**BESPONSA® (inotuzumab ozogamicin)**

BESPONSA® (inotuzumab ozogamicin) is an antibody-drug conjugate (ADC) composed of a monoclonal antibody (mAb) targeting CD22, a cell surface antigen expressed on cancer cells in almost all B-cell precursor acute lymphoblastic leukemia (ALL) patients, linked to a cytotoxic agent. Each dose of BESPONSA is administered as an IV infusion over a one-hour period.

BESPONSA is indicated for the treatment of adults with relapsed or refractory B-cell precursor ALL.

### ABOUT ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Acute lymphoblastic leukemia is an aggressive leukemia that can be fatal within a matter of months if left untreated.

While many potential treatments have been studied for relapsed or refractory ALL, only a limited number of medicines for these patients have been approved by the FDA and other regulatory authorities in the past decade.

### MECHANISM OF ACTION

BESPONSA is designed to bind to the CD22 antigen on B-cells via a monoclonal antibody (mAB) linked to a cytotoxic agent. Nonclinical data suggest once BESPONSA attaches to the CD22 antigen, the medicine is internalized by the cell, the cytotoxic agent calicheamicin is released causing cell death.

### INO-VATE ALL

The U.S. approval of BESPONSA was based on results from INO-VATE ALL, a Phase 3, randomized, open-label, international, multicenter trial that evaluated the safety and efficacy of BESPONSA compared with a defined set of chemotherapy choices in 326 adult patients with relapsed or refractory B-cell ALL.

The INO-VATE ALL study had two primary endpoints, complete response with or without hematologic remission (CR/CRi) and overall survival (OS).

Results of the trial demonstrated that:

- CR/CRi for patients treated with BESPONSA was 81% [95% CI: 72%-88%] vs 29% [95% CI: 21%-39%] for patients treated with chemotherapy.
- Among patients achieving CR/CRi, those treated with BESPONSA demonstrated higher rates of MRD-negativity (78% [95% CI: 68%-87%]) than those treated with chemotherapy (28% [95% CI: 14%-47%]).
Patients treated with BESPONSA had greater rates of hematologic stem cell transplantation (48%) compared to those treated with chemotherapy (22%).

The median overall survival (OS) for patients treated with BESPONSA was 7.7 months [95% CI: 6.0, 9.2] for patients taking BESPONSA compared to 6.2 months [95% CI: 4.7, 8.3] for patients receiving chemotherapy. The analysis of OS for patients treated with BESPONSA compared to chemotherapy did not meet the pre-specified boundary for statistical significance (HR: 0.75 [97.5% CI: 0.57-0.99]).

The U.S. labeling for BESPONSA includes a boxed warning for hepatotoxicity, including hepatic venoocclusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), and increased risk of post-HSCT non-relapse mortality. Venoocclusive disease, including fatal and life-threatening VOD, occurred in 14% of patients treated with BESPONSA. A higher post-HSCT non-relapse mortality rate occurred in patients treated with BESPONSA (39%) than chemotherapy (23%).

In patients treated with BESPONSA, the most common (≥ 20%) adverse reactions were thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinemia.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY, INCLUDING HEPATIC VENO-OCLUSIVE 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.

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.

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 Frederica’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.

Please see full Prescribing Information, including BOXED WARNING.