Product: YESCARTA

Proper Name: axicabtagene ciloleucel

Manufacturer: Kite Pharma, Incorporated

Indication: Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

Description: YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated 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.

BLA: STN BL 125643

Regulatory Milestone:

DATE	MILESTONE
12/2014	IND 16278 Submission
03/2014	orphan designation for DLBCL granted
4/2016	orphan designation for PMBCL granted
4/2016	orphan designation for FL granted
12/2015	Breakthrough Therapy Designation in 12/2015 for refractory, aggressive NHL granted
10/2016	Type B pre-BLA meeting
	BLA 125610 Submission (rolling submission)
12/2/2016	• First module
3/31/2017	• Final module
5/31/2017	Teleconference due to inadequate follow-up for efficacy
12/2016	• Independent Review Committee (IRC)
1/2017	• investigator

11/29/2017	Prescription Drug User Fee Act Action Due Date

IND 16278, submitted 12/2014, investigates axicabtagene ciloleucel in aggressive B-cell lymphomas. Axicabtagene ciloleucel was granted orphan designation for DLBCL (3/2014), PMBCL (4/2016), and FL (4/2016) and received Breakthrough Therapy Designation in 12/2015 for refractory, aggressive NHL. In a Type B pre-BLA meeting in 10/2016, FDA indicated that it was premature to submit a BLA on 12/30/2016 due to <6-month follow-up for efficacy in the ZUMA-1 study and fewer than the prespecified number of subjects in the primary analysis. FDA requested data on response and response duration after 6 months follow-up for all subjects. The Agency agreed to a rolling submission, with a late component on the chain-of-custody/chain-of-identity process validation to be received within 30 days. The first module was submitted on 12/2/2016 and the final modules on 3/31/2017. After BLA submission, a teleconference was held 5/31/2017 due to inadequate follow-up for efficacy with 12/2016 (Independent Review Committee (IRC)) and 1/2017 (investigator) data cuts. Alignment was reached to submit updated efficacy data by 6/30/2017, using a 4/26/2017 cut-off date for both investigator and IRC assessments. The PDUFA action due date is 11/29/2017.

PDUFA Goal Date: November 29, 2017

FDA approval Date: October 18, 2017

EU approval: August 23, 2018

Health Canada approval: December 10, 2020

Australian Therapeutics Goods Administration (TGA): February 11, 2020

Japanese Ministry of Health, Labor and Welfare (MHLW) approval: January 22, 2021

Package Insert: YESCARTA

Summary Basis for Regulatory Approval: October 18, 2017 Summary Basis for Regulatory Action - YESCARTA

European Public Assessment Report: October 10,2018 Assessment report - YESCARTA

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	Kite Pharma, Incorporated	
Transgene	survival motor neuron gene (SMN1)	3
Indication	YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated 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 To DLBCL arising from follicular lymphoma	3
Virus and Serotype	Retroviral vector PG13-CD19-H3	2
Cell Substrate	Autologous stably-transduced PG13 (ATCC CRL-10686™) T cell	3
Manufacturing platform	**Retroviral vector PG13-CD19-H3:** The PG13-CD19-H3 vector is produced constitutively from a stably-transduced PG13 (ATCC CRL-10686™) cell line. For production of retroviral vector under GMP, cells from a single vial of WCB are expanded and the culture supernatant is harvested, filtered, and filled into cryostorage bags. **Axicabtagene ciloleucel:** Autologous T cells genetically modified ex vivo by transduction with a retroviral vector to express an anti-CD19 CD28/CD3ζ CAR to target CD19 on the cell surface of malignant B cells.	3

Dose in vial/final container	Suspension of 2 × 106 CAR-positive viable T cells per kg of body weight, with a maximum of 2 × 108 CAR-positive viable T cells in approximately 68 mL	1
Dose / patient	2 × 106 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108 CAR-positive viable T cells	1

1. Package insert: Package Insert - YESCARTA
2. EPAR full: Yescarta
3. EPAR quality: October 10,2018 Assessment report - YESCARTA
4. FDA SBAR – quality: October 18, 2017 Summary Basis for Regulatory Action - YESCARTA

Advisory Committee:

This application was not presented to an Advisory Committee, because YESCARTA is not the first biologic in its class, and there were no critical review issues that required input from an Advisory Committee.

Safety:

Long-term safety after treatment with YESCARTA, particularly from the risk of insertional mutagenesis-related secondary malignancies, remain a concern due to the limited follow-up duration. Therefore, a post-marketing requirement (PMR) study is warranted. As a PMR, the Applicant agreed to conduct an observational registry study that will collect safety information for patients treated with marketed product, including key early adverse reactions and follow-up for 15 years for detection and evaluation of second malignancies. No routine collection of samples to evaluate for RCR is planned as part of this study.

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	TITLE	COUNTRIES
NCT02348216	1, 2	307	Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma	United States, Canada, France, Germany, Israel, Netherlands
NCT02601313	2	105	Study to Evaluate the Efficacy of Brexucabtagene Autoleucel (KTE-X19) in Participants With Relapsed/Refractory Mantle Cell Lymphoma	United States, France, Germany, Netherlands

EudraCT Numbers:

- 2015-005007-86
- 2017-002261-22
- 2019-002291-13

Publications:

- Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., Braunschweig, I., Oluwole, O. O., Siddiqi, T., Lin, Y., Timmerman, J. M., Stiff, P. J., Friedberg, J. W., Flinn, I. W., Goy, A., Hill, B. T., Smith, M. R., Deol, A., Farooq, U., McSweeney, P., … Go, W. Y. (2017). Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. The New England journal of medicine, 377(26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447
- Bouchkouj, N., Kasamon, Y. L., de Claro, R. A., George, B., Lin, X., Lee, S., Blumenthal, G. M., Bryan, W., McKee, A. E., & Pazdur, R. (2019). FDA Approval Summary: Axicabtagene Ciloleucel for Relapsed or Refractory Large B-cell Lymphoma. Clinical cancer research: an official journal of the American Association for Cancer Research, 25(6), 1702–1708. https://doi.org/10.1158/1078-0432.CCR-18-2743

- Locke, F. L., Ghobadi, A., Jacobson, C. A., Miklos, D. B., Lekakis, L. J., Oluwole, O. O., Lin, Y., Braunschweig, I., Hill, B. T., Timmerman, J. M., Deol, A., Reagan, P. M., Stiff, P., Flinn, I. W., Farooq, U., Goy, A., McSweeney, P. A., Munoz, J., Siddiqi, T., Chavez, J. C., … Neelapu, S. S. (2019). Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. The Lancet. Oncology, 20(1), 31–42. https://doi.org/10.1016/S1470-2045(18)30864-7
- Brudno, J. N., Lam, N., Vanasse, D., Shen, Y. W., Rose, J. J., Rossi, J., Xue, A., Bot, A., Scholler, N., Mikkilineni, L., Roschewski, M., Dean, R., Cachau, R., Youkharibache, P., Patel, R., Hansen, B., Stroncek, D. F., Rosenberg, S. A., Gress, R. E., & Kochenderfer, J. N. (2020). Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma. Nature medicine, 26(2), 270–280. https://doi.org/10.1038/s41591-019-0737-3
- Sesques, P., Ferrant, E., Safar, V., Wallet, F., Tordo, J., Dhomps, A., Karlin, L., Brisou, G., Vercasson, M., Hospital-Gustem, C., Schwiertz, V., Ranchon, F., Rioufol, C., Choquet, M., Sujobert, P., Ghergus, D., Bouafia, F., Golfier, C., Lequeu, H., Lazareth, A., … Bachy, E. (2020). Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. American journal of hematology, 95(11), 1324–1333. https://doi.org/10.1002/ajh.25951
- Abramson, J. S., Palomba, M. L., Gordon, L. I., Lunning, M. A., Wang, M., Arnason, J., Mehta, A., Purev, E., Maloney, D. G., Andreadis, C., Sehgal, A., Solomon, S. R., Ghosh, N., Albertson, T. M., Garcia, J., Kostic, A., Mallaney, M., Ogasawara, K., Newhall, K., Kim, Y., … Siddiqi, T. (2020). Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell

lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet (London, England), 396(10254), 839–852. https://doi.org/10.1016/S0140-6736(20)31366-0