POLICY: Oncology – Imlygic® (talimogene laherparepvec intralesional injection – Amgen)

APPROVAL DATE: 02/20/2019

OVERVIEW

Imlygic is an oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.[1] It is a limitation of use that Imlygic has not been shown to improve overall survival or have an effect on visceral metastases. Imlygic should be continued for at least 6 months, unless other treatment is required or there are no injectable lesions to treat and may also be reinitiated if new unresectable cutaneous, subcutaneous, or nodal lesions appear following a complete response. In the pivotal trial, adults with unresectable stage III (30%) or stage IV (70%) melanoma were treated for at least 6 months, or until no remaining injectable lesions. During the initial 6 months of the trial, treatment continued despite increased size or number of lesions. Following 6 months of treatment, patients could continue Imlygic until clinically relevant disease progression (i.e., disease progression associated with a decline in performance status and/or alternative therapy was needed, according to the prescriber). Imlygic requires specialized storage conditions (-130° to -94° F). Personal protective equipment (including a gown/laboratory coat, safety glasses or face shield, and gloves) while preparing or administering, and procedures for accidental exposure to Imlygic should be followed. Healthcare providers should be prepared to manage adverse events, including immune-mediated events (e.g., glomerulonephritis, vasculitis, pneumonitis) and plasmocytoma at the injection site.

Disease Overview

Oncolytic virus immunotherapy is a form of cancer therapy which uses native or genetically modified viruses to selectively enter, replicate, and lyse tumor cells.[2] Oncolytic viruses are able to be engineered to deliver therapeutic genes to cancer cells, thus, causing additional antitumor effects through cytokine secretion and induction of antitumor immune response.[3] Of note, herpes simplex virus (HSV)-1 is an attractive option for oncolytic virus therapy because it can infect a wide range of host cells and causes lysis following viral replication.[2] Imlygic, previously referred to as T-VEC, is the first oncolytic virus immunotherapy approved in the US. It is genetically modified to attenuate HSV-1, increase selectivity for cancer cells, and secrete granulocyte macrophage colony-stimulating factor (GM-CSF). Secretion of GM-CSF is intended to enhance tumor antigen presentation to the immune system and induce systemic immune responses to the tumors.[3]

Clinical Efficacy

In the pivotal trial, the initial dose of Imlygic was administered at 10^6 PFU/mL (to seroconvert HSV-seronegative patients). Subsequent doses were 10^8 PFU/mL administered 3 weeks after the first dose, then every 2 weeks. Total volume of Imlygic was up to 4.0 mL per treatment session. It may not be possible to inject all lesions at each treatment visit or over the full course of treatment. Previously injected and/or uninjected lesions may be injected at subsequent treatment visits. Continue treatment for at least 6 months unless other treatment is required or until there are no injectable lesions to treat. Imlygic may be reinitiated if new unresectable cutaneous, subcutaneous, or nodal lesions appear after a complete response. Refer to the Appendix for injection volume associated with lesion size.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for melanoma (version 1.2019 – January 19, 2018) list Imlygic as an option in multiple treatment situations, including as primary and second-line treatment for Stage III melanoma; for recurrent disease (including nodal recurrence) and second-line or subsequent therapy; for disseminated metastatic disease; and in combination with Yervoy (ipilimumab injection), for metastatic or unresectable disease following disease progression or maximal clinical benefit from BRAF targeted therapy.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Imlygic. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the criteria and dosing. 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 Imlygic as well as the monitoring required for adverse events and long-term efficacy, approval requires Imlygic to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. Melanoma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy (This includes reinitiation in patients with new lesions following a complete response). Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

- **i.** The patient is an adult ≥ 18 years of age; AND
- **ii.** Imlygic will be directly injected into metastatic, recurrent, or unresectable cutaneous, subcutaneous, or nodal lesions; AND
- **iii.** Imlygic will be administered by or under the supervision of an oncologist, dermatologist, or surgeon.

B) Patinet is Currently Receiving Imlygic. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

- **i.** The patient has remaining injectable lesions for treatment; AND
- **ii.** According to the prescriber, the patient has not experienced clinically relevant disease progression (e.g., disease progression associated with a decline in performance status and/or alternative therapy was needed); AND
- **iii.** Imlygic will be administered by or under the supervision of an oncologist, dermatologist, or surgeon.

Dosing. Approve the following dosing regimens:

A) The dose is one of the following:

- **i.** The initial dose is 10^6 (1 million) plaque-forming units (PFU)/mL; OR
- **ii.** Subsequent doses are 10^8 (100 million) PFU per mL with the second dose given 3 weeks after the initial dose and all additional doses (including reinitiation) are given once every 2 weeks; AND

B) Up to a maximum of 4 mL is administered per treatment visit.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Imlygic 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with Anti-Herpetic Viral Agents.** Imlygic is a genetically modified, live, attenuated HSV-1 that is sensitive to acyclovir. Anti-herpetic viral agents (e.g., acyclovir, valacyclovir, famciclovir) may interfere with efficacy.

2. **Immoncompromised Patients.** Imlygic is contraindicated in patients who are immunocompromised, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, acquired immunodeficiency syndrome (AIDS), or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy.

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

REFERENCES

1. Imlygic intralesional injection [prescribing information]. Thousand Oaks, CA: BioVex/Amgen; December 2018.
2. Dharmadhikari N, Mehnert JM, Kaufman HL. Oncolytic virus immunotherapy for melanoma. *Curr Treat Options Oncol*. 2015;16(3):326.
3. Moehler M, Goepfert K, Heinrich B, et al. Oncolytic virotherapy as emerging immunotherapeutic modality: potential of parvovirus h-1. *Front Oncol*. 2014;4:92.
4. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 1.2019 – November 1, 2018). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 8, 2019.

HISTORY

Type of Revision	Summary of Changes*	Approval Date
New Policy	--	08/22/2018
Early annual revision	Melanoma: Criteria for initial therapy were clarified to specifically include patients with metastatic disease.	02/20/2019

APPENDIX

Lesion Size (longest dimension)	Injection volume
> 5 cm	Up to 4 mL
> 2.5 cm to 5 cm	Up to 2 mL
> 1.5 cm to 2.5 cm	Up to 1 mL
> 0.5 cm to 1.5 cm	Up to 0.5 mL
≤ 0.5 cm	Up to 0.1 mL