I. ADMINISTRATIVE INFORMATION

Application Number: BLA 125736
Application Holder: Celgene Corporation, a Bristol-Myers Squibb Company
Initial REMS Approval: 03/2021

II. REMS GOALS

The goals of the ABECMA REMS are to mitigate the risks of cytokine release syndrome (CRS) and neurologic toxicities by:

1. Ensuring that hospitals and their associated clinics that dispense ABECMA are specially certified and have on-site immediate access to tocilizumab.
2. Ensuring that those who prescribe, dispense, or administer ABECMA are aware of how to manage the risks of CRS and neurologic toxicities.

III. REMS REQUIREMENTS

Celgene Corporation must ensure that hospitals and their associated clinics, and patients comply with the following requirements:

1. Hospitals and their associated clinics that dispense ABECMA must:

   To become certified to dispense

   1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).
   2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program requirements on behalf of the hospital and associated clinic(s).
   3. Have the authorized representative complete the Training Program provided by the REMS Program.
   4. Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program.
   5. Have the authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS Program.
   6. Train all relevant staff involved in prescribing, dispensing, or administering of ABECMA on the REMS Program requirements using the Training Program and Adverse Reaction Management Guide.
   7. Have all relevant staff involved in prescribing, dispensing, or administering of ABECMA successfully complete the Knowledge Assessment and submit it to the REMS Program.
   8. Establish processes and procedures to ensure relevant new staff involved in the prescribing, dispensing, or administration of ABECMA
9. Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).

10. Establish processes and procedures to provide patients with the Patient Wallet Card.

<table>
<thead>
<tr>
<th>Before infusion</th>
<th>11. Provide the patient with the Patient Wallet Card.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>To maintain certification to dispense if there is a change in authorized representative</th>
<th>13. Have a new Authorized Representative enroll in the REMS Program by completing the Hospital Enrollment Form.</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>To maintain certification to dispense, if ABECMA has not been dispensed at least once annually from the date of certification in the REMS Program</th>
<th>14. Train all relevant staff involved in prescribing, dispensing, or administering of ABECMA on the REMS Program requirements using the Training Program.</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. Have all relevant staff involved in prescribing, dispensing, or administering ABECMA successfully complete the Knowledge Assessment.</td>
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</table>

<table>
<thead>
<tr>
<th>At all times</th>
<th>16. Report any serious(^1) adverse events suggestive of CRS or neurologic toxicities to the REMS Program.</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Maintain records of staff training.</td>
<td></td>
</tr>
<tr>
<td>18. Maintain records that processes and procedures are in place and are being followed.</td>
<td></td>
</tr>
<tr>
<td>19. Comply with audits carried out by Celgene Corporation or a third party acting on behalf of Celgene Corporation to ensure that all training, processes, and procedures are in place and are being followed.</td>
<td></td>
</tr>
</tbody>
</table>

2. **Patients who are prescribed ABECMA:**

<table>
<thead>
<tr>
<th>Before infusion</th>
<th>1. Receive the Patient Wallet Card.</th>
</tr>
</thead>
</table>

\(^1\) For the purpose of this REMS, serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
Celgene Corporation must provide training to relevant staff who prescribe, dispense, or administer ABECMA.

The training includes the following educational materials: Training Program, Adverse Reaction Management Guide, and Knowledge Assessment. The training must be provided in-person, via live webcast, or online.

To support REMS Program operations, Celgene Corporation must:

1. Ensure ABECMA is distributed only to certified hospitals or their associated clinics.
2. Establish and maintain the REMS Program website, www.AbecmaREMS.com. The REMS Program website must include the capability to enroll, complete training online, maintain records of that training, and option to print the Prescribing Information (PI), Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website.
3. Make the REMS Program website fully operational and all REMS materials available through website and call center.
4. Establish and maintain a REMS Program Call Center for REMS participants at 1-888-423-5436.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or have been certified in the REMS Program.
6. Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, and through fax and telephone.
7. Notify hospitals and their associated clinics within 7 calendar days after they become certified in the REMS Program.

To ensure REMS participants’ compliance with the REMS program, Celgene Corporation must:

8. Verify annually that the designated authorized representative for certified hospitals and their associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.
9. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: ABECMA distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.
10. Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including decertification.
11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.
12. Audit all certified hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of ABECMA to ensure that all REMS processes and procedures are in place, functioning, and support the ABECMA REMS Program requirements. Certified hospitals and their associated clinics must also be included in Celgene Corporation’s ongoing annual audit plan.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the ABECMA REMS Program based on monitoring and evaluation of the ABECMA REMS Program.
IV. REMS ASSESSMENT TIMETABLE

Celgene Corporation must submit REMS Assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (03/XX/2021). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Celgene Corporation must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS MATERIALS

The following materials are part of the ABECMA REMS:

Enrollment Forms:

Health Care Setting:

1. Hospital Enrollment Form

Training and Educational Materials:

Patient:

2. Patient Wallet Card

Health Care Setting:

3. Training Program
4. Knowledge Assessment
5. Adverse Reaction Management Guide

Other Materials:

6. REMS Program Website
ABECMA REMS Hospital Enrollment Form

ABECMA is available only through ABECMA REMS. Only hospitals and their associated clinic(s) certified in the ABECMA REMS are permitted to dispense ABECMA.

To become certified, hospitals and their associated clinic(s) must designate an authorized representative (AR) to:
1. Complete this enrollment form.
2. Oversee implementation and compliance with ABECMA REMS requirements as outlined below.

ABECMA Hospital and Associated Clinic Responsibilities

As a condition of certification, the certified hospitals and their associated clinic(s) must:
- Ensure that when the hospital and its associated clinic(s) designate an AR, the AR must take the Training Program, successfully complete the Knowledge Assessment, and complete and submit a new Hospital Enrollment Form.
- Report any serious* adverse events suggestive of cytokine release syndrome (CRS) or neurologic toxicities to Celgene Corporation, a Bristol-Myers Squibb Company, at www.bms.com or 1-888-805-4555 or to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.
- Administer ABECMA only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
- Provide the patient with the Patient Wallet Card.
- Maintain documentation of all processes and procedures for ABECMA REMS and provide documentation upon request to Celgene or to a third party acting on behalf of Celgene.
- Comply with audits by Celgene or a third party acting on behalf of Celgene.

ABECMA Authorized Representative Responsibilities

By signing this form, I attest that I am the AR designated by my institution to coordinate the activities of the ABECMA REMS. I understand and agree to comply with the following ABECMA REMS requirements:
- I have completed the ABECMA REMS Training Program and successfully completed the Knowledge Assessment.
- I will oversee my institution’s implementation of and compliance with ABECMA REMS requirements.
- I confirm, before administering ABECMA, my institution has established processes and procedures that are subject to monitoring by Celgene or a third party acting on behalf of Celgene to help ensure compliance with the ABECMA REMS requirements, including the following:
  - Ensure that all relevant staff involved in prescribing, dispensing, or administering of ABECMA are trained on the REMS requirements using the Training Program, and successfully complete and submit the Knowledge Assessment, and records are maintained of staff training.
  - Put processes and procedures in place to ensure that staff involved in prescribing, dispensing, or administering of ABECMA are retrained on ABECMA REMS if ABECMA has not been dispensed at least once annually from the date of certification in the ABECMA REMS.
  - Prior to infusing ABECMA, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
  - Prior to infusing ABECMA, provide patients with the Patient Wallet Card.
- I have submitted a completed ABECMA REMS Knowledge Assessment to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- I will submit this completed ABECMA REMS Hospital Enrollment Form to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

*For the purpose of this REMS Program, a serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
## Hospital Information (all fields required):

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
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</thead>
<tbody>
<tr>
<td>Hospital Name</td>
<td></td>
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<tr>
<td>REMS Site ID:</td>
<td>(if providing site ID, do not fill in address below)</td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>City</td>
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<td>Phone</td>
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<td>Fax</td>
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## Associated Clinic (if applicable):

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<tr>
<th>Field</th>
<th>Information</th>
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</thead>
<tbody>
<tr>
<td>Associated Clinic Name</td>
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<td>Address</td>
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<td>Phone</td>
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<td>Fax</td>
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## Authorized Representative Information (all fields required):

<table>
<thead>
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<th>Field</th>
<th>Information</th>
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<tbody>
<tr>
<td>First Name</td>
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<tr>
<td>Last Name</td>
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<tr>
<td>Job Title</td>
<td></td>
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<tr>
<td>Employee of</td>
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<tr>
<td>○ Hospital</td>
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<tr>
<td>○ Associated Clinic</td>
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<tr>
<td>Credentials</td>
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<tr>
<td>○ MD</td>
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<td>○ DO</td>
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<td>○ PA</td>
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<td>○ RPh</td>
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<td>○ NP</td>
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<tr>
<td>○ Other (please specify):</td>
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<tr>
<td>Phone</td>
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<tr>
<td>Fax</td>
<td></td>
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<tr>
<td>Work Email Address</td>
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</table>

Complete all required fields and submit this enrollment form to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

Contact the REMS Call Center at 1-888-423-5436 or visit www.AbecmaREMS.com for more information.

Completion of this form and Knowledge Assessment does not guarantee that your institution will be certified to administer ABECMA.

Celgene will provide confirmation of ABECMA REMS Program certification via email after processing this enrollment form and confirming that all other ABECMA REMS requirements have been met.

Product orders cannot be placed until REMS certification is complete.
Information for Patient

ABECMA may cause side effects that are life-threatening and can lead to death.

Call your healthcare provider or get emergency help right away if you get any of the following:

- Difficulty breathing
- Fever (100.4°F/38°C or higher)
- Chills/shivering
- Confusion
- Dizziness or lightheadedness
- Shaking or twitching (tremor)
- Fast or irregular heartbeat
- Severe fatigue
- Severe nausea, vomiting, or diarrhea

Have this card with you at all times. Show it to any doctor who sees you and when you go to the hospital.

- Tell any healthcare provider who sees you that you are being treated with ABECMA®.
- For at least 4 weeks after receiving ABECMA, you should plan to stay within 2 hours of the location where you received treatment.
- Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after ABECMA administration.

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Information for the Healthcare Provider

This patient has received ABECMA CAR T cell therapy, a BCMA-directed genetically modified autologous T cell immunotherapy.

Following treatment with ABECMA, cytokine release syndrome (CRS) or neurologic toxicities may occur, which may be fatal or life-threatening. CRS may involve any organ system.

Contact Patient’s Oncologist Immediately for Further Information and in the Following Situations:

- The administration of steroids or cytotoxic medications.
- If the patient has a serious infection.
- Any planned invasive procedure(s) for the patient.

www.AbecmaREMS.com
Abecma® REMS Training Program
This educational module contains information regarding selected ABECMA-associated adverse reactions of cytokine release syndrome (CRS) and neurologic toxicities. These are not all of the adverse reactions associated with ABECMA. Please refer to the ABECMA Prescribing Information and Medication Guide for more information.
Indication

ABECMA is a B-cell maturation antigen (BCMA)--directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Please see full Prescribing Information, including BOXED WARNINGS and Medication Guide.
A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program to manage known or potential risks associated with a drug and is required by the United States (US) Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. ABECMA is only available under a restricted program called ABECMA REMS because of the serious risks of CRS and neurologic toxicities.

The goals of the ABECMA REMS are to mitigate the risks of CRS and neurologic toxicities by:

- Ensuring that hospitals and their associated clinic(s) that dispense ABECMA are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring that those who prescribe, dispense, or administer ABECMA are aware of how to manage the risks of CRS and neurologic toxicities.
Certification of Hospitals and Their Associated Clinic(s)

To become certified to dispense ABECMA, hospitals and their associated clinic(s) must:

1. Designate an authorized representative (AR) to carry out the certification process by completing and submitting the **Hospital Enrollment Form** on behalf of the hospital and its associated clinic(s).

2. Ensure the AR oversees implementation and compliance with ABECMA REMS requirements.

3. Administer ABECMA only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for immediate administration (within 2 hours of ABECMA infusion).

4. Ensure that if the hospital or its associated clinic(s) designate a replacement AR, the replacement AR must take the **Training Program**, complete the **Knowledge Assessment**, and complete and submit a new **Hospital Enrollment Form**.
5. Maintain documentation of all processes and procedures for the ABECMA REMS and provide documentation upon request to Celgene or to a third party acting on behalf of Celgene. Celgene Corporation is a Bristol-Myers Squibb Company.

6. Comply with audits by Celgene or a third party acting on behalf of Celgene to ensure that all training, processes, and procedures are in place and are being followed for the ABECMA REMS.
7. Report any serious adverse events suggestive of CRS or neurologic toxicities to Celgene Corporation at www.bms.com or 1-888-805-4555, or to the FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

   For the purpose of this REMS, serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
**Identifying an Authorized Representative**

The AR responsible for the hospital and its associated clinic(s) must have capacity to oversee implementation of, and compliance with, the ABECMA REMS by:

1. Ensuring that all relevant staff are trained, complete the **Knowledge Assessment**, and maintain records.

2. Having the ability to ensure that processes and procedures have been established and are being followed.

3. Having the ability to comply with audits carried out by Celgene.

It is not required that the AR be a healthcare provider.
Responsibilities of the ABECMA REMS Authorized Representative

To successfully complete ABECMA REMS certification, the designated AR must:

• Complete the ABECMA REMS Training Program (live in-person, via webcast or online), which includes review of:
  – REMS Training Program
  – REMS Adverse Reaction Management Guide

• Oversee implementation and compliance with ABECMA REMS requirements on behalf of hospitals and their associated clinic(s).

• Submit a successfully completed ABECMA REMS Knowledge Assessment to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

• Submit a successfully completed ABECMA REMS Hospital Enrollment Form to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
Responsibilities of the ABECMA REMS Authorized Representative (cont’d)

Before administering ABECMA, establish processes and procedures that are subject to monitoring by Celgene or a third party acting on behalf of Celgene to help ensure the following:

• All relevant staff involved in prescribing, dispensing, or administering of ABECMA are trained on the REMS requirements using the Training Program, and successfully complete and submit the Knowledge Assessment, and records are maintained of staff training (including a retraining process if ABECMA has not been dispensed at least once annually from the date of certification in the ABECMA REMS).

• Prior to infusing ABECMA, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours of ABECMA infusion).

• Prior to infusing ABECMA, provide patients with the Patient Wallet Card.
Completion of the ABECMA REMS Training Program and Knowledge Assessment

The following individuals are recommended to complete the ABECMA REMS Training Program, Adverse Reaction Management Guide, and the Knowledge Assessment:

• Individuals involved in prescribing, dispensing, or administering ABECMA.
• Individuals who will be the AR or may complete tasks on behalf of the AR.
• Individuals who may discuss ABECMA REMS education with patients or provide a Patient Wallet Card to a patient.
• Individuals involved in the verification, dispensing, and administration of tocilizumab.
• Individuals who may be responsible for reporting adverse events per the REMS program to the FDA or to the manufacturer.

Note: Celgene recognizes that the assignment of REMS activities may be made to different personnel in each healthcare facility. Each healthcare facility should independently assess REMS training needs to ensure that appropriate personnel are trained.
Serious Risks Associated With ABECMA
WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/ MAS, AND PROLONGED CYTOPENIA

See full Prescribing Information for complete boxed warning.

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with ABECMA. Do not administer ABECMA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

- Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with ABECMA, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with ABECMA. Provide supportive care and/or corticosteroids as needed.

- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/ MAS), including fatal and life-threatening reactions, occurred in patients following treatment with ABECMA. HLH/ MAS can occur with CRS or neurologic toxicities.

- Prolonged Cytopenia with bleeding and infection, including fatal outcomes following stem cell transplantation for hematopoietic recovery, occurred following treatment with ABECMA.

- ABECMA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ABECMA REMS.
Management of Cytokine Release Syndrome
Cytokine Release Syndrome

- CRS, including fatal or life-threatening reactions, occurred following treatment with ABECMA.
- The information in this section is based on data from the KarMMa study, a clinical trial in which 127 patients with relapsed/refractory multiple myeloma received ABECMA across a dose range of 150 to 518 x 10^6 CAR-positive T cells.
  - CRS occurred in 85% (108/127) of patients receiving ABECMA.
  - Grade 3 or higher CRS (Lee grading system1) occurred in 9% (12/127) of patients, with Grade 5 CRS reported in one (0.8%) patient.
  - Overall rate of CRS was 79%, and rate of Grade 2 CRS was 23% in patients treated in 300 x 10^6 CAR-positive T cells dose cohort (dose ranging from 277 to 339 x 10^6 CAR-positive T cells). For patients treated in 450 x 10^6 CAR-positive T cells dose cohort (dose range 447 to 518 x 10^6 CAR-positive T cells), the overall rate of CRS was 96% and rate of Grade 2 CRS was 40%. Rate of Grade 3 or higher CRS was similar across the dose range.
  - The median time-to-onset of CRS, any grade, was 1 day (range: 1 to 23 days).
  - The median duration of CRS was 7 days (range: 1 to 63 days) in all patients, including the patient who died. The median duration of CRS for the 450 x 10^6 CAR-positive T cells dose cohort was 7 days (range: 1 to 63 days), and was 6 days (range: 2 to 28 days) for the 300 x 10^6 CAR-positive T cells dose cohort.
  - 68 of 127 (54%) patients received tocilizumab; 35% (45/127) received a single dose while 18% (23/127) received more than 1 dose of tocilizumab. Overall, across the dose levels, 15% (19/127) of patients received at least 1 dose of corticosteroids for treatment of CRS. All patients that received corticosteroids for CRS received tocilizumab.
  - In the 450 x 10^6 CAR-positive T cells dose cohort, 68% (36/53) of patients received tocilizumab and 23% (12/53) received at least 1 dose of corticosteroids for treatment of CRS. This was higher than the tocilizumab use of 44% (31/70) and corticosteroid use of 10% (7/70) at the 300 x 10^6 CAR-positive T cells dose cohort.

Signs and Symptoms of CRS

- CRS is a non–antigen-specific toxicity that occurs as a result of high-level immune activation.¹
- Clinical symptoms and severity of CRS are highly variable, ranging from mild flu-like symptoms to multiorgan failure. Fever is a hallmark of CRS.
- Management can be complicated by concurrent conditions.
- Key manifestations of CRS is based on data from 127 patients with relapsed and refractory multiple myeloma receiving ABECMA who had received at least 3 prior lines of antmyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

### Key Manifestations of CRS Observed in KarMMa

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Pyrexia</td>
<td>98%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>41%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>35%</td>
</tr>
<tr>
<td>Chills</td>
<td>31%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>20%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
</tr>
</tbody>
</table>

Managing CRS

- Instruct patients to remain within 2 hours of the REMS-certified healthcare facility for at least 4 weeks following infusion.
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.
- Monitor patients at least daily for 7 days following ABECMA infusion at the REMS-certified healthcare facility for signs and symptoms of CRS.
- Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion.
- Identify CRS based on clinical presentation.
- Evaluate for and treat other causes of fever, hypoxia, and hypotension.
- If CRS is suspected, initiate symptomatic treatment with supportive care, tocilizumab, or tocilizumab and/or corticosteroids, according to the management recommendations on slides 21-22.
- Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry.
- For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.
- For CRS refractory to first line interventions such as tocilizumab or tocilizumab and corticosteroids, consider alternate treatment options (i.e., higher corticosteroid dose, alternative anti-cytokine agents, anti-T cell therapies). Refractory CRS is characterized by fevers, end-organ toxicity (e.g., hypoxia, hypotension) not improving within 12 hours of first line interventions, or development of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).
- If concurrent neurologic toxicity is suspected during CRS, administer:
  - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades on slides 21-22 and 27-28
  - Tocilizumab according to the CRS grade on slides 21-22
  - Antiseizure medication according to the neurologic toxicity grade on slides 27-28
• HLH/MAS occurred in 4% (5/127) of the patients receiving ABECMA.

• One patient treated in the 300 x 10^6 CAR-positive T cells dose cohort developed fatal multi-organ HLH/MAS with CRS. In another patient with fatal bronchopulmonary aspergillosis treated in the 450 x 10^6 CAR-positive T cells dose cohort, HLH/MAS was contributory to the fatal outcome.

• Three cases of Grade 2 HLH/MAS resolved.

• All events of HLH/MAS had an onset within 10 days of receiving ABECMA, with a median onset of 7 days (range: 4 to 9 days).

• All cases of HLH/MAS occurred in the setting of ongoing or worsening CRS. Two patients with HLH/MAS had overlapping neurotoxicity.

• Manifestations of HLH/MAS may include hypotension, hypoxia, multiple organ dysfunction, renal dysfunction, and cytopenia.

• Consider HLH/MAS in patients with progressive or refractory CRS despite treatment.

• Manage HLH/MAS per institutional guidelines.

HLH/MAS=hemophagocytic lymphohistiocytosis/macrophage activation syndrome.
**Lee Criteria\(^1\) for CRS Grading**

CRS grading is based on Lee Criteria, shown in the table below. Final grading should be done after reviewing all of the reported symptoms associated with CRS.

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>CRS Grade 1 (mild)</th>
<th>CRS Grade 2 (moderate)</th>
<th>CRS Grade 3 (severe)</th>
<th>CRS Grade 4 (life-threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP) ≤ 90 mmHg</td>
<td>N/A</td>
<td>Responds to IV fluids or single low-dose vasopressor</td>
<td>Needs high-dose or multiple vasopressors</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Need for oxygen to reach oxygen saturation (SaO(_2)) &gt; 90%</td>
<td>N/A</td>
<td>Fraction of inspired oxygen (FiO(_2)) &lt; 40%</td>
<td>FiO(_2) ≥ 40%</td>
<td>Needs ventilator support</td>
</tr>
<tr>
<td><strong>Organ toxicity</strong></td>
<td></td>
<td>Grade 2</td>
<td>Grade 3 or transaminitis</td>
<td>Grade 4 (excluding transaminitis)</td>
</tr>
</tbody>
</table>

FiO\(_2\)=fraction of inspired oxygen; IV=intravenous; SaO\(_2\)=oxygen saturation.

ABECMA CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Tocilizumab*</th>
<th>Corticosteroids†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td>
<td>If onset 72 hours or more after infusion, treat symptomatically. If onset less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td>
<td>Consider dexamethasone 10 mg IV every 24 hours.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO₂ or hypotension responsive to fluids, or low dose of one vasopressor, or Grade 2 organ toxicity.</td>
<td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td>Consider dexamethasone 10 mg IV every 12 to 24 hours.</td>
</tr>
</tbody>
</table>

IV=intravenous; FiO₂=fraction of inspired oxygen.
*Refer to tocilizumab Prescribing Information for details.
†If corticosteroids are initiated, continue corticosteroids for at least 3 doses, and taper over a maximum of 7 days.
## ABECMA CRS Grading and Management Guidance (cont’d)

<table>
<thead>
<tr>
<th>CRS Grade(^1)</th>
<th>Tocilizumab*</th>
<th>Corticosteroids†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms require and respond to aggressive intervention.</td>
<td>Per Grade 2.</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td>Fever, oxygen requirement greater than or equal to 40% FiO(_2), or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.</td>
<td>If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td></td>
</tr>
</tbody>
</table>

| **Grade 4**     |              |                  |
| Life-threatening symptoms. | Per Grade 2. | Administer dexamethasone 20 mg IV every 6 hours. |
| Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis). | After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) or other anti-T cell therapies. |

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\(^1\) IV = intravenous; FiO\(_2\) = fraction of inspired oxygen.

*Refer to tocilizumab Prescribing Information for details.

†If corticosteroids are initiated, continue corticosteroids for at least 3 doses, and taper over a maximum of 7 days.

Management of Neurologic Toxicities
Clinical Presentation of Neurologic Toxicities

- Neurologic toxicities, which may be severe or life-threatening, have occurred following treatment with ABECMA, including concurrently with CRS, after CRS resolution, or in the absence of CRS.

- Symptoms are variable, and generally occur as CRS is resolving or after CRS resolves. However, some experience neurologic toxicities in the absence of CRS.

- The information in this section is based on data from the KarMMa study, a clinical trial in which 127 patients with relapsed/refractory multiple myeloma received ABECMA across a dose range of 150 to 518 x 10⁶ CAR-positive T cells:
  - CAR T cell-associated neurotoxicity occurred in 28% (36/127) of patients receiving ABECMA, including Grade 3 in 4% (5/127) of patients.
  - One patient had ongoing Grade 2 neurotoxicity at the time of death. Two patients had ongoing Grade 1 tremor at the time of data cutoff.
  - The median time to onset of neurotoxicity was 2 days (range: 1 to 42 days).
  - CAR T cell-associated neurotoxicity resolved in 33 of 36 (92%). For patients who experienced neurotoxicity including three patients with ongoing neurotoxicity, the median duration of CAR T cell-associated neurotoxicity was 6 days (range: 1 to 578 days). Neurotoxicity resolved in 33 patients and median time to resolution was 5 days (range 1 to 61 days).
  - Thirty-four patients with neurotoxicity had CRS. The onset of neurotoxicity during CRS was observed in 29 patients, before the onset of CRS in three patients, and after the CRS event in two patients.

- The most frequently reported (greater than or equal to 5%) manifestations of CAR T cell-associated neurotoxicity include encephalopathy (20%), tremor (9%), aphasia (7%), and delirium (6%).
Management of Neurologic Toxicities

• Counsel patients to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time.

• Monitor patients at least daily for 7 days following ABECMA infusion at the REMS-certified healthcare facility for signs and symptoms of neurologic toxicities. Rule out other causes of neurologic symptoms.

• Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. Provide supportive care and/or corticosteroids as needed.

• Rule out other causes of neurologic signs or symptoms.

• If neurologic toxicity is suspected, manage according to the recommendations on slides 27-28.

• If concurrent CRS is suspected during the neurologic toxicity event, administer:
  – Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades on slides 21-22 and 27-28
  – Tocilizumab according to CRS grade on slides 21-22
  – Antiseizure medication according to neurologic toxicity grade on slides 27-28

• Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.
<table>
<thead>
<tr>
<th>Adverse event term/Neurotoxicity domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Confusion</td>
<td>Mild disorientation</td>
<td>Moderate disorientation; limiting instrumental ADL</td>
<td>Severe disorientation; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
<td>Decreased level of alertness</td>
<td>Sedation; slow response to stimuli; limiting instrumental ADL</td>
<td>Difficult to arouse</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>Awareness of receptive or expressive characteristics; not impairing ability to communicate</td>
<td>Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously</td>
<td>Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly</td>
<td>N/A</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Headache</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self-care ADL</td>
<td>N/A</td>
</tr>
<tr>
<td>Seizure</td>
<td>Brief partial seizure and no loss of consciousness</td>
<td>Brief generalized seizure</td>
<td>Multiple seizures despite medical intervention</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Tremor</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events.

# Neurologic Toxicity Grading and Management Guidance

<table>
<thead>
<tr>
<th>NT Grade¹</th>
<th>Corticosteroids and Antiseizure Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 mg IV every 12 hours for 2 to 3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. Steroids are not recommended for isolated Grade 2 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours.</td>
</tr>
</tbody>
</table>

¹IV=intravenous; NT=neurologic toxicity.

### Neurologic Toxicity Grading and Management Guidance (cont’d)

<table>
<thead>
<tr>
<th>NT Grade</th>
<th>Corticosteroids and Antiseizure Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>Start dexamethasone 10 to 20 mg IV every 6 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches.</td>
</tr>
<tr>
<td></td>
<td>If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided into 4 times a day; taper within 7 days).</td>
</tr>
<tr>
<td></td>
<td>If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m².</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>Start dexamethasone 20 mg IV every 6 hours.</td>
</tr>
<tr>
<td></td>
<td>If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g, repeated every 24 hours if needed; taper as clinically indicated).</td>
</tr>
<tr>
<td></td>
<td>If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m².</td>
</tr>
</tbody>
</table>

IV=intravenous; NT=neurologic toxicity.

Prolonged Cytopenia
Prolonged Cytopenia

- Prolonged cytopenia is defined as Grade 3 or 4 neutropenia or thrombocytopenia that has not resolved by Month 1 following ABECMA infusion.

- In the KarMMa study, 3 patients (3/127) underwent stem cell therapy for hematopoietic reconstitution due to prolonged cytopenia. Two patients underwent autologous and 1 patient underwent allogeneic stem cell transplant.

- Two of the 3 patients died from complications of prolonged cytopenia, which occurred in the setting of ongoing or prior severe CRS or HLH/MAS (lower GI bleeding and bronchopulmonary aspergillosis). The third patient recovered from neutropenia after autologous stem cell transplant.

- 41% (52/127) of patients experienced prolonged neutropenia and 49% (62/127) developed prolonged thrombocytopenia after ABECMA infusion.

- The rate of prolonged neutropenia was 49% in the 450 x 10^6 CAR-positive T cells dose cohort and 34% in the 300 x 10^6 CAR-positive T cells dose cohort.

- In 83% (43/52) of patients who recovered from Grade 3 or 4 neutropenia after Month 1, the median time to recovery from ABECMA infusion was 1.9 months. In 65% (40/62) of patients who recovered from Grade 3 or 4 thrombocytopenia, the median time to recovery was 2.1 months.

- Median time to cytopenia recovery was similar across the 300 x 10^6 and 450 x 10^6 CAR-positive T cells dose cohorts.

- Monitor and provide supportive care per institutional guidelines for prolonged cytopenia.
ABECMA Infusion Delays

Delay the infusion of ABECMA for up to 7 days if a patient has any of the following conditions:

- Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension) including those after preceding chemotherapies
- Active infections or inflammatory disorders
Reporting Adverse Events

• Reporting suspected adverse events after administration of ABECMA is important and allows continued monitoring of the risk/benefit balance of therapy.

• Report any serious adverse events suggestive of CRS or neurologic toxicities to Celgene Corporation at www.bms.com or 1-888-805-4555, or FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

– For the purpose of this REMS, serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
ABECMA REMS Program Materials

- ABECMA REMS Training Program
- ABECMA REMS Knowledge Assessment
- ABECMA REMS Hospital Enrollment Form
- ABECMA REMS Patient Wallet Card
- ABECMA REMS Adverse Reaction Management Guide
- ABECMA REMS Program Website www.AbecmaREMS.com
Patient Counseling
Patient Counseling

- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Talk to the patient about the risks of CRS and neurologic toxicities and advise patients to seek immediate medical care for any of the following:
  - CRS: fever, hypotension, tachycardia, chills, hypoxia, headache, and fatigue.
  - Neurologic toxicities: signs or symptoms associated with neurologic events including encephalopathy, confusion, seizures, tremor, aphasia, delirium, and somnolence.
  - Patients treated with ABECMA may develop secondary malignancies. In the event that a secondary malignancy occurs, advise patients to contact Bristol Myers Squibb at 1-888-805-4555 for reporting and to obtain instructions on collection of patient samples for testing of secondary malignancy of T cell origin.
- Prior to infusion, provide the patient with the Patient Wallet Card.
- Advise patients for the need to:
  - Remain within 2 hours of the REMS-certified healthcare facility for at least 4 weeks following infusion and return to the REMS-certified healthcare facility if they need medical care.
  - Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after ABECMA administration.
To learn more about the ABECMA REMS, please visit www.AbecmaREMS.com or call 1-888-423-5436.
All Risk Evaluation and Mitigation Strategy (REMS)-trained staff and authorized representatives (ARs) must complete this Knowledge Assessment. All questions must be answered correctly within 3 attempts. Completion of this Knowledge Assessment does not guarantee that your institution will be certified to administer ABECMA.

You can take the Knowledge Assessment online at www.AbecmaREMS.com or by completing a paper copy. All Knowledge Assessments taken via paper must be submitted to the AR, who must send them to Celgene Corporation, a Bristol-Myers Squibb Company, via email at REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

### Knowledge Assessment Personnel Information (all fields required):

<table>
<thead>
<tr>
<th>I am the AR</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>First Name</th>
<th>Last Name</th>
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<table>
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<table>
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<tr>
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<th>Date (MM/DD/YYYY)</th>
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### To Be Completed by the Authorized Representative:

Please indicate which questions were answered correctly by writing yes (Y) or no (N) below.

<table>
<thead>
<tr>
<th>Knowledge Assessment Attempt</th>
<th>Question</th>
<th>Total Grade (example: 7/12)</th>
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</thead>
<tbody>
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<td></td>
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<td>2</td>
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<tr>
<td>3</td>
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</tbody>
</table>

All REMS-trained staff have 3 attempts to complete this Knowledge Assessment. After a third attempt, staff must repeat the REMS Training Program before taking the Knowledge Assessment again.
1. What is the approved indication for ABECMA?
   - O A. Relapsed or refractory (R/R) large B-cell lymphoma after ≥2 prior therapies
   - O B. Adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
   - O C. Primary central nervous system myeloma
   - O D. Newly diagnosed untreated multiple myeloma

2. Which of the following is true regarding the time to onset of cytokine release syndrome (CRS)?
   - O A. Median time to onset is 1 day
   - O B. Median time to onset is 5 days
   - O C. Median time to onset is 2 days
   - O D. Rarely starts during the first week following ABECMA infusion

3. All of the following regarding neurologic toxicity related to ABECMA are correct, except:
   - O A. Neurologic toxicity always occurs concurrently with CRS
   - O B. Perform neurologic work-up as appropriate to exclude other etiologies of neurologic symptoms
   - O C. The median time to onset of neurologic toxicity is 2 days
   - O D. The most common signs or symptoms of neurologic toxicity include encephalopathy, tremor, aphasia, and delirium

4. Every ABECMA REMS-certified institution is required to have a minimum of 2 doses of tocilizumab on site for each patient prior to dispensing and administering ABECMA:
   - O True
   - O False

5. Delay the infusion of ABECMA for up to 7 days if a patient has any of the following conditions:
   - O A. Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension) including those after preceding chemotherapies
   - O B. Active infections or inflammatory disorders
   - O C. None of these
   - O D. A and B

6. A 75-year-old female treated with ABECMA 1 day ago develops a fever >38 °C, myalgias, and mild hypotension that responded to an IV fluid bolus. What is/are the appropriate next step(s) in management?
   - O A. Evaluate the patient for febrile neutropenia/sepsis by obtaining blood and urine cultures, chest X-ray, and complete blood count, and start broad spectrum antibiotics
   - O B. Administer a dose of tocilizumab
   - O C. Discharge the patient home to follow up the next day in the outpatient oncology clinic
   - O D. A and B

7. Before ABECMA infusion, patients should be given the ABECMA Patient Wallet Card and be advised to:
   - O A. Refrain from driving or operating heavy or potentially dangerous machinery until at least 8 weeks following infusion
   - O B. Remain close to the certified treating institution for at least 4 weeks following infusion
   - O C. Seek immediate medical attention if they experience signs or symptoms of CRS and/or neurologic toxicities
   - O D. All of the above

8. Clinically, ABECMA patients with CRS can manifest the following signs and symptoms, except:
   - O A. Hypotension
   - O B. A fever of 100.4 °F (38 °C) or higher
   - O C. Hives
   - O D. Chills or shaking chills

9. Two days after infusion of ABECMA, a 70-year-old female develops the following signs and symptoms of CRS: fever >38 °C, hypotension requiring intravenous fluids, and hypoxia requiring ≤40% FiO₂. This patient’s CRS grade would be most consistent with:
   - O A. Grade 1 CRS
   - O B. Grade 2 CRS
   - O C. Grade 3 CRS
   - O D. Grade 4 CRS

10. A 64-year-old male treated with ABECMA 2 days ago has moderate confusion and difficulty speaking that began an hour ago. He did not have any preceding signs or symptoms of CRS since infusion. What is/are the appropriate next step(s) in management?
    - O A. Obtain imaging of the head to evaluate for the possibility of stroke
    - O B. Start tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)
    - O C. Start dexamethasone 10 mg intravenously every 12 to 24 hours
    - O D. Start nonnonditing antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
    - O E. All of the above except B

11. A 64-year old male developed grade 2 CRS 2 days after receiving ABECMA. Despite receiving tocilizumab and steroids for 48 hours, he has progression of symptoms with worsening hypotension, hypoxia, fever, cytopenia, and worsening renal function. What is/are the appropriate next step(s) in management?
    - O A. Evaluate and treat for hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
    - O B. Optimize management of CRS if HLH/MAS is ruled out
    - O C. Optimize antibiotics, antiviral and antifungal therapy
    - O D. All of the above

12. The following were observed in the KarMMa study:
    - O A. Prolonged neutropenia in 41% and prolonged thrombocytopenia in 49% of the patients treated with ABECMA
    - O B. Median time to recovery of prolonged cytopenia was approximately 2 months post ABECMA
    - O C. Three patients (out of 127) underwent rescue stem cell transplantation for prolonged cytopenia after treatment with ABECMA
    - O D. All of the above
Guidance on Managing Cytokine Release Syndrome (CRS)

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, manage according to the recommendations in Table 1.

Patients who experience CRS should be closely monitored for cardiac and organ function until resolution of symptoms. Consider antiseizure prophylaxis with levetiracetam in patients who experience CRS.

Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry.

For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.

For CRS refractory to first line interventions such as tocilizumab or tocilizumab and corticosteroids, consider alternate treatment options (i.e., higher corticosteroid dose, alternative anti-cytokine agents, anti-T cell therapies). Refractory CRS is characterized by fevers, end-organ toxicity (e.g., hypoxia, hypotension) not improving within 12 hours of first line interventions, or development of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Antiseizure medication according to the neurologic toxicity in Table 2

Please see Table 1: CRS Grading and Management Guidance on the next page.
### Table 1: CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>Tocilizumab†</th>
<th>Corticosteroids‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>If onset 72 hours or more after infusion, treat symptomatically. If onset less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td>
<td>Consider dexamethasone 10 mg IV every 24 hours.</td>
</tr>
<tr>
<td>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.</td>
<td>Consider dexamethasone 10 mg IV every 12 to 24 hours.</td>
</tr>
<tr>
<td>Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO₂ or hypotension responsive to fluids, or low dose of 1 vasopressor, or Grade 2 organ toxicity.</td>
<td>If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Per Grade 2.</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td>Symptoms require and respond to aggressive intervention. Fever, oxygen requirement greater than or equal to 40% FiO₂ or hypotension requiring high-dose or multiple vaspressors, or Grade 3 organ toxicity or Grade 4 transaminitis.</td>
<td>If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Per Grade 2.</td>
<td>Administer dexamethasone 20 mg IV every 6 hours.</td>
</tr>
<tr>
<td>Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).</td>
<td>After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) or other anti-T cell therapies.</td>
<td></td>
</tr>
</tbody>
</table>

FiO₂=fraction of inspired oxygen; IV=intravenous.

*Lee criteria for grading CRS (Lee et al, 2014).†

†Refer to tocilizumab Prescribing Information for details.

‡If corticosteroids are initiated, continue corticosteroids for at least 3 doses, and taper over a maximum of 7 days.
**Guidance on Managing Neurologic Toxicities**

Monitor patients for signs or symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic signs or symptoms. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. If neurologic toxicity is suspected, manage according to the recommendations in Table 2. If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to CRS grade in Table 1
- Antiseizure medication according to neurologic toxicity in Table 2

**Table 2: Neurologic Toxicities Grading and Management Guidance**

<table>
<thead>
<tr>
<th>Neurologic Toxicity Grade*</th>
<th>Corticosteroids and Antiseizure Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 mg IV every 12 hours for 2 to 3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. Steroids are not recommended for isolated Grade 2 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 to 20 mg IV every 6 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided into 4 times a day; taper within 7 days). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m².</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g, repeated every 24 hours if needed; taper as clinically indicated). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m².</td>
</tr>
</tbody>
</table>

*NCI CTCAE criteria for grading neurologic toxicities version 4.03.*

**References:**
Boxed Warning

CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, AND PROLONGED CYTOPENIA

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with ABECMYA. Do not administer ABECMYA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with ABECMYA. Including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with ABECMYA. Provide supportive care and corticosteroids as needed.
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with ABECMYA. HLH/MAS can occur with CRS or neurologic toxicities.
- Prolonged cytopenia with bleeding and infection, including fatal outcomes following stem cell transplantation for hematopoietic recovery, occurred following treatment with ABECMYA.
- ABECMYA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ABECMYA REMS.

About ABECMYA REMS

ABECMYA REMS is a drug safety program to manage known or potential risks associated with a drug and is required by the United States Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. ABECMYA is only available under a restricted program called ABECMYA REMS because of the serious risks of CRS and neurologic toxicities.

The goals of ABECMYA REMS are to mitigate the risks of CRS and neurologic toxicities by:

1. Ensuring that hospitals and their associated clinics that dispense ABECMYA are specially certified and have on-site veterinarians accessible to receive (tocilizumab).
2. Ensuring that those who prescribe, dispense, or administer ABECMYA are aware of how to manage the risks of CRS and neurologic toxicities.

ABECMYA REMS Requirements

All hospitals and their associated clinics must be certified and enrolled in the ABECMYA REMS to be able to dispense ABECMYA.

All relevant staff involved in the prescribing, dispensing, or administering of ABECMYA are trained in ABECMYA REMS requirements, and must successfully complete the Knowledge Assessment and submit it to the REMS Program.

Hospital and Associated Clinic Enrollment Instructions

To become certified to dispense ABECMYA, hospitals and their associated clinics must designate an authorized representative (ARR) to complete REMS requirements, and enroll in ABECMYA REMS. The ARR must:

1. Complete one ABECMYA REMS Training Program (five components, one mandatory, one optional) which includes review of:
   - REUS Training Program
   - REUS Adverse Reaction Management Guide
2. Successfully complete the Knowledge Assessment and submit it to the REMS Program.
3. Oversee implementation and compliance with ABECMYA REMS requirements to:
   - Ensure that all relevant staff involved in prescribing, dispensing, or administering of ABECMYA are trained on the REMS requirements using the Training Program, and successfully completes and submits the Knowledge Assessment, and records are maintained of staff training.
   - Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing, or administering of ABECMYA are trained on ABECMYA REMS if ABECMYA has not been dispensed at least once annually from the date of certification in the ABECMYA REMS.
   - Prior to infusion ABECMYA, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration within 2 hours.
   - Prior to infusion ABECMYA, provide patients with the Patient Notice Card and instruct patients to remain within 2 hours of the certified healthcare facility for at least 4 weeks following ABECMYA infusions.
   - Ensure that when the hospital and its associated clinics designates an ARR, the ARR must complete the Training Program, successfully completes the Knowledge Assessment, and submit it to the REMS Program.
4. Submit a completed Hospital Enrollment Form.

Indication

ABECMYA is a Biel maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.