POLICY: Oncology – Gazyva® (obinutuzumab injection for intravenous use – Genentech, Inc.)

APPROVAL DATE: 10/09/2019

OVERVIEW

Gazyva is a humanized anti-CD20 IgG1 monoclonal antibody engineered for reduced fucose content.[1] Gazyva binds to CD20 on pre-B and mature B lymphocytes and induces cell lysis by engagement of immune effector cells, by activation of intracellular death signaling pathways, and/or by activating the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis. The reduced fucose content of Gazyva compared to rituximab results in greater ADCC activity *in vitro* in human cancer cell lines.

Gazyva is indicated for use:

- In combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia;
- In combination with bendamustine and followed by Gazyva monotherapy for the treatment of patients with follicular lymphoma who relapse or are refractory to a rituximab containing regimen;
- In combination with chemotherapy and followed by Gazyva monotherapy for patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.[1]

Dosing

The FDA approved dosing regimen for Gazyva recommends up to 6 cycles (6 months) of therapy for chronic lymphocytic leukemia.[1] For follicular lymphoma, the FDA approved dosing regimen for Gazyva recommends up to 6 months (six 28-day cycles or up to eight 21-day cycles) of therapy. Patients with relapsed or refractory follicular lymphoma who achieve stable disease, or a complete or partial response; or patients with previously untreated follicular lymphoma who achieve a complete or partial response, should continue Gazyva monotherapy for up to 2 years.

In the GADOLIN study, adult patients with rituximab refractory non-Hodgkin lymphoma were randomized to treatment with Gazyva 1,000 mg on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2 – 6 plus bendamustine 90 mg/m^2 on Days 1 and 2 of Cycles 1 – 6 or bendamustine 120 mg/m^2 on Days 1 and 2 of Cycles 1 – 6 (28-day cycles).[2] Patient without disease progression in the Gazyva plus bendamustine group could receive maintenance therapy with Gazyva 1,000 mg once every 2 months for up to 2 years. Patients in the Gazyva and bendamustine group has significantly longer progression-free survival than the bendamustine monotherapy group (median not reached vs. 14.9 months, respectively; hazard ratio: 0.55; 95% confidence interval: 0.40, 0.74; P = 0.0001).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) (version 1.2020 – August 23, 2019) recommends Gazyva as a single agent (category 2B) or in combination with chlorambucil, bendamustine, venetoclax (Category 2A), or ibrutinib (category 2B) for the first-line treatment of CLL/SLL without del(17p)/TP53 mutation; as a single agent or in combination with venetoclax for the first-line treatment of CLL/SLL with del(17p)/TP53 mutation (category 2A); and as a single agent for relapsed or refractory CLL/SLL without del(17p)/TP53 mutation (category 2A).[3,4]

The NCCN guidelines on B-Cell Lymphomas (version 4.2019 – June 18, 2019) recommend Gazyva for the first-line and second-line treatment of follicular lymphoma (grade 1 or 2) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or bendamustine; or as maintenance treatment.[3,5] The guidelines also recommend Gazyva as second-line or maintenance therapy for gastric and nongastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma. Gazyva is also recommended as a substitute for rituximab products (e.g., Rituxan, Truxima) in patients experiencing rare complications, regardless of histology.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Gazyva. Approval is recommended for those who meet the Criteria and Dosing for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Gazyva as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Gazyva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gazyva is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.** Approve for 6 months if the patient meets the following criteria (A and B):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** Gazyva is prescribed by or in consultation with an oncologist.

   Dosing. Approve the following dosing (A, B, C, and D):
   - **A)** Each individual dose must not exceed 1,000 mg administered by intravenous infusion; AND
   - **B)** The first dose is divided and administered on Day 1 (100 mg) and Day 2 (900 mg) of Cycle 1; AND
   - **C)** The patient receives a maximum of two additional doses in Cycle 1; AND
   - **D)** The patient receives a maximum of one dose in each subsequent 28-day cycle.[1]

2. **Follicular Lymphoma.** Approve for 6 months if the patient meets the following criteria (A, B, and C):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** Gazyva will be used in ONE of the following situations (i, ii, or iii):
     - **i.** In combination with chemotherapy.
       (Note: Examples include CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CVP [cyclophosphamide, vincristine, and prednisone], or bendamustine); OR
     - **ii.** For maintenance treatment following Gazyva in combination with chemotherapy; OR
     - **iii.** The patient experienced an adverse event or intolerance to a rituximab product.

(Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis);[3,5] AND

C) Gazyva is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing (A, B, and C):

A) Each individual dose must not exceed 1,000 mg administered by intravenous infusion; AND

B) The patient receives a maximum of three doses in Cycle 1; AND

C) The patient receives a maximum of one dose in each subsequent cycle (21-day cycle, 28-day cycle, or 2 month cycle).[1]

Other Uses with Supportive Evidence

3. Marginal Zone Lymphoma (Note: Includes Nodal Marginal Zone Lymphoma, Splenic Marginal Zone Lymphoma, Gastric MALT, or Nongastric MALT). Approve for 6 months if the patient meets the following criteria (A, B, and C):

A) The patient is ≥ 18 years of age; AND

B) Gazyva will be used in ONE of the following situations (i or ii):

i. Second-line or subsequent therapy for recurrent or progressive disease; OR

ii. The patient experienced an adverse event or intolerance to a rituximab product.
(Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis);[3,5] AND

C) Gazyva is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing (A, B, and C):

A) Each individual dose must not exceed 1,000 mg given by intravenous infusion; AND

B) The patient receives a maximum of three doses in Cycle 1; AND

C) The patient receives a maximum of one dose in each subsequent cycle (28-day cycle, or 2 month cycle).[2]

4. Other B-Cell Lymphomas. (Note: Includes Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, High-Grade B-Cell Lymphoma, Burkitt Lymphoma, AIDS-Related B-Cell Lymphoma, Post-Transplant Lymphoproliferative Disorders, Castleman's Disease). Approve for 6 months if the patient meets the following criteria (A, B, and C):

A) The patient is ≥ 18 years of age; AND

B) The patient experienced an adverse event or intolerance to a rituximab product.
(Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis];[3,5] AND

C) Gazyva is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing (A, B, and C):

A) Each individual dose must not exceed 1,000 mg given by intravenous infusion; AND

B) The patient receives a maximum of three doses in Cycle 1; AND

C) The patient receives a maximum of one dose in each subsequent cycle (28-day cycle, or 2 month cycle).[2]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Gazyva has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gazyva® [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2017.
2. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomized, controlled, open-label, multicenter, phase 3 trial. *Lancet Oncol*. 2016;17:1081-1093.
3. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 30, 2019. Search term: obinutuzumab.
4. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2020 – August 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 30, 2019.
5. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2019 – June 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 30, 2019.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	01/03/2019
Early annual	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Removed first-line treatment in combination with one other agent criteria, first-line single agent criteria and criteria for single agent treatment of relapsed/refractory disease.	10/09/2019