## Yescarta™ (axicabtagene ciloleucel) – New orphan drug approval

- On October 18, 2017, Kite Pharma, a Gilead company, announced the FDA approval of Yescarta (axicabtagene ciloleucel), for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

    - Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

- DLBCL is the most common type of non-Hodgkin lymphoma (NHL) in adults. Approximately 72,000 new cases of NHL are diagnosed in the U.S. each year, and DLBCL represents approximately one in three newly diagnosed cases.

    - An estimated 7,500 Americans with refractory DLBCL are eligible for chimeric antigen receptor (CAR) T-cell therapy.
    - With current standard of care, patients with refractory large B-cell lymphoma have a median overall survival of approximately 6 months, with only 7% attaining a complete remission (CR).
    - In addition, patients with large B-cell lymphoma in second or later lines of therapy have poor outcomes and greater unmet need, since nearly half of them either do not respond or relapse shortly after transplant.

- Yescarta is a genetically-modified autologous T-cell immunotherapy. Each dose of Yescarta is a customized treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a CAR that directs the T-cell to target and kill certain cancer cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.

- The safety and efficacy of Yescarta were established in a clinical trial involving more than 100 adults with refractory or relapsed large B-cell lymphoma.

    - In the study, 72% of patients treated with Yescarta responded to therapy (overall response rate), including 51% (95% CI: 41, 62) of patients who achieved CR. Furthermore, at a median follow-up of 7.9 months, patients who achieved a CR had not reached the estimated median duration of response.
    - However, 13% of patients experienced ≥ grade 3 cytokine release syndrome (CRS) and 31% experienced neurologic toxicities.

- Yescarta carries a boxed warning regarding CRS and neurologic toxicities.

    - Because of the risk for CRS and neurological toxicities, Yescarta was approved with a Risk Evaluation and Mitigation Strategy (REMS), which includes elements to assure safe use.
    - The FDA is requiring that hospitals and their associated clinics that dispense Yescarta be specially certified.
    - Moreover, to further evaluate the long-term safety, the FDA is also requiring the manufacturer to conduct a post-marketing observational study involving patients treated with Yescarta.

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- Other warnings and precautions include hypersensitivity reactions, serious infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies, and effects on ability to drive and use machines.

- The most common non-laboratory adverse reactions (≥ 20%) with Yescarta use were CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

- The recommended target dose of Yescarta is 2 x $10^6$ CAR-positive viable T-cells per kilogram of body weight given intravenously, with a maximum of 2 x $10^8$ CAR-positive viable T-cells.

    - Yescarta is for autologous use only. Patient's identity must be verified prior to infusion.
    - Patients should be administered a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of Yescarta.
    - Patients should be premedicated with acetaminophen and an H1-antihistamine.
    - Do not use a leukodepleting filter.
    - Confirm availability of Actemra® (tocilizumab) prior to infusion.
    - Thaw Yescarta prior to infusion. Once thawed, Yescarta may be stored at room temperature (20°C – 25°C) up to 3 hours.

- Yescarta is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper.

- In support of Yescarta, Kite has developed KiteKonnect™, a program that provides information, assistance, and resources for patients and healthcare providers.

- Gilead will market Yescarta at an annual cost of $373,000.

- Kite will provide initial site certification to 16 centers and is actively working to train more than 30 additional centers, with an eventual target of 70 to 90 centers across the U.S. Yescarta will be available as a frozen suspension of genetically modified autologous T-cells in one infusion bag labeled for the specific recipient.