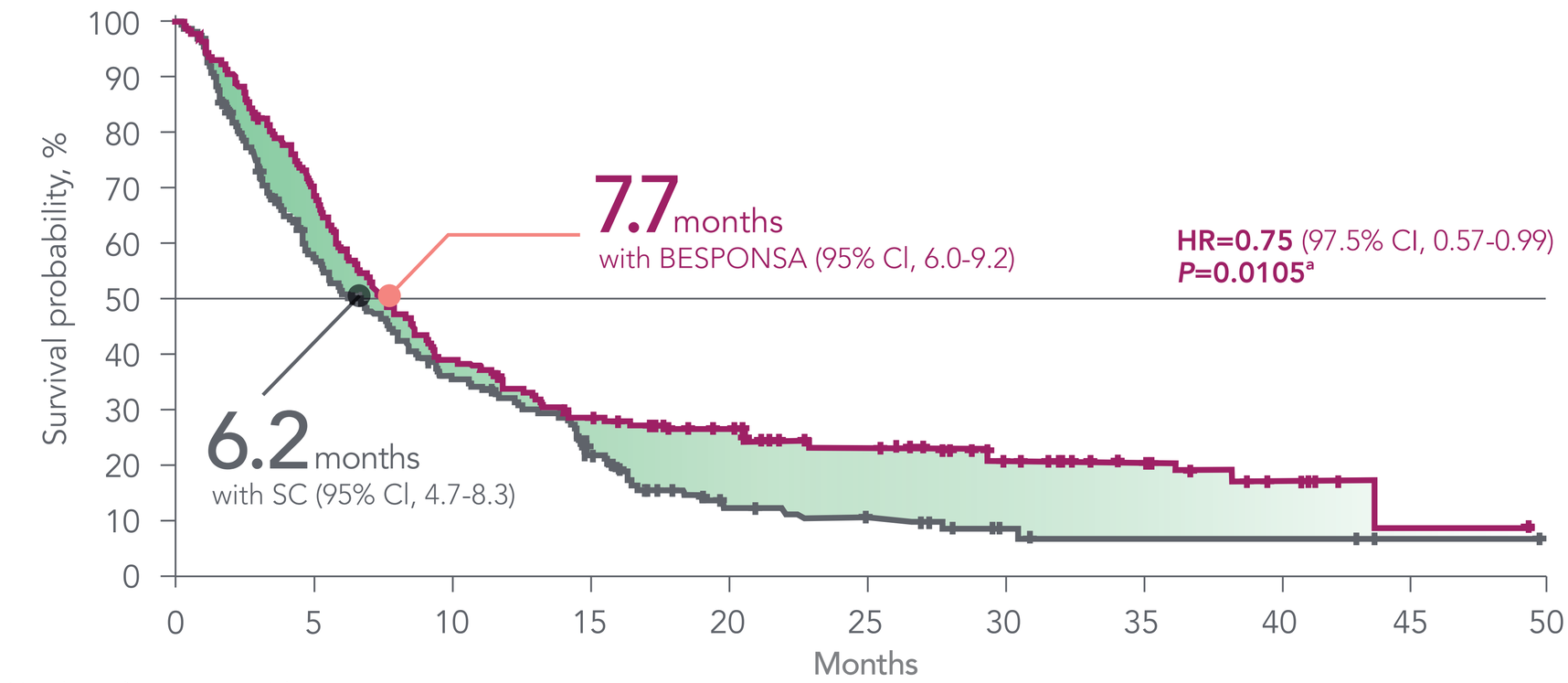
EFFICACY: MEDIAN OS

BESPONSA demonstrated a median OS of 7.7 months vs 6.2 months with SC, which represents a 25% relative reduction in the risk of death[1,2]

- The analysis of OS did not meet a prespecified boundary for statistical significance of *P*=0.0104



Number of patients at risk

BESPONSA	164	112	62	44	41	36	23	13	7	1	0
SC	162	85	51	30	17	14	5	3	3	1	0

CI=confidence interval; HR=hazard ratio; OS=overall survival; SC=standard chemotherapy.

[a]1-sided *P* value using log-rank test.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY.

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SAFETY

Summary of adverse reactions (ARs) in 164 patients receiving BESPONSA

- The most common (≥20%) ARs were thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinemia
- The most common (≥2%) serious ARs were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, VOD, and fatigue
- The most common (≥2%) ARs reported as the reason for permanent discontinuation were infection, thrombocytopenia, hyperbilirubinemia, transaminases increased, and hemorrhage
- The most common (≥5%) ARs reported as the reason for dosing interruption were neutropenia, infection, thrombocytopenia, transaminases increased, and febrile neutropenia
- The most common (≥1%) ARs reported as the reason for dose reduction were neutropenia, thrombocytopenia, and transaminases increased

VOD=hepatic veno-occlusive disease.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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SAFETY: HEPATIC VENO-OCCLUSIVE DISEASE (VOD)

Patient risk factors to consider when selecting and monitoring patients during BESPONSA treatment[1]:

- Increased age
- Later salvage lines
- Ongoing or prior liver disease
- Prior HSCT

Incidence of VOD in the INO-VATE ALL study[1-3]

- 23 out of 164 patients (14%) treated with BESPONSA experienced VOD
- 5 out of 164 patients (3%) experienced VOD during treatment with BESPONSA or in follow-up without an HSCT
- Overall, 79 out of 164 patients (48%) treated with BESPONSA proceeded to transplant
  - The risk of VOD was greater in patients who proceeded to HSCT
  - Among the 79 patients who proceeded to HSCT, 18 patients (23%) experienced VOD
  - In total, 5 fatal VOD events occurred post HSCT
  - The median time to VOD post HSCT was 15 days (range, 3-57)

Regional VOD Incidence	North America	Europe and Asia
Incidence of VOD in all patients	6.7% (5/75)	20.0% (18/89)
Incidence of VOD in post-HSCT patients	8.6%	34.1%

HSCT=hematopoietic stem cell transplant.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia [supplementary appendix]. *N Engl J Med.* 2016;375(8):740-753.

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MONITORING AND MANAGEMENT OF VOD

For patients proceeding to HSCT

During and after treatment with BESPONSA, there are several important recommendations to help mitigate the risk of VOD in patients proceeding to HSCT:

- **AVOID** the use of HSCT conditioning regimens containing dual alkylating agents
- **LIMIT** treatment with BESPONSA to 2 cycles for patients proceeding to HSCT[a]
- **MONITOR** total bilirubin. Total bilirubin ≥ ULN prior to HSCT was significantly associated with an increased risk of VOD
  - Monitor liver tests closely during the first month post HSCT, then less frequently thereafter according to standard medical practice

For all patients

- A greater number of treatment cycles with BESPONSA was associated with increased risk of VOD
- **MONITOR** closely for signs and symptoms of VOD; these may include elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites
- **MONITOR** liver tests, including ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose of BESPONSA
  - Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA
- Permanently **DISCONTINUE** BESPONSA if VOD (any grade) occurs

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; HSCT=hematopoietic stem cell transplant; MRD=minimal residual disease; ULN=upper limit of normal.

[a]A third cycle may be considered for patients who do not achieve CR/CRi and MRD-negativity after 2 cycles.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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SAFETY: POST-HSCT NON-RELAPSE MORTALITY (NRM)

- VOD and infections were the most common causes of post-HSCT NRM
- Overall, 48% (79/164) of patients in the BESPONSA arm and 22% (35/162) of patients in the SC arm had a follow-up HSCT
- Post-HSCT NRM was higher with BESPONSA (39%; 31/79) vs SC (23%; 8/35), resulting in a higher Day 100 mortality rate

HSCT=hematopoietic stem cell transplant; SC=standard chemotherapy; VOD=hepatic veno-occlusive disease.

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SAFETY: MYELOSUPPRESSION

Myelosuppression was observed in patients receiving BESPONSA

Monitoring and management of myelosuppression

- Monitor complete blood counts prior to each dose of BESPONSA, and monitor for signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression during treatment with BESPONSA
- As appropriate, administer prophylactic anti-infectives and employ surveillance testing during and after treatment with BESPONSA
- Management may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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SAFETY: INFUSION-RELATED REACTIONS

Incidence of infusion-related reactions

In the INO-VATE ALL study, infusion-related reactions were observed in patients treated with BESPONSA.

- Infusion-related reactions (all Grade 2) were reported in 4/164 (2%) patients
- Infusion-related reactions generally occurred in Cycle 1 shortly after the end of the BESPONSA infusion and resolved spontaneously or with medical management

Monitoring and management of infusion-related reactions

Premedicate with a corticosteroid, antipyretic, and antihistamine prior to dosing.

- Monitor patients closely during and for at least 1 hour after the end of infusion for the potential onset of infusion-related reactions, including symptoms such as fever, chills, rash, or breathing problems
- Interrupt the infusion and institute appropriate medical management if an infusion-related reaction occurs
- Depending on the severity of the infusion-related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines
- For severe or life-threatening infusion reactions, permanently discontinue BESPONSA

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SAFETY: QT INTERVAL PROLONGATION

Incidence of QT interval prolongation

In the INO-VATE ALL study, increases in QT interval corrected for heart rate using Fridericia's formula (QTcF) of ≥60 msec from baseline were measured in 4/162 (3%) patients.

- No patients had QTcF values greater than 500 msec
- Grade 2 QT prolongation was reported in 2/164 (1%) patients
- No ≥Grade 3 QT prolongation or events of Torsades de Pointes (TdP) were reported

Monitoring and management of QT interval prolongation

- Administer BESPONSA with caution in patients who have a history of or predisposition for QTc prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances
- Obtain electrocardiograms (ECGs) and electrolytes prior to the start of treatment, and after initiation of any drug known to prolong QTc, and periodically monitor as clinically indicated during treatment

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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SAFETY: EMBRYO-FETAL TOXICITY AND USE IN PATIENTS OF REPRODUCTIVE POTENTIAL

Management and patient counseling

BESPONSA can cause embryo-fetal harm when administered to pregnant women.

- Advise females of reproductive potential to avoid becoming pregnant while receiving BESPONSA
  - Females of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 8 months after the final dose of BESPONSA
  - Advise women to contact their healthcare provider if they become pregnant or if pregnancy is suspected during treatment with BESPONSA
- Advise males with female partners of reproductive potential to use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose of BESPONSA
- Inform pregnant women of the potential risk to the fetus
- Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with BESPONSA and for at least 2 months after the last dose

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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SAFETY: COMMON (≥10%) ADVERSE REACTIONS (1 of 2)

Common (≥10%) adverse reactions				
BODY SYSTEM ADVERSE REACTION	**BESPONSA** (N=164)		**SC** (N=143)	
	All grades, %	**Grade ≥3, %**	**All grades, %**	**Grade ≥3, %**
INFECTIONS				
Infection	48	28	76	54
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Thrombocytopenia	51	42	61	59
Neutropenia	49	48	45	43
Anemia	36	24	59	47
Leukopenia	35	33	43	42
Febrile neutropenia	26	26	53	53
Lymphopenia	18	16	27	26
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	12	1	13	2
NERVOUS SYSTEM DISORDERS				
Headache	28	2	27	1
VASCULAR DISORDERS				
Hemorrhage	33	5	28	5

SC=standard chemotherapy.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

Please see full Prescribing Information, including BOXED WARNING here, and Important Safety Information on pages 4-6.

BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

SAFETY: COMMON (≥10%) ADVERSE REACTIONS (2 of 2)

Common (≥10%) adverse reactions				
BODY SYSTEM ADVERSE REACTION	**BESPONSA** (N=164)		**SC** (N=143)	
	All grades, %	**Grade ≥3, %**	**All grades, %**	**Grade ≥3, %**
GASTROINTESTINAL DISORDERS				
Nausea	31	2	46	0
Abdominal pain	23	3	23	1
Diarrhea	17	1	38	1
Constipation	16	0	24	0
Vomiting	15	1	24	0
Stomatitis	13	2	26	3
HEPATOBILIARY DISORDERS				
Hyperbilirubinemia	21	5	17	6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	35	5	25	3
Pyrexia	32	3	42	6
Chills	11	0	11	0
INVESTIGATIONS				
Transaminases increased	26	7	13	5
Gamma-glutamyltransferase increased	21	10	8	4
Alkaline phosphatase increased	13	2	7	0

SC=standard chemotherapy.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

SAFETY: LABORATORY ABNORMALITIES

Laboratory abnormalities						
	BESPONSA			SC		
	n	All grades, %	Grade 3/4, %	n	All grades, %	Grades 3/4, %
HEMATOLOGY						
Platelet count decreased	161	98	76	142	100	99
Hemoglobin decreased	161	94	40	142	100	70
Leukocytes decreased	161	95	82	142	99	98
Neutrophil count decreased	160	94	86	130	93	88
Lymphocytes (absolute) decreased	160	93	71	127	97	91
CHEMISTRY						
GGT increased	148	67	18	111	68	17
AST increased	160	71	4	134	32	4
ALP increased	158	57	1	133	52	3
ALT increased	161	49	4	137	46	4
Blood bilirubin increased	161	36	5	138	35	6
Lipase increased	139	32	13	90	20	2
Hyperuricemia	158	16	3	122	11	0
Amylase increased	143	15	2	102	9	1

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; SC=standard chemotherapy.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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TREATMENT DURATION

The recommended number of cycles of BESPONSA will vary depending on both response to treatment and plans for further therapeutic intervention with HSCT.

For patients proceeding to HSCT	For patients not proceeding to HSCT
• The recommended duration of treatment with BESPONSA is 2 cycles • A third cycle may be considered for those patients who do not achieve CR/CRi and MRD-negativity after 2 cycles	• Up to a maximum of 6 cycles may be administered

Patients who do not achieve CR/CRi within 3 cycles should discontinue treatment.

CR=complete remission; CRi=complete remission with incomplete hematologic recovery; HSCT=hematopoietic stem cell transplant; MRD=minimal residual disease.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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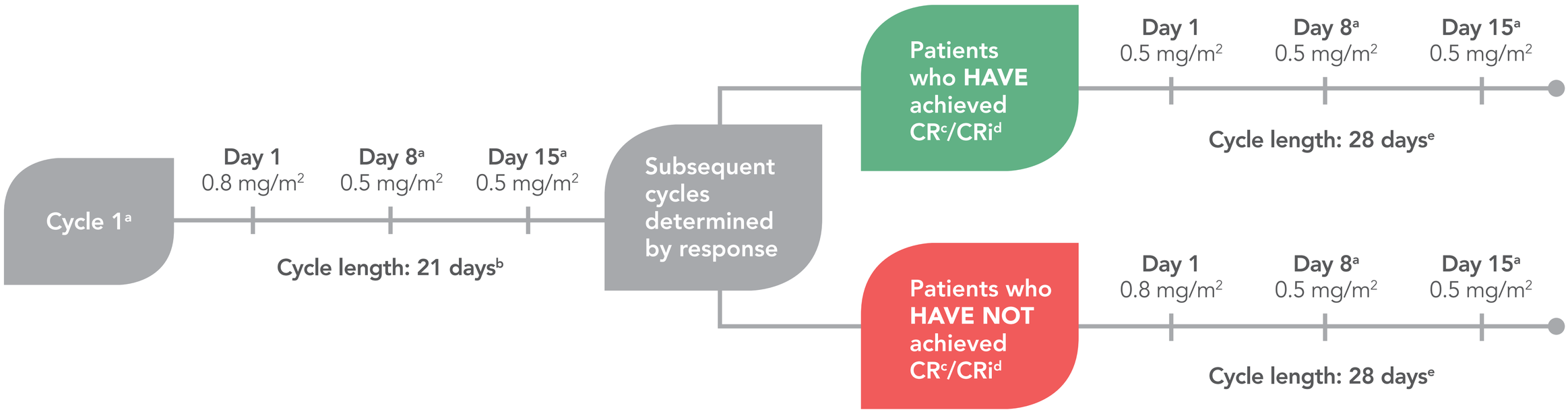
BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

DOSING

BESPONSA should be administered by 1-hour IV infusion on Days 1, 8, and 15 of each 3- to 4-week cycle



Premedicate before each dose

- Premedication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing

Cytoreduction

- For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count of less than or equal to 10,000/mm^3 is recommended prior to the first dose

CR=complete remission; CRi=complete remission with incomplete hematologic recovery; IV=intravenous.

Dose is based on the patient's body surface area (m^2).

[a]+/- 2 days (maintain minimum of 6 days between doses).

[b]For patients who achieve CR/CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (ie, 7-day treatment-free interval starting on Day 21).

[c]CR is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 x 10^9/L and absolute neutrophil counts [ANC] ≥1 x 10^9/L), and resolution of any extramedullary disease.

[d]CRi is defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets <100 x 10^9/L and/or ANC <1 x 10^9/L), and resolution of any extramedullary disease.

[e]7-day treatment-free interval starting on Day 21.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

DOSE MODIFICATIONS: HEMATOLOGIC TOXICITIES

If the dose is reduced due to BESPONSA-related toxicity, the dose must not be re-escalated

Criteria	Dose modification(s)
If prior to BESPONSA treatment ANC was ≥1 × 10^9/L	If ANC decreases, then interrupt the next cycle of treatment until recovery of ANC to ≥1 × 10^9/L • Discontinue BESPONSA if low ANC persists for greater than 28 days and is suspected to be related to BESPONSA
If prior to BESPONSA treatment platelet count was ≥50 × 10^9/L[a]	If platelet count decreases, then interrupt the next cycle of treatment until platelet count recovers to ≥50 × 10^9/L[a] • Discontinue BESPONSA if low platelet count persists for greater than 28 days and is suspected to be related to BESPONSA
If prior to BESPONSA treatment ANC was <1 × 10^9/L and/or platelet count was <50 × 10^9/L[a]	If ANC or platelet count decreases, then interrupt the next cycle of treatment until at least one of the following occurs: • ANC and platelet counts recover to at least baseline levels for the prior cycle, or • ANC recovers to ≥1 × 10^9/L and platelet count recovers to ≥50 × 10^9/L,[a] or • Stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease is considered to be due to the underlying disease (not considered to be related to BESPONSA)

- **Doses within a treatment cycle (ie, on Days 8 and/or 15) do not need to be interrupted due to neutropenia or thrombocytopenia**

ANC=absolute neutrophil count.

[a]Platelet count used for dosing should be independent of blood transfusion.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

Please see full Prescribing Information, including BOXED WARNING here, and Important Safety Information on pages 4-6.

BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

DOSE MODIFICATIONS: NONHEMATOLOGIC TOXICITIES

Nonhematologic toxicity	Dose modification(s)
VOD or other severe liver toxicity	Permanently discontinue treatment.
Total bilirubin >1.5 × ULN and AST/ALT >2.5 × ULN	Interrupt dosing until recovery of total bilirubin to ≤1.5 × ULN and AST/ALT to ≤2.5 × ULN prior to each dose unless due to Gilbert's syndrome or hemolysis. • Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 × ULN or AST/ALT does not recover to ≤2.5 × ULN
Infusion-related reaction	Interrupt the infusion and institute appropriate medical management. • Depending on the severity of the infusion-related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines • For severe or life-threatening infusion reactions, permanently discontinue treatment
Nonhematologic toxicity ≥Grade 2[a]	Interrupt treatment until recovery to Grade 1 or pretreatment grade levels prior to each dose.

- **Dose interruptions within a treatment cycle are recommended for nonhematologic toxicities**

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; VOD=hepatic veno-occlusive disease.
[a]Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.
Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

Please see full Prescribing Information, including BOXED WARNING here, and Important Safety Information on pages 4-6.

DOSE MODIFICATIONS: DOSE INTERRUPTION

Dose modifications depending on the duration of dosing interruption due to nonhematologic toxicities

Duration of dose interruption due to toxicity	Dose modification(s)
<7 days (within a cycle)	Interrupt the next dose (maintain a minimum of 6 days between doses).
≥7 days	Omit the next dose within the cycle.
≥14 days	Once adequate recovery is achieved, decrease the total dose by 25% for the subsequent cycle. • If further dose modification is required, then reduce the number of doses to 2 per cycle for subsequent cycles • If a 25% decrease in the total dose followed by a decrease to 2 doses per cycle is not tolerated, then permanently discontinue treatment
>28 days	Consider permanent discontinuation of treatment.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

PREPARATION AND ADMINISTRATION (1 of 2)

Dosing of BESPONSA is based on body surface area (BSA) and will vary by patient[1]

BESPONSA is supplied in a 0.9 mg single-dose vial for reconstitution and further dilution

- After calculating the patient dose (in mg) and number of vials needed, reconstitute each vial with 4 mL of Sterile Water for Injection, USP, to obtain a concentration of 0.25 mg/mL of BESPONSA that delivers 3.6 mL (0.9 mg)
  - Use reconstituted solution immediately or after refrigeration at 36-46°F (2-8°C) for up to 4 hours
- Withdraw the calculated patient dose from the vials and add the reconstituted solution to an infusion container with 0.9% Sodium Chloride Injection, USP, to obtain a total volume of 50 mL
  - Use diluted solution immediately or after storage at room temperature 68-77°F (20-25°C) for up to 4 hours or after being refrigerated at 36-46°F (2-8°C) for up to 3 hours
- Do not freeze the reconstituted or diluted solution

BESPONSA should be administered at room temperature 68-77°F (20-25°C) by IV infusion over 1 hour at a rate of 50 mL/h

- Maximum time from reconstitution through the end of administration is ≤8 hours
- Do not mix or administer BESPONSA as an infusion with other medicinal products

BESPONSA is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration.[1,2]

IV=intravenous; USP=United States Pharmacopeia.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY.

Please see full Prescribing Information, including BOXED WARNING here, and Important Safety Information on pages 4-6.

PREPARATION AND ADMINISTRATION (2 of 2)

Administration materials[1,2]

- Filtration is not required; however, if diluted solution is filtered, polyethersulfone (PES)-, polyvinylidene fluoride (PVDF)-, or hydrophilic polysulfone (HPS)-based filters are recommended
  - Do not use filters made of nylon or mixed cellulose ester (MCE)
- Infusion lines made of polyvinyl chloride (PVC), polypropylene, polyethylene, or polybutadiene are recommended
- Amber, dark brown, or green bags, or a foil light-protective covering should be used over the IV bag during dose administration

IV=intravenous.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** Data on file. Pfizer Inc., New York, NY.

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PATIENT COUNSELING (1 of 2)

Advice for patients	
Hepatotoxicity, including VOD	• Liver problems, including severe, life-threatening, or fatal VOD, and increases in liver tests may develop during BESPONSA treatment • Patients should seek immediate medical advice if they experience symptoms of VOD, which may include elevated bilirubin, rapid weight gain, and abdominal swelling that may be painful • Patients should carefully consider the benefit/risk of BESPONSA treatment if they have a prior history of VOD or serious ongoing liver disease
Increased risk of post-HSCT non-relapse mortality	• There is an increased risk of post-HSCT non-relapse mortality after receiving BESPONSA; the most common causes of post-HSCT non-relapse mortality included infection and VOD • Patients should report signs and symptoms of infection
Myelosuppression	• Decreased blood counts, which may be life-threatening, may develop during BESPONSA treatment; complications associated with decreased blood counts may include infections, which may be life-threatening or fatal, and bleeding/hemorrhage events • Signs and symptoms of infection, bleeding/hemorrhage, or other effects of decreased blood counts should be reported during treatment with BESPONSA

HSCT=hematopoietic stem cell transplant; VOD=hepatic veno-occlusive disease.

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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BESPONSA® inotuzumab ozogamicin INJECTION FOR IV INFUSION 0.9 mg single-dose vial

PATIENT COUNSELING (2 of 2)

Advice for patients	
Infusion-related reactions	• Contact their healthcare provider if they experience symptoms such as fever, chills, rash, or breathing problems during the infusion of BESPONSA
QT interval prolongation	• Symptoms that may indicate significant QTc prolongation include dizziness, lightheadedness, and syncope. Patients should report these symptoms and the use of all medications to their healthcare provider
Embryo-fetal toxicity	• Females of reproductive potential should avoid becoming pregnant while receiving BESPONSA – Females of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 8 months after the final dose of BESPONSA – Women should contact their healthcare provider if they become pregnant or if pregnancy is suspected during treatment with BESPONSA • Males with female partners of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose of BESPONSA • Inform pregnant women of the potential risk to the fetus • Because of the potential for adverse reactions in breastfed infants, women should not breastfeed during treatment with BESPONSA and for at least 2 months after the last dose
Lactation	• Women should not breastfeed while receiving BESPONSA and for 2 months after the last dose

Reference: BESPONSA Prescribing Information. New York, NY: Pfizer Inc.

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SUMMARY

BESPONSA is the first and only FDA-approved CD22-directed antibody-drug conjugate indicated for the treatment of adults with relapsed or refractory B-cell precursor ALL[1-3]

- The efficacy and safety of BESPONSA was established in the INO-VATE ALL study: a Phase 3, open-label, randomized trial vs standard chemotherapy
- The efficacy of BESPONSA was established on the basis of CR, duration of CR, and the proportion of MRD-negative CR in the first 218 randomized patients
- BESPONSA should be administered by 1-hour IV infusion on Days 1, 8, and 15 of each 3- to 4-week cycle
- BESPONSA has a **BOXED WARNING** for hepatotoxicity, including VOD, and increased risk of post-HSCT NRM

To learn more about BESPONSA, visit our website at **BesponsaHCP.com**

For access and support, call **1-877-744-5675** or visit **PfizerOncologyTogether.com**

ALL=acute lymphoblastic leukemia; CR=complete remission; HSCT=hematopoietic stem cell transplant; IV=intravenous; MRD=minimal residual disease; NRM=non-relapse mortality; VOD=hepatic veno-occlusive disease.

References: 1. BESPONSA Prescribing Information. New York, NY: Pfizer Inc. **2.** National Cancer Institute. http://www.cancer.gov/about-cancer/treatment/drugs/leukemia. Accessed June 5, 2019. **3.** Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(8):740-753.

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