

Angiogenesis Inhibitors:
Avastin® (bevacizumab)
Alymsys® (bevacizumab-maly)
Mvasi® (bevacizumab-awwb)
Cyramza® (ramucirumab)
Vegzelma® (bevacizumab-adcd)
Zaltrap® (ziv-aflibercept)
Zirabev® (bevacizumab-bvzr)
Effective 06/05/23

Plan	<input checked="" type="checkbox"/> MassHealth UPPL <input type="checkbox"/> Commercial/Exchange	Program Type	<input checked="" type="checkbox"/> Prior Authorization <input type="checkbox"/> Quantity Limit <input type="checkbox"/> Step Therapy
Benefit	<input type="checkbox"/> Pharmacy Benefit <input checked="" type="checkbox"/> Medical Benefit (NLX)		
Specialty Limitations			
Contact Information	Specialty Medications		
	All Plans	Phone: 866-814-5506	Fax: 866-249-6155
	Non-Specialty Medications		
	MassHealth	Phone: 877-433-7643	Fax: 866-255-7569
	Commercial	Phone: 800-294-5979	Fax: 888-836-0730
	Exchange	Phone: 855-582-2022	Fax: 855-245-2134
	Medical Specialty Medications (NLX)		
	All Plans	Phone: 844-345-2803	Fax: 844-851-0882
Exceptions	N/A		

Overview

Avastin® (bevacizumab) is recombinant, humanized monoclonal antibody (mAb) indicated for the treatment of cervical cancer, metastatic colorectal cancer (mCRC), non-squamous non-small cell lung cancer (NSCLC), glioblastoma, metastatic renal cell carcinoma, ovarian cancer (stage III or IV following initial resection, platinum-resistant, or platinum-sensitive), and hepatocellular carcinoma; often as a part of combination therapy.

Alymsys® (bevacizumab-maly), Mvasi® (bevacizumab-awwb), Vegzelma® (bevacizumab-adcd), and Zirabev® (bevacizumab-bvzr) are biosimilars to the reference product Avastin® (bevacizumab). Alymsys® (bevacizumab-maly) has all of the same FDA-approved indications as Avastin® (bevacizumab) except for several ovarian cancer indications and hepatocellular carcinoma. Mvasi® (bevacizumab-awwb), Vegzelma® (bevacizumab-adcd) and Zirabev® (bevacizumab-bvzr) have all of the same FDA-approved indications as Avastin® (bevacizumab) except for hepatocellular carcinoma.

Cyramza® (ramucirumab) is a fully human immunoglobulin G1 (IgG1) mAb that is indicated for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy; in combination with docetaxel, for the treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy; in combination with FOLFIRI (irinotecan plus 5- fluorouracil [5-FU]/leucovorin), for the

treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine; and as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL and have been treated with sorafenib.

Zaltrap® (ziv-aflibercept) is a fully humanized recombinant fusion protein that functions as a decoy VEGF receptor that is indicated for patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen.

No PA	Require PA
Alternatives vary by specific malignancy and may include systemic chemotherapy (e.g., platinum [cisplatin, carboplatin]-containing regimens for non-small cell lung cancer).	Alymsys® (bevacizumab-maly) Avastin® (bevacizumab) Cyramza® (ramucirumab) Mvasi® (bevacizumab-awwb) Vegzelma® (bevacizumab-adcd) Zaltrap® (ziv-aflibercept) Zirabev® (bevacizumab-bvzr)

Coverage Guidelines

Authorization may be reviewed on a case by case basis for members who are new to the plan currently receiving treatment with requested medication excluding when the product is obtained as samples or via manufacturer’s patient assistance programs.

OR

Authorization may be granted for members when all the following criteria are met, and documentation is provided:

Alymsys® (bevacizumab-maly), **Avastin®** (bevacizumab), **Mvasi®** (bevacizumab-awwb), **Zirabev®** (bevacizumab-bvzr), and **Vegzelma®** (bevacizumab-adcd)

Prescriber provides documentation of **ONE** of the following:

1. Diagnosis of **cervical cancer**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Requested agent will be used in combination with paclitaxel and cisplatin OR paclitaxel and topotecan
2. **ALL** of the following:
 - a. Diagnosis of **ONE** of the following:
 - i. recurrent glioblastoma
 - ii. Ovarian cancer
 - iii. Fallopian cancer
 - iv. Primary peritoneal cancer
 - b. Prescriber is an oncologist
 - c. Appropriate dosing (weight required)
3. Diagnosis of **metastatic colorectal cancer (mCRC)**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Requested agent will be used in combination with fluoropyrimidine-, capecitabine-, oxaliplatin-, or irinotecan-containing therapy



4. Diagnosis of **metastatic renal cell carcinoma (mRCC)**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. If predominant clear cell histology, requested agent will be used in combination with interferon alfa
5. Diagnosis of **metastatic non-small cell lung cancer (NSCLC)** (subtype adenocarcinoma or large cell carcinoma)
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Requested agent will be used in combination with carboplatin and paclitaxel (See appendix)
6. Diagnosis of **Nonsquamous NSCLC with EGFR mutation positive** (e.g., Exon 19 deletion or L858R) – off label
 - a. Prescriber is an oncologist
 - b. Requested agent will be used in combination with erlotinib
7. Diagnosis of **adenocarcinoma, large cell, NSCLC not otherwise specified with PD-L1 expression positive** – off label
 - a. Prescriber is an oncologist
 - b. Requested agent will be used in combination with carboplatin, paclitaxel and atezolizumab *
8. Diagnosis of **advanced or metastatic NSCLC (initial therapy)**
 - a. Prescriber is an oncologist
 - b. Member is documented to have a contraindication to PD-1 or PD-L1 inhibitors**
 - c. **ONE** of the following:
 - i. Requested agent will be used in combination with carboplatin and pemetrexed
 - ii. Requested agent will be used in combination with cisplatin and pemetrexed
9. Diagnosis of **advanced or metastatic NSCLC (maintenance therapy)**
 - a. Prescriber is an oncologist
 - b. **ONE** of the following:
 - i. Requested agent will be used as monotherapy
 - ii. Requested agent will be used in combination with atezolizumab
 - iii. Requested agent will be used in combination with pemetrexed

**(If positive response to first-line therapy or member noted to have stable disease, bevacizumab plus atezolizumab can be continued together without carboplatin and paclitaxel)*

****(Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (i.e., EGFR exon 19 deletion or L858R, ALK rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.*

Avastin® (bevacizumab)

Prescriber provides documentation of **ONE** of the following:

1. Diagnosis of **unresectable or metastatic hepatocellular carcinoma (HCC)**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Requested agent will be used in combination with Tecentriq® (atezolizumab)
 - d. Member has Child-Pugh Class A
2. **ALL** of the following:
 - a. Diagnosis of one of the following:
 - i. Wet age-related macular degeneration (AMD)



- ii. Macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR) or myopic choroidal neovascularization (mCNV)
- b. Requested dosing is 1.25 mg intravitreally every four or eight weeks or as needed

Cyramza® (ramucirumab)

Prescriber provides documentation of **ALL** of the following:

1. Diagnosis of **gastric or GEJ adenocarcinoma**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Physician documented of an inadequate response or adverse reaction to ONE, or contraindication to BOTH of the following:
 - i. fluoropyrimidine-containing chemotherapy regimen
 - ii. platinum-containing chemotherapy regimen
3. Diagnosis of **HCC**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Alpha fetoprotein (AFP) \geq 400 ng/mL
 - d. Physician documented of an inadequate response, adverse reaction, or contraindication to Nexavar® (sorafenib)
4. Diagnosis of **mCRC**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. Requested agent will be used in combination with FOLFIRI (irinotecan, leucovorin and 5-fluorouracil) or irinotecan
 - d. Physician documented of an inadequate response, adverse reaction, or contraindication to a 5-fluorouracil/leucovorin or capecitabine-based regimen
5. Diagnosis of **NSCLC**
 - a. Prescriber is an oncologist
 - b. Appropriate dosing (weight required)
 - c. **ONE** of the following:
 - i. **ALL** of the following:
 1. Requested agent will be used in combination with docetaxel
 2. Physician documented of an inadequate response, adverse reaction, or contraindication to a platinum-containing chemotherapy regimen
 - ii. **ALL** of the following:
 1. Requested agent will be used in combination with erlotinib
 - iii. Physician documentation of an EGFR exon 19 deletion or exon 21 L858R mutation
 - iv. Physician documented of an inadequate response, adverse reaction, or contraindication to Tagrisso® (osimertinib) and **ONE** of the following:
 1. Gilotrif® (afatinib)
 2. Iressa® (gefitinib)

Zaltrap® (ziv-aflibercept)

Prescriber provides documentation of **ALL** of the following:

1. Diagnosis of **mCRC**
2. Prescriber is an oncologist
3. Appropriate dosing (weight required)
4. Requested agent will be used in combination with either irinotecan or FOLFIRI



5. Physician documented of an inadequate response or adverse reaction to ONE of the following regimens or a contraindication to ALL of the following regimens:
 - a. CAPEOX
 - b. FOLFOX
 - c. A fluoropyrimidine (capecitabine or 5-FU)
 - d. oxaliplatin-based therapy
6. Physician documented of an inadequate response, adverse reaction, or a contraindication to a bevacizumab product

Continuation of Therapy

Resubmission by prescriber will infer a positive response to therapy.

Limitations

1. Initial approvals will be granted for 6 months.
2. Reauthorizations will be granted for the following:
 - a. Avastin® (bevacizumab) for diagnosis of Wet AMD or macular edema following RVO, DME, DR, or mCNV: 12 months
 - b. All other agents: 6 months

Appendix

Chemotherapy Regimens

Platinum-based chemotherapy regimens that may be used to treat NSCLC often include cisplatin and carboplatin.

Platinum-based chemotherapy regimens that may be used to treat gastric cancer often include cisplatin, carboplatin, and oxaliplatin. Fluoropyrimidine include fluorouracil (5-FU) or capecitabine.

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2022. 2021 Dec 20 [cited 2022 Jan 14]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
2. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast*. 2014 Oct;23(5):489-502. doi: 10.1016/j.breast.2014.08.009.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Ovarian Cancer. Version 3.2021. 2021 Sep 9 [cited 2021 Sep 20] Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Cervical Cancer. Version 1.2022. 2021 Oct 26 [cited 2022 Jan 14]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Colon Cancer. Version 3.2021. 2021 Sep 10 [cited 2021 Sep 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
6. NCCN Practice Guidelines in Oncology. Rectal Cancer Version 2.2021 [guideline on the Internet]. 2021 Sep 10 [cited 2021 Dec 3]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer. Version 1.2022. 2021 Dec 7 [cited 2022 Jan 14]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.



8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Central Nervous System Cancers. Version 2.2021. 2021 Sep 8 [cited 2021 Sep 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Kidney Cancer. Version 4.2022. 2021 Dec 21 [cited 2022 Jan 14]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Hepatobiliary Cancers. Version 5.2021. 2021 Sep 12 [cited 2022 Jan 14]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.
11. National Comprehensive Cancer Network (NCCN). NCCN Guidelines For Treatment Of Cancer By Site [webpage on the internet]. NCCN; 2021 [cited 2021 Apr 28]. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx#site
12. Cyramza® [package insert]. Indianapolis (IN): Eli Lilly & Co; 2021 Jun.
13. Lilly's CYRAMZA™ (ramucirumab) Becomes First FDA-Approved Treatment for Advanced Gastric Cancer After Prior Chemotherapy [press release on the Internet]. Indianapolis (IN): Eli Lilly & Co; 2014 Apr 21 [cited 2017 Aug 7]. Available from: <http://lilly.mediaroom.com/index.php?s=9042&item=137294>.
14. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Gastric Cancer Version 2.2022. 2022 Jan 11 [cited 2022 Jan 14]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
15. Zaltrap® [package insert]. Bridgewater (NJ): Sanofi-Aventis U.S. LLC; 2020 Nov.
16. Abraham J. Ziv-aflibercept plus FOLFIRI improves survival in second-line treatment of metastatic colorectal cancer. *Commun Oncol*. 2012;9:1201.
17. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausova J, Macarulla T, et al. Addition of Ziv-aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial In Patients With Metastatic Colorectal Cancer Previously Treated with an Oxaliplatin-Based Regimen. *J Clin Oncol*. 2012.
18. Covert DJ, Han DP. Retinal vein occlusion: Treatment. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2021 Sep [cited 2021 Sep 20]. Available from: <http://www.utdol.com/utd/index.do>.
19. Arroyo JG, Age-related macular degeneration: Treatment and prevention. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2021 Apr [cited 2021 Sep 20]. Available from: <http://www.utdol.com/utd/index.do>.
20. Fraser CE, D'Amico DJ, Shah AR, Diabetic retinopathy: Prevention and treatment. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2021 Aug [cited 2021 Sep 20]. Available from: <http://www.utdol.com/utd/index.do>.
21. Cheung CMG, Arnold JJ, Holz FG, Park KH, Lai TYY, Larsen M, et al. Myopic Choroidal Neovascularization: Review, Guidance, and Consensus Statement on Management. *Ophthalmology*. 2017;124(11):1690-1711.
22. Eli Lilly and Company. A Study of Paclitaxel With or Without Ramucirumab (IMC-1211B) in Metastatic Gastric Adenocarcinoma (RAINBOW). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 Aug 7]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01170663>.
23. Alymsys® (bevacizumab-maly) [package insert]. Bridgewater (NJ): Amneal Pharmaceuticals LLC; 2022 Apr.
24. Vegzelma® [package insert]. Incheon, Republic of Korea: Celltrion, Inc.; 2022 Nov.

Review History

02/08/2023 - Reviewed and created for Feb P&T; Matched MH UPPL criteria. Added Cyramza and Zaltrep criteria. Renamed criteria to "Angiogenesis Inhibitors." Added Alymsys (bevacizumab-maly). Information for off-label utilization of intravitreal Avastin for wet AMD, macular edema following RVO, DME, or DR added to criteria. Clarified approval durations. Formatting updates. Effective 4/1/23.



05/10/23 – Reviewed and updated for P&T. Added Vegzelma® (bevacizumab-adcd) to policy. Added indication of myopic choroidal neovascularization (mCNV) for Avastin. Effective 6/5/23

