Reference number(s)
2477-A

STANDARD MEDICARE PART B MANAGEMENT

AVASTIN (bevacizumab) – Oncology
ALYMSYS (bevacizumab-maly) – Oncology
MVASI (bevacizumab-awwb) – Oncology
VEGZELMA (bevacizumab-adcd) - Oncology
ZIRABEV (bevacizumab-bvzr) – Oncology

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Metastatic colorectal cancer (mCRC)
   i. Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer.
   ii. Avastin/Alymsys/Mvasi/Vegzelma/Zirabev in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen.
2. First-line non-squamous non-small cell lung cancer (NSCLC)
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer.
3. Recurrent glioblastoma (GBM)
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev is indicated for the treatment of recurrent glioblastoma in adults.
4. Metastatic renal cell carcinoma (mRCC)
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.
5. Persistent, recurrent, or metastatic cervical cancer
   Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.
6. Epithelial ovarian, fallopian tube, or primary peritoneal cancer
   i. Avastin/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, followed by Avastin/Mvasi/Vegzelma/Zirabev as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
   ii. Avastin/Alymsys/Mvasi/Vegzelma/Zirabev, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

iii. Avastin/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin/Mvasi/Vegzelma/Zirabev as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

7. Hepatocellular carcinoma
   Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

B. Compendial Uses
1. Advanced gastric cancer
2. Advanced liver carcinoma
3. Breast cancer
4. Central nervous system (CNS) cancers
   i. Glioma (WHO Grade 1)
   ii. Diffuse high grade gliomas
   iii. Glioblastoma
   iv. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
   v. Oligodendroglioma (WHO Grade 2 or 3)
   vi. Intracranial and spinal ependymoma (excludes subependymoma)
   vii. Medulloblastoma
   viii. Primary central nervous system lymphoma
   ix. Meningiomas
   x. Limited and extensive brain metastases
   xi. Metastatic spine tumors
5. Necrosis of central nervous system due to exposure to ionizing radiation
6. Malignant pleural mesothelioma, Malignant peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
7. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
8. Soft tissue sarcoma
   i. Angiosarcoma
   ii. Solitary fibrous tumor/Hemangiopericytoma
9. Uterine neoplasms/Endometrial carcinoma
10. Vulvar carcinoma
11. Small bowel adenocarcinoma
12. Ampullary adenocarcinoma
13. Appendiceal adenocarcinoma
14. Anal adenocarcinoma
15. Renal cell carcinoma

C. Nationally Covered Indications
CMS covers bevacizumab for use in specific clinical trials (NCI-CMS Pilot Project). Refer to the Appendix for a list of these covered clinical trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

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II. CRITERIA FOR INITIAL APPROVAL

A. Colorectal cancer

Authorization of 12 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma.

B. Non-small cell lung cancer
Authorization of 12 months may be granted for treatment of symptomatic local, recurrent, unresectable, advanced or metastatic non-squamous non-small cell lung cancer.

C. Renal cell cancer
Authorization of 12 months may be granted for treatment of relapsed or stage IV renal cell cancer.

D. Cervical/Vaginal cancer
Authorization of 12 months may be granted for treatment of persistent, recurrent, or metastatic cervical or vaginal cancer.

E. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
Authorization of 12 months may be granted for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and malignant sex cord stromal tumors.

F. Hepatocellular carcinoma
Authorization of 12 months may be granted for treatment of unresectable or metastatic hepatocellular carcinoma, when the requested medication will be used as initial treatment in combination with atezolizumab.

G. Gastric cancer
Authorization of 12 months may be granted for treatment of gastric cancer.

H. Liver cancer
Authorization of 12 months may be granted for treatment of liver cancer.

I. Central nervous system (CNS) cancer
Authorization of 12 months may be granted for treatment of the following types of CNS cancer:
1. Glioma (WHO Grade 1)
2. Diffuse high grade gliomas
3. Glioblastoma
4. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
5. Oligodendroglioma (WHO Grade 2 or 3)
6. Intracranial and spinal ependymoma (excluding subependymoma)
7. Medulloblastoma
8. Primary central nervous system lymphoma
9. Meningiomas
10. Limited and extensive brain metastases
11. Metastatic spine tumors

J. Necrosis of central nervous system due to exposure to ionizing radiation
Authorization of 3 months may be granted for treatment of central nervous system necrosis due to exposure to ionizing radiation.

K. Uterine neoplasms/Endometrial carcinoma
Authorization of 12 months may be granted for treatment of progressive, advanced, recurrent, or metastatic uterine neoplasms or endometrial carcinoma.

L. Mesothelioma

1. Authorization of 12 months may be granted for treatment of malignant pleural mesothelioma, malignant peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when any of the following criteria are met:
   i. As first-line therapy for unresectable disease in combination with pemetrexed and either cisplatin or carboplatin, followed by single-agent maintenance bevacizumab
   ii. As subsequent therapy in combination with pemetrexed and either cisplatin or carboplatin if immunotherapy was administered as first-line treatment
2. Authorization of 12 months may be granted for treatment of malignant peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when used in combination with atezolizumab as subsequent therapy.

M. Breast cancer
Authorization of 12 months may be granted for treatment of recurrent or metastatic breast cancer.

N. Soft tissue sarcoma
1. Authorization of 12 months may be granted for treatment of angiosarcoma, as single agent therapy.
2. Authorization of 12 months may be granted for treatment of solitary fibrous tumor or hemangiopericytoma, in combination with temozolomide.

O. Vulvar carcinoma
Authorization of 12 months may be granted for treatment of unresectable locally advanced, recurrent, or metastatic vulvar carcinoma, including squamous cell carcinoma and adenocarcinoma.

P. Small bowel adenocarcinoma
Authorization of 12 months may be granted for treatment of small bowel adenocarcinoma.

Q. Ampullary adenocarcinoma
Authorization of 12 months may be granted for treatment of intestinal-type ampullary adenocarcinoma that is progressive, unresectable, or metastatic.

R. NCD indications
Authorization of 12 months may be granted for treatment of patients enrolled in any of the studies listed in the Appendix section.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Authorization for 3 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat central nervous system necrosis due to exposure to ionizing radiation.
   3. The member is receiving benefit from therapy.

B. Authorization for 12 months may be granted when all of the following criteria are met:
   1. The member is currently receiving therapy with the requested medication.
   2. The requested medication is being used to treat an indication enumerated in Section II (excluding central nervous system necrosis due to exposure to ionizing radiation).
   3. The member is receiving benefit from therapy. Benefit is defined as:
      i. No evidence of unacceptable toxicity while on the current regimen and

ii. No evidence of disease progression while on the current regimen.

IV. APPENDIX

NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project (Studies in Various Stages of Development)

Study ID #	Study Title
C80405	Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab, or with the combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum
E2204	An Intergroup Randomized Phase II Study of Bevacizumab or Cetuximab in Combination with Gemcitabine and in Combination with Chemoradiation (Capecitabine and Radiation) in Patients with Completely-Resected Pancreatic Carcinoma
E4203	Phase II Study of Treatment Selection Based Upon Tumor Thymidylate Synthase Expression in Previously Untreated Patients with Metastatic Colorectal Cancer
E5202	Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers
E5204	Intergroup Randomized Phase III Study of Post-Operative Oxaliplatin, 5-Fluorouracil and Leucovorin with or without Bevacizumab in Patients with Stage II or III Rectal Cancer Receiving Pre-Operative Radiation and a 5-Fluorouracil-Based Regimen
NSABP-R-04	A Clinical Trial Comparing Preoperative Radiation Therapy and Capecitabine with or without Oxaliplatin with Preoperative Radiation Therapy and Continuous Intravenous Infusion 5-Fluorouracil with or without Oxaliplatin in the Treatment of Patients with Operable Carcinoma of the Rectum
RTOG-0522	Phase III Trial of Concurrent Accelerated Radiation & Cisplatin vs Concurrent Accelerated Radiation, Cisplatin, & Cetuximab (Followed by Surgery for Selected Patients) for Stage III & IV Head & Neck Carcinomas
S0502	Phase III Randomized Study of Imatinib, with or without Bevacizumab, in Patients with Metastatic or Unresectable Gastrointestinal Stromal Tumors
7325	Dose-Dense and Dose-Intense Alternating Irinotecan/Capecitabine & Oxaliplatin/Capecitabine: Phase I in Solid Tumors and Phase II with Bevacizumab as First-Line Therapy of Advanced Colorectal Cancer

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Avastin, Alymsys, Mvasi, Vegzelma, and Zirabev.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Vulvar cancer
4. NCCN Guideline: Cervical cancer
5. NCCN Guideline: Small bowel adenocarcinoma
6. NCCN Guideline: Peritoneal mesothelioma
7. NCCN Guideline: Pleural mesothelioma
8. NCCN Guideline: Non-small cell lung cancer
9. NCCN Guideline: Hepatocellular carcinoma
10. NCCN Guideline: Central nervous system cancers
11. NCCN Guideline: Ampullary adenocarcinoma
12. NCCN Guideline: Ovarian cancer, including fallopian tube cancer and primary peritoneal cancer
13. NCCN Guideline: Kidney cancer
14. NCCN Guideline: Uterine neoplasms
15. NCCN Guideline: Soft tissue sarcoma
16. NCCN Guideline: Colon cancer
17. NCCN Guideline: Rectal cancer
18. National Coverage Determination (NCD) for Anti-cancer Chemotherapy for Colorectal Cancer (110.17)
19. NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Avastin, Alymsys, Mvasi, Vegzelma, and Zirabev are covered in addition to the following:

1. Inclusion in NCI/CTEP-sponsored studies selected for inclusion in NCI-CMS pilot project
2. Advanced gastric cancer
3. Advanced liver carcinoma
4. Breast cancer
5. Central nervous system (CNS) cancers
    i. Glioma (WHO Grade 1)
    ii. Diffuse high grade gliomas
    iii. Glioblastoma
    iv. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
    v. Oligodendroglioma (WHO Grade 2 or 3)
    vi. Intracranial and spinal ependymoma (excludes subependymoma)
    vii. Medulloblastoma
    viii. Primary central nervous system lymphoma
    ix. Meningiomas
    x. Limited and extensive brain metastases
    xi. Metastatic spine tumors
6. Necrosis of central nervous system due to exposure to ionizing radiation
7. Malignant pleural mesothelioma, Malignant peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
8. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer

9. Soft tissue sarcoma
    i. Angiosarcoma
    ii. Solitary fibrous tumor/Hemangiopericytoma
10. Uterine neoplasms/Endometrial carcinoma
11. Vulvar carcinoma
12. Small bowel adenocarcinoma
13. Ampullary adenocarcinoma
14. Appendiceal adenocarcinoma
15. Anal adenocarcinoma
16. Renal cell carcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using bevacizumab for the below listed indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. Central nervous system (CNS) cancers
    i. Glioma (WHO Grade 1)
    ii. Diffuse high grade gliomas
    iii. Glioblastoma
    iv. IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
    v. Oligodendroglioma (WHO Grade 2 or 3)
    vi. Intracranial and spinal ependymoma (excludes subependymoma)
    vii. Medulloblastoma
    viii. Primary central nervous system lymphoma
    ix. Meningiomas
    x. Limited and extensive brain metastases
    xi. Metastatic spine tumors
2. Necrosis of central nervous system due to exposure to ionizing radiation
3. Malignant pleural mesothelioma, Malignant peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
4. Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
5. Soft tissue sarcoma
    i. Angiosarcoma
    ii. Solitary fibrous tumor/Hemangiopericytoma
6. Uterine neoplasms/Endometrial carcinoma
7. Vulvar carcinoma
8. Small bowel adenocarcinoma
9. Ampullary adenocarcinoma
10. Appendiceal adenocarcinoma
11. Anal adenocarcinoma
12. Renal cell carcinoma

Support for using bevacizumab for advanced gastric cancer, advanced liver carcinoma and breast cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit

Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Use of bevacizumab in an NCI/CTE-sponsored study is covered according to the conditions outlined in National Coverage Determination Manual section 110.17 Anti-Cancer Chemotherapy for Colorectal Cancer.

VII. REFERENCES

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