For adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL)

MAKING REMISSION* POSSIBLE

81% (88/109) of patients achieved remission* with BESPONSA compared to 29% (32/109) of patients with chemotherapy.

*Remission means that no leukemia cells can be seen when looking at bone marrow under a microscope. Remission rates include both complete remission (CR) and complete remission with incomplete hematologic recovery (CRi). CR means you are in remission, and that blood counts are in normal ranges. CRi also means you are in remission, but that some blood counts are not yet back within normal ranges.

The Food and Drug Administration approved BESPONSA based on the results of the clinical trial that showed treatment with BESPONSA compared to chemotherapy improved CR rates (36% vs 17%), length of CR (8.0 months vs 4.9 months), and minimal residual disease-negative (MRD-negative) CR rates (90% vs 32%). Once you have achieved remission, additional measurements can be taken using advanced tests that can detect minuscule amounts of leukemia cells that can’t be seen under a microscope. An MRD-negative remission means that no remaining leukemia cells can be detected.

INDICATION
BESPONSA® (inotuzumab ozogamicin) is a prescription medicine used to treat adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). It is not known if BESPONSA is safe and effective in children under 18 years of age.

SELECTED SAFETY INFORMATION
WARNING: RISK OF LIVER PROBLEMS AND INCREASED RISK OF DEATH AFTER STEM CELL TRANSPLANT
BESPONSA can cause liver problems that can be severe, life-threatening, or fatal, including a condition called veno-occlusive disease (VOD). This condition can occur during treatment with BESPONSA or following subsequent treatment with a stem cell transplant. This condition was more common in patients who had elevated liver tests or who received dual alkylating agents in preparation for their stem cell transplant. Patients may be at a higher risk of VOD if they:

- Receive a stem cell transplant after treatment with BESPONSA
- Are of older age
- Have previously received a stem cell transplant
- Received multiple treatments for their ALL prior to BESPONSA
- Have ongoing or a history of liver problems
- Receive a greater number of BESPONSA treatment cycles

Your doctor should perform liver tests periodically during treatment, and may modify or stop your treatment with BESPONSA.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
If you’re reading this brochure, you’ve probably just been told that your condition needs further treatment. This brochure may help you understand more about relapsed or refractory ALL, and explains why BESPONSA may be the right treatment option for you.

What you will find in this brochure:

- About acute lymphoblastic leukemia (ALL) ........................................ 3
- How BESPONSA works ........................................................................ 4
- How other patients responded ............................................................ 5
- Possible side effects ............................................................................... 8
- What to tell your doctor ...................................................................... 10
- When to contact your doctor ............................................................... 11
- Taking BESPONSA ............................................................................. 12
- Pfizer Oncology Together™ ................................................................. 14
- Additional resources ........................................................................... 16
- Talking with your doctor ................................................................... 17
- Important Safety Information .............................................................. 18

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- Liver problems: Call your doctor right away if you experience rapid weight gain, yellowing of the whites of the eyes, or abdominal swelling that may be painful. The risk of developing VOD is increased after receiving treatment with BESPONSA. Discuss with your doctor the benefit/risk of BESPONSA treatment if you have a prior history of VOD or serious ongoing liver disease

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
About acute lymphoblastic leukemia (ALL)

What is relapsed or refractory ALL?

<table>
<thead>
<tr>
<th>Relapsed ALL</th>
<th>Refractory ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>You achieved remission with your previous cancer treatment, but your ALL has returned.</td>
<td>Your ALL did not respond to the previous cancer treatment.</td>
</tr>
</tbody>
</table>

What are the goals of treatment in relapsed or refractory ALL?

- While the goals of treatment can differ for each patient, the primary goal of treatment in relapsed or refractory ALL is to achieve remission
- Some patients also hope to receive a stem cell transplant, which offers a chance for cure of their ALL

What are the treatment options for relapsed or refractory ALL?

The treatment landscape is evolving, and new therapies continue to become available. Your doctor will decide which treatment option is best for you. These may include:

- **Chemotherapy**
  You were likely prescribed chemotherapy as part of your initial ALL treatment regimen. Chemotherapy refers to a variety of drugs that damage or kill cells throughout the body.

- **Targeted therapies**
  Several different therapies are available that target specific proteins on ALL cells, such as CD19, CD22, and CD20.

- **Stem cell transplant**
  A procedure that replaces the blood-forming stem cells in your bone marrow with healthy cells, restoring normal blood cell growth.

- **CAR T-cell therapy**
  A gene therapy that can help your immune system to better recognize and fight your cancer, used in patients whose ALL is refractory to their prior treatment or who have relapsed multiple times.

- **Clinical trials**
  Clinical trials aim to study if an investigational therapy may offer a benefit to patients.

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- **Increased risk of death after stem cell transplant**: Call your doctor right away if you experience any signs and symptoms of infection or liver problems. There is an increased risk of death due to infection and VOD after receiving BESPONSA.

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
How BESPONSA works

How is BESPONSA different from chemotherapy?

- BESPONSA® (inotuzumab ozogamicin) is a type of medicine called an antibody-drug conjugate. BESPONSA is designed to find and attach to a specific protein, called CD22, found on leukemia cells.
- Once BESPONSA attaches to the CD22 protein, it enters the cell to deliver the drug, causing cell death.
- By specifically targeting CD22, BESPONSA may offer different benefits and tolerability than chemotherapy.

Why might BESPONSA be right to treat ALL?

- BESPONSA is the first and only therapy approved to target CD22, a specific protein that occurs on the surface of ALL cells.
- The CD22 protein is present on most leukemia cells in over 90% of patients with ALL, as well as on normal B cells, but is not present on most other types of healthy cells.

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- Low blood cell counts: Low blood cell counts and complications of low blood cell counts, including bleeding and infections, which may be severe, life-threatening, and fatal, have occurred with BESPONSA. **Call your doctor right away** if you experience signs and symptoms of infection (for example, redness, swelling), unexpected bleeding or bruising, blood in your urine or stools, or fever.

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
How was BESPONSA studied?

326 adults

BESPONSA was evaluated versus chemotherapy in a large, global clinical trial in 326 adults with relapsed or refractory ALL.

BESPONSA was studied in patients who were Philadelphia chromosome (Ph)-positive or Ph-negative in first or second relapse, or who were refractory to their previous treatment.

Helpful terms: 

Remission: Remission means that no leukemia cells can be seen when looking at bone marrow under a microscope. Remission rates include both complete remission (CR) and complete remission with incomplete hematologic recovery (CRi).

- CR means you are in remission, and that blood counts are in normal ranges
- CRi also means you are in remission, but that some blood counts are not yet back within normal ranges

MRD-negative (minimal residual disease–negative) remission: Once you have achieved remission, additional measurements can be taken using advanced tests that can detect minuscule amounts of leukemia cells that can’t be seen under a microscope.

- An MRD-negative remission means that no remaining leukemia cells can be detected

Length of remission: The period of time that patients are in a remission (either CR or CRi).

Median: The midpoint in a range of numbers, where exactly half of the numbers are below and half of the numbers are above that point.

The FDA approval of BESPONSA was based on results from the clinical trial that showed BESPONSA improved the rate of CR, the median length of CR, and the rate of MRD-negative CR versus chemotherapy.

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- Infusion-related reactions: Inform your doctor right away if you experience fever, chills, rash, or breathing problems during or following your BESPONSA infusion

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
How other patients responded (cont’d)

What were the results with BESPONSA compared to chemotherapy?

MORE PATIENTS ACHIEVED REMISSION

81%
(88/109)
of patients achieved remission with BESPONSA

- Remissions lasted a median of 5.4 months
- Of these 88 patients in remission, 78% (69/88) were MRD-negative

29%
(32/109)
of patients achieved remission with chemotherapy

- Remissions lasted a median of 3.5 months
- Of these 32 patients in remission, 28% (9/32) were MRD-negative

Of patients who received BESPONSA:
- 36% (39/109) achieved CR that lasted a median of 8.0 months, and 90% (35/39) of them were MRD-negative
- 45% (49/109) achieved CRi that lasted a median of 4.6 months, and 69% (34/49) of them were MRD-negative

Of patients who received chemotherapy:
- 17% (19/109) achieved CR that lasted a median of 4.9 months, and 32% (6/19) of them were MRD-negative
- 12% (13/109) achieved CRi that lasted a median of 2.9 months, and 23% (3/13) of them were MRD-negative

SELECTED SAFETY INFORMATION
BESPONSA may cause serious side effects, including:
- Heart problems: Call your doctor right away if you feel dizzy, lightheaded, or faint or have very slow, very fast, or abnormal heartbeats. Tell your doctor about all the medicines you take
How other patients responded (cont’d)

MORE PATIENTS WERE ABLE TO RECEIVE STEM CELL TRANSPLANT

48%  
(79/164)  
of patients received stem cell transplant after BESPONSA

22%  
(35/162)  
of patients received stem cell transplant after chemotherapy

Stem cell transplant is an important treatment option in relapsed or refractory ALL. Your doctor may want you to be in remission before receiving stem cell transplant.

In the clinical study, more patients were able to receive stem cell transplant after achieving remission with BESPONSA than with chemotherapy.

There was no difference found in the median length of time patients lived after treatment with BESPONSA compared to chemotherapy.

SELECTED SAFETY INFORMATION

Before taking BESPONSA, tell your doctor about all of your medical conditions, including if you:

- Have liver disease or a history of liver problems
- Have an infection
- Have ever experienced symptoms such as fever, chills, rash, or breathing problems during or shortly after your BESPONSA infusion
- Have heart problems, including an event of QT prolongation

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
BESPONSA is associated with a risk of liver problems and increased risk of death after stem cell transplant. BESPONSA can cause liver problems that can be severe, life-threatening, or fatal, including a condition called veno-occlusive disease (VOD). This condition can occur during treatment with BESPONSA or following subsequent treatment with a stem cell transplant. This condition was more common in patients who had elevated liver tests or who received dual alkylating agents in preparation for their stem cell transplant. Patients may be at a higher risk of VOD if they:

- Receive a stem cell transplant after treatment with BESPONSA
- Have previously received a stem cell transplant
- Have ongoing or a history of liver problems
- Are of older age
- Received multiple treatments for their ALL prior to BESPONSA
- Receive a greater number of BESPONSA treatment cycles

SELECTED SAFETY INFORMATION
Before taking BESPONSA, tell your doctor about all of your medical conditions, including if you:

- Are pregnant, plan to become pregnant, or if pregnancy is suspected while taking BESPONSA. Avoid becoming pregnant during treatment with BESPONSA. BESPONSA can cause harm to an unborn baby
  - Females who are able to become pregnant should use effective contraception during treatment with BESPONSA and for at least 8 months after the last dose
  - Males of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose
Possible side effects (cont’d)

Serious side effects
BESPONSA may cause serious side effects that can be severe, life-threatening, or even lead to death. These include:

- Liver problems, including a condition called hepatic VOD
- Increased risk of death after stem cell transplant
- Low blood cell counts
- Infusion-related reactions
- Heart problems
- Harm to an unborn baby

Common side effects
The most common side effects experienced with BESPONSA were:

- Low platelet counts (thrombocytopenia)
- Fatigue
- Low white blood cell counts with and without fever (neutropenia, febrile neutropenia, and leukopenia)
- Infection
- Bleeding
- Pain in the abdomen
- Fever
- Nausea
- Headache
- Low red blood cell counts (anemia)
- Increases in lab tests measuring liver function

SELECTED SAFETY INFORMATION
Before taking BESPONSA, tell your doctor about all of your medical conditions, including if you:

- Are breastfeeding or plan to breastfeed. Avoid breastfeeding during treatment with BESPONSA and for at least 2 months after the final dose
Tell your doctor about all of your medical conditions, including if you:

- **Have a history of liver problems**, liver disease, or a condition called VOD
- **Have an infection**
- **Have ever experienced symptoms such as fever, chills, rash, or breathing problems** during or shortly after the BESPONSA infusion
- **Have heart problems**, including a condition called QT prolongation
- **Are pregnant**, plan to become pregnant, or if pregnancy is suspected while taking BESPONSA. Avoid becoming pregnant during treatment with BESPONSA. BESPONSA can cause harm to an unborn baby
  - Females who are able to become pregnant should use effective contraception during treatment with BESPONSA and for at least 8 months after the last dose
  - Males of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose
- **Are breastfeeding or plan to breastfeed**. Avoid breastfeeding during treatment with BESPONSA and for at least 2 months after the final dose

**SELECTED SAFETY INFORMATION**

**Common Side Effects of BESPONSA**

The most common side effects are low platelet counts (thrombocytopenia), low white blood cell counts with and without fever (neutropenia, febrile neutropenia, and leukopenia), infection, low red blood cell counts (anemia), fatigue, bleeding, fever, nausea, headache, increases in lab tests measuring liver function, and pain in the abdomen.
When to contact your doctor

Call your doctor right away if you experience any of the signs and symptoms associated with the following side effects:

- Liver problems, including a condition called VOD: Rapid weight gain, yellowing of the white of the eyes, or abdominal swelling that may be painful
  - The risk of developing VOD is increased after receiving treatment with BESPONSA
- Low blood cell counts: Signs and symptoms of infection (for example, redness or swelling), unexpected bleeding or bruising, blood in your urine or stools, or fever
- Signs and symptoms of infection
- Infusion-related reactions: Fever, chills, rash, or breathing problems during or following the BESPONSA infusion
- Heart problems: Dizziness, lightheadedness, or fainting, or very slow, very fast, or abnormal heartbeats

These are not all the possible side effects of BESPONSA. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. For more information, ask your doctor or pharmacist.

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- Liver problems: Call your doctor right away if you experience rapid weight gain, yellowing of the whites of the eyes, or abdominal swelling that may be painful. The risk of developing VOD is increased after receiving treatment with BESPONSA. Discuss with your doctor the benefit/risk of BESPONSA treatment if you have a prior history of VOD or serious ongoing liver disease

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
Taking BESPONSA® (inotuzumab ozogamicin)

How is BESPONSA given?

BESPONSA is a prescription medicine given over a 1-hour period by intravenous (IV) infusion. IV infusion may be the same way you received chemotherapy treatments in the past.

- Prior to your infusion, you will be given a steroid, acetaminophen, and an antihistamine to help reduce the chance of infusion reactions.
- You may be observed for an hour after your infusion.
- BESPONSA is not mixed with chemotherapy or any other anticancer drugs.

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- Increased risk of death after stem cell transplant: Call your doctor right away if you experience any signs and symptoms of infection or liver problems. There is an increased risk of death due to infection and VOD after receiving BESPONSA

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
When will I receive BESPONSA?

BESPONSA IS GIVEN ONCE A WEEK, FOR 3 OR 4 WEEKS PER CYCLE

<table>
<thead>
<tr>
<th>DOSE 1</th>
<th>DOSE 2</th>
<th>DOSE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Week 2</td>
<td>Week 3 or 4</td>
</tr>
</tbody>
</table>

Treatment cycles may last between 3 and 4 weeks. Your doctor may delay or skip a dose based on your specific response or needs.

How long will treatment with BESPONSA last?

You may receive only 1 or up to 6 treatment cycles of BESPONSA. Your doctor will determine the number of treatment cycles that is right for you.

- If your doctor plans for you to receive a transplant, you may receive only 2 or 3 treatment cycles of BESPONSA
- If you do not achieve remission by the third cycle, your doctor should stop treating you with BESPONSA

Where will I receive BESPONSA?

- BESPONSA may be given in an outpatient setting, and you may be able to return home after your infusion
- Your doctor will determine if a hospital stay is needed based on your overall health

SELECTED SAFETY INFORMATION

BESPONSA may cause serious side effects, including:

- Low blood cell counts: Low blood cell counts and complications of low blood cell counts, including bleeding and infections, which may be severe, life-threatening, and fatal, have occurred with BESPONSA. **Call your doctor right away** if you experience signs and symptoms of infection (for example, redness, swelling), unexpected bleeding or bruising, blood in your urine or stools, or fever

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
Financial assistance
We’re committed to helping you get your prescribed BESPONSA medicine. Pfizer Oncology Together can help you understand your insurance and identify what financial support may be available.

- **Commerically insured**
  Resources for eligible commercial, private, employer, and state health insurance marketplace patients.

- **Medicare/government insured**
  Help identifying resources for patients with Medicare, Medicaid, and other government insurance plans.

- **Uninsured**
  Help identifying resources for patients without any form of healthcare coverage.

For live, personalized support, visit PfizerOncologyTogether.com or call 1-877-744-5675 (Monday-Friday 8 AM-8 PM ET).

SELECTED SAFETY INFORMATION
BESPONSA may cause serious side effects, including:

- **Infusion-related reactions**: Inform your doctor right away if you experience fever, chills, rash, or breathing problems during or following your BESPONSA infusion

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
**Personalized support**
Managing day-to-day life after diagnosis can be overwhelming, but you don’t have to do it alone. With Pfizer Oncology Together, you’ll have a dedicated point of contact who will talk with you one-on-one and provide you with resources to help with some of the day-to-day challenges you may be facing.*

**Emotional support**
Find resources for emotional support and other daily challenges. These resources include an independent organization’s helpline, support groups, and a free app designed to help you connect with loved ones.

**Ongoing education**
Get guidance on living with your condition, including nutritional information, communication tips, and toolkits specific to your prescribed medicine.

**Transportation and lodging**
Connect to an independent organization that helps eligible patients find rides and lodging for treatment-related appointments.

**Workplace guidance**
Receive information to help you prepare for leaving or returning to work after being diagnosed.

**Financial support**
Get help identifying financial assistance resources—regardless of your insurance coverage.

*Some services are provided through third-party organizations that operate independently and are not controlled by Pfizer. Availability of services and eligibility requirements are determined solely by these organizations.

**SELECTED SAFETY INFORMATION**
BESPONSA may cause serious side effects, including:

- **Heart problems:** Call your doctor right away if you feel dizzy, lightheaded, or faint or have very slow, very fast, or abnormal heartbeats. Tell your doctor about all the medicines you take.

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
Additional resources

In this section, you will find a list of additional resources for information on ALL, as well as support groups for both patients and their caregivers.

Information and support groups

<table>
<thead>
<tr>
<th>Information and support groups</th>
<th>Website URL</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Leukemia &amp; Lymphoma Society</td>
<td><a href="http://www.lls.org">www.lls.org</a></td>
<td>1-800-955-4572</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td><a href="http://www.cancer.org">www.cancer.org</a></td>
<td>1-800-227-2345</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td><a href="http://www.cancer.gov">www.cancer.gov</a></td>
<td>1-800-422-6237</td>
</tr>
</tbody>
</table>

Facing cancer isn’t easy, but Pfizer’s LivingWith™ may help

LivingWith™ is a free app for people living with cancer and those who love them. Designed to help you connect with loved ones, ask for the support you need, remember important information from doctor’s visits, and stay organized, all in one place.

Visit ThisIsLivingWithCancer.com to learn more. Available in English and Spanish. Download LivingWith™ for free. The LivingWith™ app is available to anyone living with cancer and their caregivers, and is not specific to BESPONSA.

SELECTED SAFETY INFORMATION

Before taking BESPONSA, tell your doctor about all of your medical conditions, including if you:

- Have liver disease or a history of liver problems
- Have an infection
- Have ever experienced symptoms such as fever, chills, rash, or breathing problems during or shortly after your BESPONSA infusion
- Have heart problems, including an event of QT prolongation

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
Talking with your doctor

While taking BESPONSA, it is important that you feel informed and comfortable with your treatment plan.

**Suggested questions to help discuss your treatment**

- What makes BESPONSA an appropriate treatment choice for me?
- How will I be treated with BESPONSA?
- Can I continue working during treatment?
- Can I be on other medications during my treatment with BESPONSA?
- Is there anything I can do to help with side effects?
- Could stem cell transplant or other additional therapies be an option after treatment with BESPONSA?
- How will treatment with BESPONSA impact my daily life and future plans?

**If you have other questions, write them down, so you remember to ask your doctor**

SELECTED SAFETY INFORMATION

Before taking BESPONSA, tell your doctor about all of your medical conditions, including if you:

- Are pregnant, plan to become pregnant, or if pregnancy is suspected while taking BESPONSA. Avoid becoming pregnant during treatment with BESPONSA. BESPONSA can cause harm to an unborn baby
  - Females who are able to become pregnant should use effective contraception during treatment with BESPONSA and for at least 8 months after the last dose
  - Males of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose
Important Safety Information

WARNING: RISK OF LIVER PROBLEMS AND INCREASED RISK OF DEATH AFTER STEM CELL TRANSPLANT

BESPONSA can cause liver problems that can be severe, life-threatening, or fatal, including a condition called veno-occlusive disease (VOD). This condition can occur during treatment with BESPONSA or following subsequent treatment with a stem cell transplant. This condition was more common in patients who had elevated liver tests or who received dual alkylating agents in preparation for their stem cell transplant. Patients may be at a higher risk of VOD if they:

- Receive a stem cell transplant after treatment with BESPONSA
- Have previously received a stem cell transplant
- Have ongoing or a history of liver problems
- Are of older age
- Received multiple treatments for their ALL prior to BESPONSA
- Receive a greater number of BESPONSA treatment cycles

Your doctor should perform liver tests periodically during treatment, and may modify or stop your treatment with BESPONSA.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

BESPONSA may cause serious side effects, including:

- Liver problems: Call your doctor right away if you experience rapid weight gain, yellowing of the whites of the eyes, or abdominal swelling that may be painful. The risk of developing VOD is increased after receiving treatment with BESPONSA. Discuss with your doctor the benefit/risk of BESPONSA treatment if you have a prior history of VOD or serious ongoing liver disease
- Increased risk of death after stem cell transplant: Call your doctor right away if you experience any signs and symptoms of infection or liver problems. There is an increased risk of death due to infection and VOD after receiving BESPONSA
- Low blood cell counts: Low blood cell counts and complications of low blood cell counts, including bleeding and infections, which may be severe, life-threatening, and fatal, have occurred with BESPONSA. Call your doctor right away if you experience signs and symptoms of infection (for example, redness, swelling), unexpected bleeding or bruising, blood in your urine or stools, or fever
- Infusion-related reactions: Inform your doctor right away if you experience fever, chills, rash, or breathing problems during or following your BESPONSA infusion
- Heart problems: Call your doctor right away if you feel dizzy, lightheaded, or faint or have very slow, very fast, or abnormal heartbeats. Tell your doctor about all the medicines you take

Please see full Prescribing Information, including BOXED WARNING, at the end of this brochure.
Before taking BESPONSA, tell your doctor about all of your medical conditions, including if you:

- Have liver disease or a history of liver problems
- Have an infection
- Have ever experienced symptoms such as fever, chills, rash, or breathing problems during or shortly after your BESPONSA infusion
- Have heart problems, including an event of QT prolongation
- Are pregnant, plan to become pregnant, or if pregnancy is suspected while taking BESPONSA. Avoid becoming pregnant during treatment with BESPONSA. BESPONSA can cause harm to an unborn baby
  - Females who are able to become pregnant should use effective contraception during treatment with BESPONSA and for at least 8 months after the last dose
  - Males of reproductive potential should use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose
- Are breastfeeding or plan to breastfeed. Avoid breastfeeding during treatment with BESPONSA and for at least 2 months after the final dose

Common Side Effects of BESPONSA

The most common side effects are low platelet counts (thrombocytopenia), low white blood cell counts with and without fever (neutropenia, febrile neutropenia, and leukopenia), infection, low red blood cell counts (anemia), fatigue, bleeding, fever, nausea, headache, increases in lab tests measuring liver function, and pain in the abdomen.

These are not all of the possible side effects of BESPONSA. Tell your doctor if you have any side effect that bothers you or that does not go away. For more information, ask your doctor or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

INDICATION

BESPONSA is a prescription medicine used to treat adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). It is not known if BESPONSA is safe and effective in children under 18 years of age.

Please see full Prescribing Information, including BOXED WARNING, at the end of this brochure.
For more information, visit BESPONSA.com

Please see Important Safety Information on pages 18-19 and full Prescribing Information, including BOXED WARNING, at the end of this brochure.
BESPONSA is a CD22-directed antibody-drug conjugate (ADC) indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

**INDICATIONS AND USAGE**

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

**DOSAGE AND ADMINISTRATION**

- **Pre-medicate with a corticosteroid, antipyretic, and antihistamine prior to all infusions.**
- **Dosing regimens for Cycle 1 and subsequent cycles, depending on the response to treatment,** are shown below. See full prescribing information for dosing details.

<table>
<thead>
<tr>
<th>Dosing regimen for Cycle 1</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients:</td>
<td>0.8 mg/m²</td>
<td>0.5 mg/m²</td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Cycle length</td>
<td>21 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing regimen for subsequent cycles depending on response to treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who have achieved a CR or CRi:</td>
<td>0.5 mg/m²</td>
<td>0.5 mg/m²</td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Cycle length</td>
<td>28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who have not achieved a CR or CRi:</td>
<td>0.8 mg/m²</td>
<td>0.5 mg/m²</td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Cycle length</td>
<td>28 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**WARNINGS AND PRECAUTIONS**

- **Hepatotoxicity**: See full prescribing information for complete boxed warning.
- **Hepatotoxicity, including fatal and life-threatening VOD occurred in patients who received BESPONSA.**
- **A higher post-HSCT non-relapse mortality rate occurred in patients receiving BESPONSA.**

**ADVERSE REACTIONS**

- QT interval prolongation: Obtain electrocardiograms (ECGs) and electrolytes at baseline and monitor during treatment. Monitor more frequently when using concomitant medications known to prolong QT interval.
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

**CONTRAINDICATIONS**

- None

**DRUG INTERACTIONS**

- See full prescribing information for instructions on reconstitution of lyophilized powder, and preparation and administration of reconstituted drug.

**USE IN SPECIFIC POPULATIONS**

- Lactation: Advise not to breastfeed.

**Pregnancy**

- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

**NONCLINICAL TOXICOLOGY**

- 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

**DESCRIPTION**

- The most common (> 20%) adverse reactions are thrombocytopenia, neutropenia, infection, anemia, fatigue, hemorrhage, pyrexia, nausea, headache, and hyperbilirubinemia.

**CLINICAL STUDIES**

- To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Table 1 shows the recommended dosing regimens.

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- **Pre-medicate before each dose** [see Dosage and Administration (2.2)].
- For the first cycle, the recommended total dose of BESPONSA for all patients is 1.8 mg/m² per cycle, administered as 3 divided doses on Day 1 (0.8 mg/m²), Day 8 (0.5 mg/m²), and Day 15 (0.5 mg/m²). Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), and/or to allow recovery from toxicity.
- For subsequent cycles:
  - In patients who achieve a CR or CRi, the recommended total dose of BESPONSA is 1.5 mg/m² per cycle, administered as 3 divided doses on Day 1 (0.5 mg/m²), Day 8 (0.5 mg/m²), and Day 15 (0.5 mg/m²). Subsequent cycles are 4 weeks in duration.
  - OR
  - In patients who do not achieve a CR or CRi, the recommended total dose of BESPONSA is 1.8 mg/m² per cycle given as 3 divided doses on Day 1 (0.8 mg/m²), Day 8 (0.5 mg/m²), and Day 15 (0.5 mg/m²). Subsequent cycles are 4 weeks in duration.
  - OR
  - For patients proceeding to hematopoietic stem cell transplant (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 or CRi and minimal residual disease (MRD) negativity after 2 cycles [see Warnings and Precautions (5.1)].
  - OR
  - For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered.

Table 1 shows the recommended dosing regimens.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing regimen for Cycle 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.8 mg/m²</td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Cycle length</td>
<td>21 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Dosing regimen for subsequent cycles depending on response to treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who have achieved a CR&lt;sup&gt;c&lt;/sup&gt; or CRi&lt;sup&gt;d&lt;/sup&gt;:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.5 mg/m²</td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Cycle length</td>
<td>28 days&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Patients who have not achieved a CR&lt;sup&gt;c&lt;/sup&gt; or CRi&lt;sup&gt;d&lt;/sup&gt;:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.8 mg/m²</td>
<td>0.5 mg/m²</td>
</tr>
<tr>
<td>Cycle length</td>
<td>28 days&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR-complete remission; CRi-complete remission with incomplete hematologic recovery.
<sup>a</sup> 1-2 days (maintain minimum of 6 days between doses).
<sup>b</sup> Dose is based on the patient’s body surface area (m²).
<sup>c</sup> For patients who achieve a CR or a CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e., 7-day treatment-free interval starting on Day 21).
<sup>d</sup> CR is defined as < 5% blasts in the bone marrow and the absence of peripheral blood blasts. Full recovery of peripheral blood counts (platelets ≥ 100 × 10⁹/L and absolute neutrophil counts [ANC] ≥ 1 × 10⁹/L) and resolution of any extramedullary disease.
<sup>e</sup> CRi is defined as < 5% blasts in the bone marrow and the absence of peripheral blood blasts. Incomplete recovery of peripheral blood counts (platelets < 100 × 10⁹/L and/or ANC < 1 × 10⁹/L) and resolution of any extramedullary disease.
<sup>f</sup> 7-day treatment-free interval starting on Day 21.

2.2 Recommended Pre-medications and Cyto reduction

- Premedication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing. Patients should be observed during and for at least 1 hour after the end of infusion for symptoms of infusion related reactions [see Warnings and Precautions (5.4)].
- For patients with circulating lymphoblasts, cyto reduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count of less than or equal to 10,000/mm³ is recommended prior to the first dose.

2.3 Dose Modification

Modify the dose of BESPONSA for toxicities (see Tables 2-4). BESPONSA doses within a treatment cycle (i.e., Days 8 and/or 15) do not need to be interrupted due to neutropenia or thrombocytopenia, but dosing interruptions within a cycle are recommended for non-hematologic toxicities. If the dose is reduced due to BESPONSA-related toxicity, the dose must not be re-escalated.

Table 2. BESPONSA Dose Modifications for Hematologic Toxicities

<table>
<thead>
<tr>
<th>Criteria</th>
<th>BESPONSA Dose Modification(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If prior to BESPONSA treatment ANC was greater than or equal to 1 × 10⁹/L. Discontinue BESPONSA if low ANC persists for greater than 28 days and is suspected to be related to BESPONSA.</td>
<td></td>
</tr>
<tr>
<td>If prior to BESPONSA treatment platelet count was greater than or equal to 50 × 10⁹/L.</td>
<td></td>
</tr>
<tr>
<td>If prior to BESPONSA treatment ANC was less than 1 × 10⁹/L and/or platelet count was less than 50 × 10⁹/L.</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. BESPONSA Dose Modifications for Non-hematologic Toxicities

<table>
<thead>
<tr>
<th>Non-hematologic Toxicity</th>
<th>Dose Modification(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOD or other severe liver toxicity</td>
<td>Permanently discontinue treatment [see Warnings and Precautions (5.1)].</td>
</tr>
<tr>
<td>Total bilirubin greater than 1.5 × ULN and AST/ALT greater than 2.5 × ULN</td>
<td>Interrupt dosing until recovery of total bilirubin to less than or equal to 1.5 × ULN and AST/ALT to less than or equal 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 less than or equal to 1.5 × ULN or AST/ALT does not recover to less than or equal to 2.5 × ULN [see Warnings and Precautions (5.4)].</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>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 [see Warnings and Precautions (5.4)].</td>
</tr>
<tr>
<td>Non-hematologic toxicity greater than or equal to Grade 2&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.</td>
</tr>
</tbody>
</table>

Abbreviations: ALT-alanine aminotransferase; AST-aspartate aminotransferase; ULN=upper limit of normal; VOD=venoocclusive disease.
<sup>g</sup> Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.
2.4 Instructions for Reconstitution, Dilution, and Administration

Protect the reconstituted and diluted BESPONSA solutions from light. Do not freeze the reconstituted or diluted solution.

The maximum time from reconstitution through the end of administration should be less than or equal to 8 hours, with less than or equal to 4 hours between reconstitution and dilution.

Reconstitution:

- BESPONSA is a cytotoxic drug. Follow applicable special handling and disposal procedures.
- Calculate the dose (mg) and number of vials of BESPONSA required.
- 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 mg (0.9 mg).
- Gently swirl the vial to aid dissolution. DO NOT SHAKE.
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to opalescent, colorless to slightly yellow, and essentially free of visible foreign matter.
- See Table 5 for storage times and conditions for the reconstituted solution.

Dilution:

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to the patient’s body surface area. Withdraw this amount from the vial(s) using a syringe. Discard any unused reconstituted BESPONSA solution left in the vial.
- Add reconstituted solution to an infusion container with 0.9% Sodium Chloride Injection, USP, to make a total volume of 50 mL. An infusion container made of polyvinyl chloride (PVC) (di(2-ethylhexyl)phthalate (DEHP)- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or ethylene vinyl acetate (EVA) is recommended.
- Gently invert the infusion container to mix the diluted solution. DO NOT SHAKE.
- See Table 5 for storage times and conditions for the diluted solution.

Administration:

- See Table 5 for storage times and conditions for prior to and during administration of the diluted solution.
- Filteration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES)-, polyvinylidene fluoride (PVDF)-, or hydrophilic polyolefin (polypropylene and/or polyethylene), or polybutadiene are recommended. Do not mix BESPONSA or administer as an infusion with other medicinal products.

Do not mix BESPONSA or administer as an infusion with other medicinal products.

Table 5 shows the storage times and conditions for reconstitution, dilution, and administration of BESPONSA.

---

### Table 4. BESPONSA Dosage Modifications Depending on Duration of Dosing Interruption Due to Non-Hematologic Toxicity Toxicities

<table>
<thead>
<tr>
<th>Duration of Dose Interruption Due to Toxicity</th>
<th>Dose Modification(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 7 days (within a cycle)</td>
<td>Interrupt the next dose (maintain a minimum of 6 days between doses).</td>
</tr>
<tr>
<td>Greater than or equal to 7 days</td>
<td>Omit the next dose within the cycle.</td>
</tr>
<tr>
<td>Greater than or equal to 14 days</td>
<td>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.</td>
</tr>
<tr>
<td>Greater than 28 days</td>
<td>Consider permanent discontinuation of treatment.</td>
</tr>
</tbody>
</table>

---

### Table 5. Storage Times and Conditions for Reconstituted and Diluted BESPONSA Solution

<table>
<thead>
<tr>
<th>Maximum time from reconstitution through end of administration less than or equal to 8 hours*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstituted Solution</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>BESPONSA contains no bacteriostatic preservatives</td>
</tr>
</tbody>
</table>

---

*With less than or equal to 4 hours between reconstitution and dilution.

---

3. **DOSE FORMS AND STRENGTHS**

For Injection: 0.9 mg as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution.

4. **CONTRAINDICATIONS**

None.

5. **WARNINGS AND PRECAUTIONS**

5.1 Hepatotoxicity, Including Hepatic Veno-occlusive Disease (VOD) (also known as Sinusoidal Obstruction Syndrome)

In the INO-VATE ALL trial, hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD was observed in 23/164 patients (14%) in the BESPONSA arm during or following treatment or following a HSCT after completion of treatment. VOD was reported up to 56 days after the last dose during treatment or during follow-up without an intervening HSCT. The median time from subsequent HSCT to onset of VOD was 15 days (range: 4-56 days) in the BESPONSA arm, among the 79 patients who proceeded to a subsequent HSCT, VOD was reported in 18/79 patients (23%), and among all 164 patients treated, VOD was reported in 5/164 patients (3%) during study therapy or in follow-up without an intervening HSCT.

The risk of VOD was greater in patients who underwent HSCT after BESPONSA treatment; use of HSCT conditioning regimens containing 2 alkylating agents (e.g., busulfan in combination with other alkylating agents) and last total bilirubin level greater than or equal to the ULN before HSCT are 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. Patients who have experienced prior VOD or have serious ongoing hepatic liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) are at an increased risk for worsening of liver disease, including developing 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. Due to the potential for VOD to worsen, post-transplantation HSCT is not recommended in patients with ongoing VOD at the time of transplantation. The risk of VOD with BESPONSA is 2 cycles; a third cycle may be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycles [see Dosage and Administration (2.1)]. For patients who proceed to HSCT, monitor liver tests closely during the first month post-HSCT, then less frequently thereafter, according to standard medical practice.

In the INO-VATE ALL trial, increases in liver tests were reported. Grade 3/4 ALT, AST, and total bilirubin abnormal liver tests occurred in 7/160 (4%), 7/161 (4%), and 8/161 patients (5%), respectively.

In all patients, monitor liver tests, including ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose of BESPONSA. Elevations of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA [see Dosage and Administration (2.3)].

5.2 Increased Risk of Post-Transplant Non-relapse Mortality

In the INO-VATE ALL trial, a higher post-HSCT non-relapse mortality rate was observed in patients receiving BESPONSA compared to the Investigator’s choice of chemotherapy arm, resulting in a higher Day 100 post-HSCT mortality rate.

Overall, 79/164 patients (48%) in the BESPONSA arm and 35/162 patients (22%) in the Investigator’s choice of chemotherapy arm had a follow-up HSCT. The post-HSCT non-relapse mortality rate was 31/79 (39%) and 8/35 (23%) in the BESPONSA arm compared to the Investigator’s choice of chemotherapy arm, respectively.

In the BESPONSA arm, the most common causes of post-HSCT non-relapse mortality were infections (5/18 patients) and patients who died due to MOF (2 patients) and/or infections (3 patients). For patients who died due to MOF or infection, 1 patient died due to infection, and 1 patient died due to MOF and infection.

Monitor closely for toxicities post-HSCT, including signs and symptoms of infection and VOD [see Warnings and Precautions (5.1, 5.3)].

5.3 Myelosuppression

In the INO-VATE ALL trial, myelosuppression was observed in patients receiving BESPONSA [see Adverse Reactions (6.1)].

Thrombocytopenia and neutropenia were reported in 83/164 patients (51%) and 81/164 patients (49%), respectively. Grade 3 thrombocytopenia and neutropenia were reported in 23/164 patients (14%) and 33/164 patients (20%), respectively. Grade 4 thrombocytopenia and neutropenia were reported in 46/164 patients (28%) and 45/164 patients (27%), respectively. Fibrile neutropenia, which may be life-threatening, was reported in 80/164 patients (5%). For patients who were in CR or CRi at the end of treatment, the recovery of platelet counts to > 50,000/mm\(^3\) was later than 45 days after the last dose in 15/164 patients (9%) who received BESPONSA and 3/162 patients (2%) who received Investigator’s choice of chemotherapy.

Complications associated with myelosuppression (including infections and bleeding/hemorrhagic events) were observed in patients receiving BESPONSA [see Adverse Reactions (6.1)]. Fibrile neutropenia, which may be life-threatening, was reported in 58/164 patients (35%). Fatal infections, including pneumonia, neutropenic sepsis, sepsis, septic shock, and pseudomonal sepsis, were reported in 8/164 patients (5%). Bacterial, viral, and fungal infections were reported.

Hemorrhagic events were reported in 54/164 patients (33%). Grade 3 or 4 hemorrhagic events were reported in 8/164 patients (5%). One Grade 5 (fatal) hemorrhagic event (intra-abdominal hemorrhage) was reported in 1/164 patients (1%). The most common hemorrhagic event was epistaxis which was reported in 24/164 patients (15%).
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 of severe infection, bleeding/hemorrhage, or other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA [see Dosage and Administration (2.3)].

5.4 Infusion Related Reactions

In the INO-VATE ALL trial, infusion related reactions were observed in patients who received BESPONSA. Infusion related reactions (all Grade 2) were reported in 4/164 patients (2%). Infusion related reactions generally occurred in Cycle 1 shortly after the end of the BESPONSA infusion and resolved spontaneously or with medical management. Premedicate with a corticosteroid, antipyretic, and antihistamine prior to dosing [see Dosage and Administration (2.2)].

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 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 [see Dosage and Administration (2.3)].

5.5 QT Interval Prolongation

In the INO-VATE ALL trial, increases in QT interval corrected for heart rate using Fridericia's formula (QTcF) of ≥ 60 msec from baseline were measured in 4/162 patients (3%). No patients had QTcF values greater than 500 msec [see Clinical Pharmacology (12.2)]. Grade 2 QT prolongation was reported in 2/164 patients (1%). No ≥ Grade 3 QT prolongation or events of Torsade de Points were reported [see Adverse Reactions (6.1)].

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 [see Drug Interactions (7)], and in patients with electrolyte disturbances [see Drug Interactions (7)]. Obtain electrocardiograms (ECGs) and electrolytes prior to the start of treatment, after initiation of any drug known to prolong QTc, and periodically, as clinically indicated during treatment [see Drug Interactions (7), Clinical Pharmacology (12.2)].

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, BESPONSA can cause embryo-fetal harm when administered to a pregnant woman. In animal studies, inotuzumab ozogamicin caused embryo-fetal toxicities, starting at a dose that was approximately 4 times the exposure in patients at the maximum recommended dose, based on the area under the concentration-time curve (AUC). Advise females of reproductive potential to use effective contraception during treatment with BESPONSA and for at least 8 months after the last dose of BESPONSA. Apprise pregnant women of the potential risk to the fetus. Advise women to contact their healthcare provider if they become pregnant or if pregnancy is suspected during treatment with BESPONSA [see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)].

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatotoxicity, including hepatic VOD (also known as SOS) [see Warnings and Precautions (5.1)]
- Increased risk of post-transplant non-relapse mortality [see Warnings and Precautions (5.2)]
- Myelosuppression [see Warnings and Precautions (5.3)]
- Infusion related reactions [see Warnings and Precautions (5.4)]
- QT interval prolongation [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions described in this section reflect exposure to BESPONSA in 164 patients with relapsed or refractory ALL who participated in a randomized clinical study of BESPONSA versus Investigator's choice of chemotherapy (fludarabine + cytarabine + granulocyte colony-stimulating factor [FLAG], mitoxantrone + cytarabine [MXN/Ara-C], or high dose cytarabine [HiDAC]) (INO-VATE ALL Trial [NCT01564784]) [see Clinical Studies (14)].

Of the 164 patients who received BESPONSA, the median age was 47 years (range: 18-78 years). 56% were male, 68% had received 1 prior treatment regimen for ALL, 31% had received 2 prior treatment regimens for ALL, 68% were White, 19% were Asian, and 2% were Black.

In patients who received BESPONSA, the median duration of treatment was 8.9 weeks (range: 0.1-26.4 weeks), with a median of 3 treatment cycles started in each patient. In patients who received Investigator's choice of chemotherapy, the median duration of treatment was 0.9 weeks (range: 0.1-15.6 weeks), with a median of 1 treatment cycle started in each patient.

In patients who received 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.

In patients who received BESPONSA, the most common (≥ 2%) serious adverse reactions were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, VOD, and fatigue.

In patients who received BESPONSA, the most common (≥ 2%) adverse reactions reported as the reason for permanent discontinuation were infection (6%), thrombocytopenia (2%), hyperbilirubinemia (2%), transaminases increased (2%), and hemorrhage (2%); the most common (≥ 5%) adverse reactions reported as the reason for dose interruption were neutropenia (17%), infection (10%), thrombocytopenia (10%), transaminases increased (6%), and febrile neutropenia (5%); and the most common (≥ 1%) adverse reactions reported as the reason for dose reduction were neutropenia (1%), thrombocytopenia (1%), and transaminases increased (1%).

VOD was reported in 23/164 patients (14%) who received BESPONSA during or following treatment or following a HSCT after completion of treatment [see Warnings and Precautions (5.1)].

Table 6 shows the adverse reactions with ≥ 10% incidence reported in patients with relapsed or refractory ALL who received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HiDAC).

### Table 6. Adverse Reactions With ≥ 10% Incidence in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HiDAC)

<table>
<thead>
<tr>
<th>Body System</th>
<th>BESPONSA (N=164)</th>
<th>FLAG, MXN/Ara-C, or HiDAC (N=143*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>48</td>
<td>28</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Chills</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

Adverse reactions included treatment-emergent all-causality events that commenced on or after Cycle 1 Day 1, with ≥ 42 days after the last dose of BESPONSA, but prior to the start of a new anticancer treatment (including HSCT).

Preferred terms were retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Severity grade of adverse reactions were according to NCI CTCAE version 3.0.

Abbreviations: ALL=acute lymphoblastic leukemia; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HiDAC=high dose cytarabine; HSCT=hematopoietic stem cell transplant.
Table 7 shows the clinically important laboratory abnormalities reported in patients treated with BESPONSA included: lipase increased (9%), abdominal distension (6%), and lipemia (5%).

Additional adverse reactions (all grades) that were reported in less than 10% of patients treated with BESPONSA included: lipase increased (9%), abdominal distension (6%), amylase increased (5%), hyperuricemia (4%), ascites (4%), infusion related reaction (2%), cystitis (3%), and hypotension (3%).

Table 7. Laboratory Abnormalities in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator’s Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>N</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>N</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>161</td>
<td>98</td>
<td>76</td>
<td>142</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>161</td>
<td>94</td>
<td>40</td>
<td>142</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>Leukocytes decreased</td>
<td>161</td>
<td>95</td>
<td>82</td>
<td>142</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>160</td>
<td>94</td>
<td>86</td>
<td>130</td>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>Lymphocytes (absolute) decreased</td>
<td>160</td>
<td>93</td>
<td>71</td>
<td>127</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>148</td>
<td>67</td>
<td>18</td>
<td>111</td>
<td>68</td>
<td>17</td>
</tr>
<tr>
<td>AST increased</td>
<td>160</td>
<td>71</td>
<td>4</td>
<td>134</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>ALP increased</td>
<td>158</td>
<td>57</td>
<td>1</td>
<td>133</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>ALT increased</td>
<td>161</td>
<td>49</td>
<td>4</td>
<td>137</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>161</td>
<td>36</td>
<td>5</td>
<td>138</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>139</td>
<td>32</td>
<td>13</td>
<td>90</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>158</td>
<td>16</td>
<td>3</td>
<td>122</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>143</td>
<td>15</td>
<td>2</td>
<td>102</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

Seventy grade of laboratory abnormalities according to NCI CTCAE version 3.0.

Abbreviations: ALL=acute lymphoblastic leukemia; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST-aspartate aminotransferase; GGT=gamma-glutamyltransferase; HIDA=HIDA-high dose cytarabine; MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients; NCI CTCAE-National Cancer Institute Common Toxicity Criteria for Adverse Events.

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to inotuzumab ozogamicin in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In clinical studies of BESPONSA in patients with relapsed or refractory ALL, the immunogenicity of BESPONSA was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-inotuzumab ozogamicin antibodies. For patients whose sera tested positive for anti-inotuzumab ozogamicin antibodies, a cell-based luminescence assay was performed to detect neutralizing antibodies.

In clinical studies of BESPONSA in patients with relapsed or refractory ALL, 7/236 patients (3%) tested positive for anti-inotuzumab ozogamicin antibodies. No patients tested positive for neutralizing anti-inotuzumab ozogamicin antibodies in patients who tested positive for anti-inotuzumab ozogamicin antibodies. The presence of anti-inotuzumab ozogamicin antibodies did not affect clearance following BESPONSA treatment.

7. **DRUG INTERACTIONS**

**Drugs That Prolong the QT Interval**

Concomitant use of BESPONSA with drugs known to prolong the QT interval or induce Torsades de Pointes may increase the risk of a clinically significant QTc interval prolongation [see Clinical Pharmacology (12.2)]. Discontinue or use alternative concomitant drugs that do not prolong QTc interval while the patient is using BESPONSA. When it is not feasible to avoid concomitant use of drugs known to prolong QTc, obtain ECGs and electrolytes prior to the start of treatment, after initiation of any drug known to prolong QTc, and periodically monitor as clinically indicated during treatment [see Warnings and Precautions (5.5)].

8. **USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action and findings from animal studies [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)], BESPONSA can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on BESPONSA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In rat embryo-fetal development studies, inotuzumab ozogamicin caused embryo-fetal toxicity at maternal systemic exposures that were ≥0.4 times the exposure in patients at the maximum recommended dose, based on AUC [see Data]. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2%-4% and 15%-20%, respectively.

**Data**

**Animal Data**

In animal-fetal development studies in rats, pregnant animals received daily intravenous doses of inotuzumab ozogamicin up to 0.36 mg/kg during the period of organogenesis. Embryo-fetal toxicities including increased resorptions and fetal growth retardation as evidenced by decreased live fetal weights and delayed skeletal ossification were observed at ≥0.11 mg/kg (approximately 2 times the exposure in patients at the maximum recommended dose, based on AUC). Fetal growth retardation also occurred at 0.04 mg/kg (approximately 0.4 times the exposure in patients at the maximum recommended dose, based on AUC).

In an embryo-fetal development study in rabbits, pregnant animals received daily intravenous doses up to 0.15 mg/kg (approximately 3 times the exposure in patients at the maximum recommended dose, based on AUC) during the period of organogenesis. At a dose of 0.15 mg/kg, slight maternal toxicity was observed in the absence of any effects on embryo-fetal development.

8.2 Lactation

**Risk Summary**

There are no data on the presence of inotuzumab ozogamicin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. 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.

8.3 Females and Males of Reproductive Potential

**Pregnancy Testing**

Based on its mechanism of action and findings from animal studies, BESPONSA can cause embryo-fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]. Verify the pregnancy status of females of reproductive potential prior to initiating BESPONSA.
BESPONSA. Advise females of reproductive potential to use effective contraception [see Clinical Pharmacology (12.3)].

Females
Based on findings in animals, BESPONSA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

Males
Based on findings in animals, BESPONSA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use
In the INO-VATE ALL trial, 30/164 patients (18%) treated with BESPONSA were ≥ 65 years of age. No differences in responses were identified between older and younger patients.

Based on a population pharmacokinetic analysis in 765 patients, no adjustment to the starting dose is required based on age [see Clinical Pharmacology (12.3)].

8.6 Hepatic Impairment
Based on a population pharmacokinetic analysis, the clearance of inotuzumab ozogamicin in patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST/GGT any level; n=150) was similar to patients with normal hepatic function (total bilirubin/AST/GGT less than or equal to ULN; n=611). In patients with moderate (total bilirubin greater than 1.5-3 × ULN and AST/GGT any level; n=5) and severe hepatic impairment (total bilirubin greater than 3 × ULN and AST/GGT any level; n=1), inotuzumab ozogamicin clearance did not appear to be reduced [see Clinical Pharmacology (12.3)]. No adjustment to the starting dose is required when administering BESPONSA to patients with total bilirubin less than or equal to 1.5 × ULN and AST/ALT less than or equal to 2.5 × ULN [see Dosage and Administration (2.3)]. There is limited safety information available in patients with total bilirubin greater than 1.5 × ULN and/or AST/ALT greater than 2.5 × ULN prior to dosing. Intermittent dosing until recovery of total bilirubin to less than or equal to 1.5 × ULN and AST/ALT to less than or equal 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 less than or equal to 1.5 × ULN or AST/ALT does not recover to less than or equal to 2.5 × ULN [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

11. DESCRIPTION

Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate (ADC). Inotuzumab recognizes human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic agent that is covalently attached to the antibody via a linker. Nonclinical data suggest that the antitumor activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate (ADC). Inotuzumab recognizes human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic agent that is covalently attached to the antibody via a linker. Nonclinical data suggest that the antitumor activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

12.2 Pharmacodynamics

During the treatment period, the pharmacodynamic response to BESPONSA was characterized by the depletion of CD22-positive leukemic blasts.

Cardiac Electrophysiology

In a randomized clinical study in patients with relapsed or refractory ALL, increases in QTcF of ≥ 60 msec from baseline were measured in 4/162 patients (3%) in the BESPONSA arm and 3/124 patients (2%) in the Investigator’s choice of chemotherapy arm. Increases in QTcF of ≥ 500 msec were observed in none of the patients in the BESPONSA arm and 1/124 patients (1%) in the Investigator’s choice of chemotherapy arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest mean (upper bound of the 2-sided 90% CI) for QTcF was 15.3 (21.1) msec, which was observed at Cycle 4/Day 1/1 hour in the BESPONSA arm [see Warnings and Precautions (5.5)].

12.3 Pharmacokinetics

The mean C∞ of inotuzumab ozogamicin was 308 ng/mL. The mean simulated total AUC per cycle was 100,000 ng×h/mL. In patients with relapsed or refractory ALL, steady-state drug concentration was achieved by Cycle 4. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was predicted by Cycle 4.

Distribution

N-acetyl-gamma-calicheamicin dimethylhydrazide is approximately 97% bound to human plasma proteins in vitro. In humans, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L.

Elimination

The pharmacokinetics of inotuzumab ozogamicin was well characterized by a 2-compartment model with linear and time-dependent clearance components. In 234 patients with relapsed or refractory ALL, the clearance of inotuzumab ozogamicin at steady state was 0.0333 L/h and the terminal half-life (t½) was 12.3 days. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was predicted by Cycle 4.

Metabolism

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide was primarily metabolized via nonenzymatic reduction. In humans, N-acetyl-gamma-calicheamicin dimethylhydrazide serum levels were typically below the limit of quantitation.

Specific Populations

The effect of intrinsic factors on inotuzumab ozogamicin pharmacokinetics was assessed using a population pharmacokinetic analysis unless otherwise specified. Age (18 to 92 years of age), sex, and race (Asian versus non-Asian [Caucasian, Black, and Unspecified]) had no clinically significant effect on the pharmacokinetics of inotuzumab ozogamicin.

11. DESCRIPTION

Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody inotuzumab, specific for human CD22; 2) N-acetyl-gamma-calicheamicin, which causes double-stranded DNA breaks; and 3) an acid-cleavable linker composed of the condensation product of 4-(4-acetylphenoxyl)-butanoic acid (AcBut) and 3-methyl-3-mercaptopbutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab.

Inotuzumab ozogamicin has an approximate molecular weight of 160 kDa. The average number of calicheamicin derivative molecules conjugated to each inotuzumab molecule is approximately 6 with a distribution from 2-8. Inotuzumab ozogamicin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the semisynthetic calicheamicin derivative is produced by microbial fermentation followed by synthetic modification.

BESPONSA (inotuzumab ozogamicin) for Injection is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous administration. Each single-dose vial delivers 0.9 mg inotuzumab ozogamicin. Inactive ingredients are polysorbate 80 (0.36 mg), sodium chloride (2.16 mg), sucrose (180 mg), and tromethamine (8.64 mg). After reconstitution with 4 mL of Sterile Water for Injection, USP, the final concentration is 0.25 mg/mL of inotuzumab ozogamicin with a deliverable volume of 3.6 mL (0.9 mg) and a pH of approximately 8.0.
13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin. In toxicity studies, rats were dosed weekly for 4 or 26 weeks with inotuzumab ozogamicin at doses up to 4.1 mg/m² and 0.73 mg/m², respectively. After 26 weeks of dosing, rats developed hepatocellular adenomas in the liver at 0.73 mg/m² (approximately 2 times the exposure in patients at the maximum recommended dose, based on AUC). Additional findings in female reproductive organs occurred in repeat-dose toxicity studies and included decreased ovarian and uterine weights, and ovarian and uterine atrophy. Findings in male reproductive organs occurred in repeat-dose toxicity studies and included decreased testicular weights, testicular degeneration, hypospermia, and prostatic and seminal vesicle atrophy. Testicular degeneration and hypospermia were nonreversible following a 4-week nondosing period. In the chronic studies of 26-weeks duration, adverse effects on reproductive organs occurred at ≥0.07 mg/m² in male rats and at 0.73 mg/m² in female monkeys [see Use In Specific Populations (8.3)].

14. CLINICAL STUDIES

Patients With Relapsed or Refractory ALL –INO-VATE ALL

The safety and efficacy of BESPONSA were evaluated in INO-VATE ALL (NCT01564784) a randomized (1:1), open-label, international, multicenter study with patients in relapsed or refractory ALL. Patients were stratified at randomization based on duration of first remission (<12 months or ≥12 months, salvage treatment (Salvage 1 or 2) and patient age at randomization (<55 or ≥55 years). Eligible patients were ≥18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. All patients were required to have ≥5% bone marrow blasts and to have received 1 or 2 previous induction chemotherapy regimens for ALL. Patients with Philadelphia chromosome-positive B-cell precursor ALL were required to have disease that failed treatment with at least 1 tyrosine kinase inhibitor and standard chemotherapy. Table 1 shows the dosing regimen used to treat patients.

Among all 326 patients who were randomized to receive BESPONSA (N=164) or Investigator’s choice of chemotherapy (N=162), 215 patients (66%) had received 1 prior treatment regimen for ALL, and 108 patients (33%) had received 2 prior treatment regimens for ALL. The median age was 47 years (range: 18-79 years), 276 patients (85%) had Philadelphia chromosome-negative ALL, 206 patients (63%) had a duration of first remission <12 months, and 55 patients (17%) had undergone a HSCT prior to receiving BESPONSA or Investigator’s choice of chemotherapy. The two treatment groups were generally balanced with respect to the baseline demographics and disease characteristics. All evaluable patients had B-cell precursor ALL that expressed CD22, with ≥90% of evaluable patients exhibiting ≥70% leukemic blast CD22 positivity prior to treatment, as assessed by flow cytometry performed at a central laboratory. The efficacy of BESPONSA was established on the basis of CR, the duration of CR, and proportion of MRD-negative CR (<1×10⁹ of bone marrow nucleated cells by flow cytometry) in the first 218 patients randomized. CR, duration of remission (DoR), and MRD results in the initial 218 randomized patients were consistent with those seen in all 326 randomized patients.

Table 8 shows the efficacy results from this study.

| Table 8. Efficacy Results in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator’s Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC) |
|--------------------------------------------------|--|---|---|---|---|
| Responding (CR/CRi) patients | n | (% [95% CI]) | n | (% [95% CI]) | n | (% [95% CI]) |
| BESPONSA (N=109) | 39 (35.8) [26.8-45.5] | 19 (17.4) [10.8-25.9] | 49 (45.0) [35.4-54.8] | 13 (11.9) [6.5-19.5] | 88 (80.7) [72.1-87.7] | 22 (29.4) [21.0-38.8] |
| CR (Complete Remission) | n | p-value<0.0001 | n | p-value<0.0001 | n | p-value<0.0001 |
| Median, months | 8.0 | 4.9 | 4.6 | 2.9 | 5.4 | 3.5 |
| [<95% CI] | [4.9-10.4] | [2.9-7.2] | [3.7-5.7] | [0.6-5.7] | [4.8-2.0] | [2.9-6.6] |
| MRD-negativity | n | 35 | 6 | 34 | 3 | 69 | 9 |
| Rate (n as %) | 35/39 (89.7) [75.8-97.1] | 6/19 (31.6) [12.8-56.6] | 34/49 (69.4) [54.6-81.7] | 3/13 (23.1) [5.9-53.8] | 69/88 (78.4) [68.4-86.5] | 9/32 (28.1) [13.7-46.7] |

Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high-dose cytarabine; HR=hazard ratio; MRD=minimal residual disease; MXN/Ara-C=mitoxantrone + cytarabine; N=n=number of patients; OS=overall survival; PFS=progression-free survival.

Among the initial 218 patients, as per EAC assessment, 32/109 patients (29%) in the BESPONSA arm achieved complete remission with partial hematologic recovery (CRh); defined as <5% blasts in the bone marrow, ANC >0.5 x 10⁹/L, and platelet counts >50 x 10⁹/L but not meeting full recovery of peripheral blood counts versus 6/109 patients (6%) in the Investigator’s choice of chemotherapy arm, and 71/109 patients (65%) in the BESPONSA arm achieved CR/CRh versus 25/109 patients (23%) in the Investigator’s choice of chemotherapy arm. Overall, 79/164 patients (48%) in the BESPONSA arm and 35/162 patients (22%) in the Investigator’s choice of chemotherapy arm had a follow-up HSCT.

Figure 1 shows the analysis of overall survival (OS). The analysis of OS did not meet the pre-specified boundary for statistical significance.

15. REFERENCES

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BESPONSA (inotuzumab ozogamicin) for Injection is supplied as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution. Each vial delivers 0.9 mg inotuzumab ozogamicin. Each carton (NDC 0008-0100-01) contains one single-dose vial.

16.2 Storage and Handling

Refrigerate (2-8°C; 36-46°F) BESPONSA vials and store in the original carton to protect from light. Do not freeze.

BESPONSA is a cytotoxic drug. Follow applicable special handling and disposal procedures.1

17. PATIENT COUNSELING INFORMATION

Hepatotoxicity, Including Hepatic Veno-occlusive Disease (VOD) (also known as Sinusoidal Obstruction Syndrome)

Inform patients that liver problems, including severe, life-threatening, or fatal VOD, and increases in liver tests may develop during BESPONSA treatment. Inform patients that they 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. Inform patients that they should carefully consider the benefit/risk of BESPONSA treatment if they have a prior history of VOD or serious ongoing liver disease [see Warnings and Precautions (5.1)].

Increased Risk of Post-HSCT Non-Relapse Mortality

Inform patients that there is an increased risk of post-HSCT non-relapse mortality after receiving BESPONSA, that the most common causes of post-HSCT non-relapse mortality included infection and VOD. Advise patients to report signs and symptoms of infection [see Warnings and Precautions (5.2)].

Myelosuppression

Inform patients that decreased blood counts, which may be life-threatening, may develop during BESPONSA treatment and that complications associated with decreased blood counts may include infections, which may be life-threatening or fatal, and bleeding/hemorrhage events. Inform patients that signs and symptoms of infection, bleeding/hemorrhage, or other effects of decreased blood counts should be reported during treatment with BESPONSA [see Warnings and Precautions (5.3)].

Infusion Related Reactions

Advising patients to contact their healthcare provider if they experience symptoms such as fever, chills, rash, or breathing problems during the infusion of BESPONSA [see Warnings and Precautions (5.4)].

QT Interval Prolongation

Inform patients of symptoms that may be indicative of significant QTc prolongation including dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and the use of all medications to their healthcare provider [see Warnings and Precautions (5.5)].

Embryo-Fetal Toxicity

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 [see Use in Specific Populations (8.3)]. Advise females of reproductive potential to avoid becoming pregnant while receiving BESPONSA. Advise women to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with BESPONSA. Inform the patient of the potential risk to the fetus [see Warnings and Precautions (5.7), Use in Specific Populations (8.1)].

Lactation

Advise women against breastfeeding while receiving BESPONSA and for 2 months after the last dose [see Use in Specific Populations (8.2)].

This product's label may have been updated. For current full prescribing information, please visit www.BESPONSA.com.