LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.517

Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Treatment

Effective Date: **Jan. 1, 2027***	RELATED MEDICAL POLICIES:
Last Revised: Sep. 8, 2026	5.01.518 BCR-ABL Kinase Inhibitors
Replaces: N/A	5.01.534 Multiple Receptor Tyrosine Kinase Inhibitors
	5.01.544 Prostate Cancer Targeted Therapies
*This policy has been revised. Click here to view the current version.	5.01.549 Off-Label Use of Drugs and Biologic Agents
	5.01.591 Immune Checkpoint Inhibitors
	5.01.603 Epidermal Growth Factor Receptor (EGFR) Inhibitors

Select a hyperlink below to be directed to that section.

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RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Angiogenesis is the creation of new blood vessels. The body controls this process through chemical signals. Everything is usually in balance so that new blood vessels are created only when needed. In cancer, however, as a tumor grows it demands more oxygen and nutrients, which are delivered by blood vessels. Tumors can send signals to nearby normal cells to start creating more blood vessels. There are certain drugs that interfere with these signals. These drugs reduce or stop the blood vessel growth that tumors need. This policy describes when these drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Note: No review is needed for eye-related injections; these are considered standard of care.

Drug	Medical Necessity
Injectable Drugs	
First-line • **Mvasi (bevacizumab-awwb) IV** • **Vegzelma (bevacizumab-adcd)** • **Zirabev (bevacizumab-bvzr) IV**	**Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), and Zirabev (bevacizumab-bvzr) may be considered medically necessary no earlier than 28 days following major surgery and until surgical wound is fully healed.** **Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), and Zirabev (bevacizumab-bvzr) may be considered medically necessary when the following criteria are met:** • The individual is diagnosed with 1 of the following: ○ Metastatic colorectal cancer, in combination with an intravenous 5-fluorouracil or equivalent (e.g., capecitabine, floxuridine) based regimen for first or second-line treatment ○ Metastatic colorectal cancer, in combination with irinotecan or oxaliplatin for second-line treatment in individuals who have progressed on a first-line bevacizumab product-containing regimen ○ Metastatic colorectal cancer in combination with Lonsurf (trifluridine and tipiracil) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy (e.g., cetuximab or panitumumab) ○ Unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel for first-line treatment ○ Recurrent glioblastoma in adults ○ Metastatic renal cell carcinoma in combination with interferon alfa

Drug	Medical Necessity
Injectable Drugs	
	○ Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan ○ Epithelial ovarian, fallopian tube, or primary peritoneal cancer: ▪ In combination with carboplatin and paclitaxel, followed by a bevacizumab product as a single agent, for stage III or IV disease following initial surgical resection ▪ In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease ▪ In combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by a bevacizumab product as a single agent, for platinum-sensitive recurrent disease ○ Hepatocellular carcinoma (HCC) in combination with Tecentriq (atezolizumab) for the treatment of individuals with unresectable or metastatic HCC who have not received prior systemic therapy **AND** • Medication is administered no earlier than 28 days following major surgery and after adequate wound healing has occurred **Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), and Zirabev (bevacizumab-bvzr) are considered investigational for all other uses, including advanced adenocarcinoma of the pancreas.** **Note:** Mvasi (bevacizumab-awwb) and Zirabev (bevacizumab-bvzr) are biosimilars to Avastin (bevacizumab).
Second-line • **Alymsys (bevacizumab-maly) IV** • **Avastin (bevacizumab)** • **Avzivi (bevacizumab-tnjn) IV**	**Alymsys (bevacizumab-maly), Avastin (bevacizumab), Avzivi (bevacizumab-tnjn), and Jobevne (bevacizumab-nwgd) may be considered medically necessary no earlier than 28 days following major surgery and until surgical wound is fully healed.**

Drug	Medical Necessity
Injectable Drugs	
• **Jobevne (bevacizumab-nwgd) IV**	**Alymsys (bevacizumab-maly), Avastin (bevacizumab), Avzivi (bevacizumab-tnjn), and Jobevne (bevacizumab-nwgd) may be considered medically necessary when the following criteria are met:** • The individual is diagnosed with 1 of the following: ○ Metastatic colorectal cancer, in combination with an intravenous 5-fluorouracil or equivalent (e.g., capecitabine, floxuridine) based regimen for first or second-line treatment ○ Metastatic colorectal cancer, in combination with irinotecan or oxaliplatin for second-line treatment in individuals who have progressed on a first-line bevacizumab product-containing regimen ○ Metastatic colorectal cancer in combination with Lonsurf (trifluridine and tipiracil) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy (e.g., cetuximab or panitumumab) ○ Unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel for first-line treatment ○ Recurrent glioblastoma in adults ○ Metastatic renal cell carcinoma in combination with interferon alfa ○ Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan ○ Epithelial ovarian, fallopian tube, or primary peritoneal cancer: ▪ In combination with carboplatin and paclitaxel, followed by a bevacizumab product as a single agent, for stage III or IV disease following initial surgical resection ▪ In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease

Drug	Medical Necessity
Injectable Drugs	
	▪ In combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by a bevacizumab product as a single agent, for platinum-sensitive recurrent disease ○ Hepatocellular carcinoma (HCC) in combination with Tecentriq (atezolizumab) for the treatment of individuals with unresectable or metastatic HCC who have not received prior systemic therapy **AND** • The individual has had an inadequate response or intolerance to Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), **AND** Zirabev (bevacizumab-bvzr) **AND** • Medication is administered no earlier than 28 days following major surgery and after adequate wound healing has occurred **Alymsys (bevacizumab-maly), Avastin (bevacizumab), Avzivi (bevacizumab-tnjn), and Jobevne (bevacizumab-nwgd) are considered investigational for all other uses, including advanced adenocarcinoma of the pancreas.** **Note:** Alymsys (bevacizumab-maly), Avzivi (bevacizumab-tnjn), Jobevne (bevacizumab-nwgd), and Vegzelma (bevacizumab-adcd) are biosimilars to Avastin (bevacizumab).
Cyramza (ramucirumab) IV	**Cyramza (ramucirumab) may be considered medically necessary for the treatment of:** • Advanced or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- (e.g., 5-fluorouracil, capecitabine) or platinum- (e.g. cisplatin, carboplatin, oxaliplatin) containing chemotherapy when used as a single agent or in combination with paclitaxel • Metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations as first-line therapy when used in combination with erlotinib

Drug	Medical Necessity
Injectable Drugs	
	• Metastatic NSCLC with disease progression on or after platinum-(e.g. cisplatin, carboplatin, oxaliplatin) based chemotherapy when used in combination with docetaxel. Individuals with EGFR or ALK genomic tumor aberrations should have disease progression on US Food and Drug Administration (FDA) -approved therapy for these aberrations prior to receiving Cyramza • Metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) when used in combination with FOLFIRI (irinotecan, folinic acid, and fluorouracil) • Hepatocellular carcinoma (HCC) in individuals who have an alpha fetoprotein of at least 400 ng/mL and have been treated with sorafenib when used as a single agent
Zaltrap (ziv-aflibercept) IV	**Zaltrap (ziv-aflibercept) may be considered medically necessary for the treatment of metastatic colorectal cancer (mCRC) when the following criteria are met:** • The individual has mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen **AND** • Zaltrap is used in combination with 5-fluorouracil or equivalent (e.g., capecitabine, floxuridine), leucovorin, irinotecan-(FOLFIRI)

Drug	Medical Necessity
Oral Drugs	
Fruzaqla (fruquintinib)	**Fruzaqla (fruquintinib) may be considered medically necessary for the treatment of metastatic colorectal cancer when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy **AND** • Has been previously treated with an anti-vascular endothelial growth factor (VEGF) therapy

Drug	Medical Necessity
Oral Drugs	
	AND • Has been previously treated with an anti-endothelial growth factor receptor (EGFR) therapy if RAS wild-type and medically appropriate
Lenalidomide (generic)	**Lenalidomide may be considered medically necessary for the treatment of myelodysplastic syndrome when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has transfusion-dependent anemia **AND** • The dose is limited to 10 mg per day **Lenalidomide may be considered medically necessary for the treatment of multiple myeloma when the following criteria are met:** • The individual is aged 18 years or older **AND** • Lenalidomide is used in combination with dexamethasone at a dose not to exceed 25 mg per day **OR** • As maintenance therapy following hematopoietic stem cell transplantation (auto-HSCT) **Lenalidomide may be considered medically necessary for the treatment of mantle cell lymphoma (MCL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has relapsed or progressed after two prior therapies, one of which includes bortezomib **AND** • The dose is limited to 25 mg per day

Drug	Medical Necessity
Oral Drugs	
	Lenalidomide may be considered medically necessary for treatment of previously treated follicular lymphoma (FL) when the following criteria are met: • The individual is aged 18 years or older **AND** • Lenalidomide is used in combination with a rituximab product **AND** • The dose is limited to 20 mg per day **Lenalidomide may be considered medically necessary for the treatment of previously treated marginal zone lymphoma (MZL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Lenalidomide is used in combination with a rituximab product **AND** • The dose is limited to 20 mg per day
Revlimid (lenalidomide)	**Revlimid (lenalidomide) may be considered medically necessary for the treatment of myelodysplastic syndrome when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has transfusion-dependent anemia **AND** • Has tried and had an inadequate response or intolerance to generic lenalidomide **AND** • The dose is limited to 10 mg per day **Revlimid (lenalidomide) may be considered medically necessary for the treatment of multiple myeloma when the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity
Oral Drugs	
	• Revlimid is used in combination with dexamethasone at a dose not to exceed 25 mg per day **OR** • As maintenance therapy following hematopoietic stem cell transplantation (auto-HSCT) **AND** • Has tried and had an inadequate response or intolerance to generic lenalidomide **Revlimid (lenalidomide) may be considered medically necessary for the treatment of mantle cell lymphoma (MCL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has relapsed or progressed after two prior therapies, one of which includes bortezomib **AND** • Has tried and had an inadequate response or intolerance to generic lenalidomide **AND** • The dose is limited to 25 mg per day **Revlimid (lenalidomide) may be considered medically necessary for the treatment of previously treated follicular lymphoma (FL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Revlimid is used in combination with a rituximab product **AND** • Has tried and had an inadequate response or intolerance to generic lenalidomide **AND** • The dose is limited to 20 mg per day

Drug	Medical Necessity
Oral Drugs	
	Revlimid (lenalidomide) may be considered medically necessary for the treatment of previously treated marginal zone lymphoma (MZL) when the following criteria are met: • The individual is aged 18 years or older **AND** • Revlimid is used in combination with a rituximab product **AND** • Has tried and had an inadequate response or intolerance to generic lenalidomide **AND** • The dose is limited to 20 mg per day
Generic pomalidomide	**Generic pomalidomide may be considered medically necessary, in combination with dexamethasone, for treatment of multiple myeloma when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) (e.g., bortezomib, carfilzomib, ixazomib) **AND** • Has demonstrated disease progression on or within 60 days of completion of the last prior therapy **AND** • The dose is limited to 4 mg per day **Generic pomalidomide may be considered medically necessary, in combination with Darzalex Faspro (daratumumab and hyaluronidase-fihj) and dexamethasone, for the treatment of multiple myeloma when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI) (e.g., bortezomib, carfilzomib, ixazomib) **AND** • The dose is limited to 4 mg per day

Drug	Medical Necessity
Oral Drugs	
	Generic pomalidomide may be considered medically necessary for the treatment of adult individuals with Kaposi sarcoma (KS) when the following criteria are met: • The individual is aged 18 years or older **AND** • Has AIDS-related KS and had an inadequate response to highly active antiretroviral therapy (HAART) **OR** • Has KS and is HIV-negative **AND** • The dose is limited to 5 mg per day
Pomalyst (pomalidomide)	**Pomalyst (pomalidomide) may be considered medically necessary, in combination with dexamethasone, for treatment of multiple myeloma when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) (e.g., bortezomib, carfilzomib, ixazomib) **AND** • Has demonstrated disease progression within 60 days of completion of the last prior therapy **AND** • Has tried and had an inadequate response or intolerance to generic pomalidomide **AND** • The dose is limited to 4 mg per day **Pomalyst (pomalidomide) may be considered medically necessary, in combination with Darzalex Faspro (daratumumab and hyaluronidase-fihj) and dexamethasone, for the treatment of multiple myeloma when the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity
Oral Drugs	
	• Has received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI) (e.g., bortezomib, carfilzomib, ixazomib) **AND** • Has tried and had an inadequate response or intolerance to generic pomalidomide **AND** • The dose is limited to 4 mg per day **Pomalyst (pomalidomide) may be considered medically necessary for the treatment of adult individuals with Kaposi sarcoma (KS) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has AIDS-related KS and had an inadequate response to highly active antiretroviral therapy (HAART) **OR** • Has KS and is HIV-negative **AND** • Has tried and had an inadequate response or intolerance to generic pomalidomide **AND** • The dose is limited to 5 mg per day

Drug	Investigational
As listed	**All other uses of the medications listed in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in this policy may be approved up to 6 months.**
Re-authorization criteria	**All drugs may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

Code	Description
HCPCS	
J9035	Injection, bevacizumab (Avastin), 10 mg
J9308	Injection, ramucirumab (Cyramza), 5 mg
J9400	Injection, ziv-aflibercept (Zaltrap), 1 mg
J9999	Not otherwise classified, antineoplastic drugs (use: to report Avzivi)
Q5107	Injection, bevacizumab-awwb, biosimilar (Mvasi), 10 mg
Q5118	Injection, bevacizumab-bvzr, biosimilar (Zirabev), 10 mg
Q5126	Injection, bevacizumab-maly, biosimilar (Alymsys), 10 mg
Q5129	Injection, bevacizumab-adcd biosimilar (Vegzelma), 10 mg
Q5160	Injection, bevacizumab-nwgd (Jobevine), biosimilar, 10 mg (new code effective 01/01/26)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Fruzaqla (fruquintinib), generic lenalidomide, generic pomalidomide, Pomalyst (pomalidomide), and Revlimid (lenalidomide) are managed through the pharmacy benefit.

Alymsys (bevacizumab-maly), Avastin (bevacizumab), Avzivi (bevacizumab-tnjn), Cyramza (ramucirumab), Jobevne (bevacizumab-nwgd), Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), Zaltrap (ziv-aflibercept), and Zirabev (bevacizumab-bvzr) are managed through the medical benefit.

Evidence Review

Description

Cancer is characterized by the uncontrolled growth and spread of malignant cells. Nearly 1.9 million Americans will be diagnosed with cancer in 2022, and approximately 610,000 will die of the disease. The good news is the cancer death rate for men and women combined fell 32% from its peak in 1991 to 2019.

Conventional cytotoxic cancer chemotherapy has been one of the major medical advances realized in the last few decades. Although directed toward certain biologic targets thought to be involved in cellular growth and proliferation, typically they have not discriminated well between rapidly dividing normal cells (e.g., bone marrow, gastrointestinal tract) and tumor cells, frequently resulting in toxicities. In addition, tumor responses to traditional cytotoxic cancer chemotherapies can be unpredictable and brief.

"Targeted chemotherapies" (e.g., monoclonal antibodies, tyrosine kinase inhibitors, antisense inhibitors of growth factor receptors) are the newest therapeutic approach. These agents have been designed to interfere with molecular targets that have a role in tumor growth and progression (e.g., tyrosine kinase, vascular endothelial growth factor, epithelial growth factor, farnesyl transferase inhibition). These targets are typically preferentially located on/in tumor cells, thus these therapies have a higher specificity for tumor cells. The promise of these agents is they will provide a broader therapeutic index with less toxicity. They may also be useful in combination with traditional cytotoxic chemotherapies, immunotherapies or radiation to produce additive or synergistic activity without overlap in toxicity profiles.

Epidermal growth factor receptor (EGFR) and tyrosine kinases play a critical role in the modulation of growth factor signaling. The binding of a ligand to EGFR induces the phosphorylation and activation of tyrosine kinase signal pathways. The induction of the signaling pathways enhances activities such as up regulation of RAS, RAF and mitogen-activated phosphorylation which develops cellular growth and invasive capacity. EGFR activation also stimulates vascular endothelial growth factor (VEGF), which is the primary inducer of angiogenesis. As solid tumors cannot grow without the nutritional support provided by a blood supply, angiogenesis plays a key role in the progression of these tumors.

EGFR and/or VEGF over expression have been identified in a variety of solid and hematological malignancies (e.g., colon, lung, breast, kidney, liver, CML). Furthermore, increasing VEGF levels have been correlated with poor prognosis in many of these same pathologies. As a result, VEGF and other angiogenesis inhibitors have been developed and investigated for the treatment of these conditions. However, much remains to be learned regarding the rational integration of these therapies into cancer treatment regimens and methods to optimize the selection of individuals most likely to benefit.

The VEGF and miscellaneous angiogenesis inhibiting agents currently available are as follows:

Drug Name	Pharmacology	Administration	FDA-approved Uses
Bevacizumab (Avastin)	VEGF receptor inhibitor (Mab)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube or primary peritoneal cancer, hepatocellular carcinoma
Bevacizumab-adcd (Vegzelma)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube or primary peritoneal cancer
Bevacizumab-awwb (Mvasi)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, and cervical cancer
Bevacizumab-bvzr (Zirabev)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube or primary peritoneal cancer
Bevacizumab-maly (Alymsys)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma,

Drug Name	Pharmacology	Administration	FDA-approved Uses
			metastatic renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube or primary peritoneal cancer
Bevacizumab-nwgd (Jobevne)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube or primary peritoneal cancer
Bevacizumab-tnjn (Avzivi)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non- small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube or primary peritoneal cancer
Ramucirumab (Cyramza)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic gastric gastric or gastroesophageal junction adenocarcinoma, metastatic colorectal cancer, metastatic non- small cell lung cancer, metastatic hepatocellular carcinoma
Ziv-aflibercept (Zaltrap)	VEGF trap	IV (Clinic)	Metastatic colorectal cancer
Fruquintinib (Fruzaqla)	VEGF receptor inhibitor	Oral (Rx)	Metastatic colorectal cancer
Lenalidomide (Revlimid)	Not understood	Oral (Rx)	Myelodysplastic syndrome (MDS), multiple myeloma, mantel cell lymphoma
Pomalidomide (Pomalyst)	Not understood	Oral (Rx)	Multiple myeloma, Kaposi sarcoma

Fruzaqla (fruquintinib) is a small molecule kinase inhibitor of VEGF-1, -2, and -3. In vitro studies showed fruquintinib inhibited VEGF-mediated endothelial cell proliferation and tubular formulation. In vitro and in vivo studies showed fruquintinib inhibited VEGF-induced VEGFR-2 phosphorylation.

Revlimid (lenalidomide) and Pomalyst (pomalidomide) are angiogenesis inhibitors with pharmacology similar to that of thalidomide. The mechanism by which lenalidomide and pomalidomide inhibit angiogenesis is not well understood. Both agents are approved for treatment of multiple myeloma. Lenalidomide is approved for treatment of MDS as well.

Alymsys (bevacizumab-maly), Avastin (bevacizumab), Avzivi (bevacizumab-tnjn), Jobevne (bevacizumab-nwgd), Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), and Zirabev

(bevacizumab-bvzr) are recombinant humanized monoclonal antibodies that inhibits angiogenesis and new blood vessel survival by binding and inhibiting the interaction of human vascular endothelial growth factor (VEGF) to its receptors on endothelial cells. VEGF is a key component of endothelial cell proliferation and new blood vessel formation that supports the growth of many tumor types, including colorectal cancer.

Cyramza (ramucirumab) is a VEGFR2 antagonist that specifically binds VEGFR2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGFR2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. Ramucirumab inhibited angiogenesis in an in vivo animal model.

Zaltrap (ziv-aflibercept) is a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1. Ziv-aflibercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) K-1 mammalian expression system. Ziv-aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa).

Ziv-aflibercept acts as a soluble receptor that binds to human VEGF-A (equilibrium dissociation constant KD of 0.5 pM for VEGF-A165 and 0.36 pM for VEGF-A121), to human VEGF-B (KD of 1.92 pM), and to human PlGF (KD of 39 pM for PlGF-2). By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability.

National Comprehensive Cancer Center Compendium

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium is based directly on the NCCN Clinical Practice Guidelines in Oncology. The compendium lists specific panel recommendations for off-label uses of drugs, and each recommendation is supported by a level of evidence category.

The NCCN Categories of Evidence and Consensus used in the recommendations are:

- Category 1: The recommendation is based on high level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.
- Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

- Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).
- Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

In June 2008, the NCCN Compendium became one of four references for Centers for Medicare & Medicaid Services (CMS) for oncology coverage policy.

In its Medicare Benefit Policy Manual (October 24, 2008), CMS describes this change and states that, in general, a use identified by the NCCN Compendium is "medically accepted" if the indication is a category 1 or 2A as defined by NCCN. A use is "not medically accepted" if the indication is a category 3 in NCCN.

The local CMS contractor, Noridian Administrative Services (NAS), has issued an additional coverage statement regarding Category 2B:

"NAS recognizes NCCN Categories of Evidence Levels Category 1 and Category 2A ONLY as medically accepted indications. If a provider chooses to use NCCN level 2B in support of a chemotherapeutic drug used off-label in an anti-cancer chemotherapeutic regimen, NAS expects that the provider will make available to NAS significant peer-reviewed Phase II or Phase III studies demonstrating such support. In the absence of such studies, level 2B evidence does not support such use."

Breast Cancer

Breast cancer is the most common cancer in women and is the leading cause of death for women 40-55 years of age. While advances have been made with the introduction of endocrine therapies, new chemotherapies, and biologics, and early detection has significantly improved the outlook for women with the disease, recurrence remains an ongoing concern. In addition, treatment of advanced breast cancer remains a challenge. VEGF levels are increased in approximately 30-60% of breast cancers and many studies show a link between VEGF and prognosis; hence the recent targeting of EGF inhibitors toward the disease.

Two randomized, controlled Phase III trials of Avastin (bevacizumab) have been conducted in individuals with metastatic breast cancer (Miller et al., 2002 and Miller et al., 2005). The earlier study examined the therapeutic benefit of adding bevacizumab 15 mg/kg every three weeks to daily capecitabine compared to capecitabine alone in 462 individuals with metastatic breast cancer refractory to taxanes and anthracyclines. The primary endpoint of progression-free

survival (PFS) was not met (4.86 versus 4.17 months, P=0.857). Although, RR was significantly higher for the combination compared with capecitabine alone independently assessed RR: 19.8 versus 9.1%, respectively, P=0.001; investigator-assessed RR: 30.2 versus 19.1%, respectively, P=0.006. The combination was well tolerated, and the incidence and severity of capecitabine-related toxicities were not affected by concurrent use of bevacizumab, and bevacizumab-related adverse events were as expected. The latter study was a randomized, open-label study in individuals with metastatic breast cancer who were receiving first-line paclitaxel with or without bevacizumab 10 mg/kg every two weeks. The primary objective of the study is PFS. A preliminary report for 715 individuals randomized to the two treatments showed a significant increase in median PFS for the bevacizumab + paclitaxel group compared with the paclitaxel alone group (10.97 months versus 6.11 months, respectively, P<0.001). A significant two-fold increase in RR for the bevacizumab + paclitaxel group compared with paclitaxel alone (28.2 versus 14.2%, P<0.0001) was also observed. Adverse events were as expected based on data from previous trials of bevacizumab.

Lung Cancer

NSCLC is potentially curable if diagnosed early (Stage I or II). Unfortunately, approximately 75% of cases are not identified until the individual has locally advanced or metastatic disease (i.e., stage III or IV). Overall five year survival is only about 15%.

Currently, the use of osimertinib is NCCN recommended as preferred therapy for individuals with advanced NSCLC who have an EGFR exon 19 deletion or an L858R mutation regardless of performance status (i.e., Eastern Cooperative Oncology Group (ECOG) performance status 0-4). Use of osimertinib as preferred applies to when the EGFR mutation was discovered prior to first-line systemic therapy, or the EGFR mutation was discovered during first-line systemic therapy.

As understanding of the pathophysiology of NSCLC has improved, and because most individuals with advanced disease continue to progress following first-line chemotherapy and ultimately die within a year, newer therapies have been developed that have demonstrated value in prolonging survival in this setting. Single-agent docetaxel is considered the standard for comparison for second-line therapy of advanced or recurrent metastatic NSCLC. Recently, a large randomized head-to-head study showed pemetrexed 500 mg/m^2 provided similar response and survival rates with less severe adverse events and fewer hospitalizations compared to docetaxel 75 mg/m^2.

Recently, in a US Cooperative Group Phase III clinical trial (Sandler et al., 2005), 444 individuals with Stage IIIB or IV non-squamous cell NSCLC were randomly assigned to paclitaxel plus

carboplatin (PC) and 434 to PC plus bevacizumab 15 mg/kg every three weeks (PC+B). Most individuals (86%) had Stage IV disease. Individuals receiving PC+B had a higher response rate, and modestly longer progression-free (PFS) and overall survival (OS). See **Table 1** below.

Table 1. Study E4599: Response to Bevacizumab + Placlitaxel/Carboplatin in Individuals with Advanced NSCLC (707 Evaluable Individuals)

	PC Alone (n=350)	PC + B (n=357)	P-value
Response Rate, %	10.0	27.2	<0.0001
PFS, months	4.5	6.4	<0.0001
OS, months	10.2	12.5	0.0075

Both regimens were generally well tolerated. Selected adverse events (PC versus PC+B) included neutropenia (16.4% versus 24%), thrombocytopenia (0 versus 1.4%), hemorrhage (0.7% versus 4.5%), and hypertension (0.7% versus 6.0%). The incidence of hemoptysis was decreased compared with an initial phase 2 trial in individuals with NSCLC, but five of eight cases in the PC+B group were fatal.

Myelodysplastic Syndrome

The efficacy and safety of Revlimid (lenalidomide) were evaluated in individuals with transfusion dependent anemia in Low or Intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single arm, multi-center study. The major study was not designed nor powered to prospectively compare the efficacy of the two dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity. This major study enrolled 148 individuals who had RBC transfusion dependent anemia. RBC-transfusion dependence was defined as having received ≥ 2 units of RBCs within eight weeks prior to study treatment. The study enrolled individuals with absolute neutrophil counts ≥ 500 cells/mm3, platelet counts ≥ 50,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal, and serum direct bilirubin ≤ 2.0 mg/dL. Granulocyte colonystimulating factor was permitted for individuals who developed neutropenia or fever in association with neutropenia. The frequency of RBC-transfusion independence was modified from the International Working Group (IWG)

response criteria for MDS. RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (eight weeks) during the treatment period.

Transfusion independence was seen in 99/148 (67%) individuals (95% CI [59, 74]). The median duration from the date when RBC transfusion independence was first declared (i.e., the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range of 0 to >67 weeks). Ninety percent of individuals who achieved a transfusion benefit did so by completion of three months in the study. RBC-transfusion independence rates were unaffected by age or gender. The dose of lenalidomide was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of the 148 individuals; the median time to the first dose reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265 days). A second dose reduction or interruption due to adverse events was required in 50 (33.8%) of the 148 individuals. The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).

Multiple Myeloma

Two randomized studies were conducted to evaluate the efficacy and safety of lenalidomide. These multicenter, multinational, double-blind, placebo-controlled studies compared lenalidomide plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone, in individuals with multiple myeloma who had received at least one prior treatment. In both studies, individuals in the lenalidomide/dexamethasone group took 25 mg of lenalidomide orally once daily on days one to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Individuals in the placebo/dexamethasone group took one placebo capsule on days one to 28 of each 28-day cycle. Individuals in both treatment groups took 40 mg of dexamethasone orally once daily on days one to four, nine to 12, and 17 to 20 of each 28-day cycle for the first four cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days one to four of each 28-day cycle after the first four cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity.

The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease or death due to

progressive disease. Preplanned interim analyses of both studies showed that the combination of lenalidomide/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow individuals in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination. Pomalidomide is a newer agent similar to lenalidomide that offers potential to extend benefit in individuals that have progressed on prior therapies.

Ovarian Cancer

Small prospective trials in ovarian cancer have established the single-agent activity of bevacizumab in recurrent ovarian cancer In one study, 63 individuals with recurrent ovarian cancer were treated with bevacizumab 15 mg/kg IV every three weeks. Individuals had received up to two prior cytotoxic regimens. Forty-two percent entered had platinum-sensitive disease. Overall RR was 17.7%, median duration of response was 10.25 months, and 38.7% of individuals were progression-free at six or more months. No gastrointestinal perforations were noted.

In a second study, reported by Cannistra et al., 44 individuals with platinum-resistant disease were evaluated. Individuals were required to progress on or within six months of platinum-based chemotherapy and then receive either liposomal doxorubicin or topotecan and progress on or within three months of that therapy. Individuals had received up to three prior regimens. The majority of individuals had primary platinum-resistant ovarian cancer (83.7%), with 16.3% of individuals entering with platinum-resistant disease after their second platinum-based regimen. Fifty-nine percent of individuals received liposomal doxorubicin, 25% topotecan, and 16% both drugs prior to study entry. The response rate to bevacizumab in this refractory heavily pretreated population was 16% (7/44 individuals, all partial responses). The expected response rate to cytotoxic chemotherapy in this poor prognosis individual population is less than 10%, establishing single-agent activity of bevacizumab. The original accrual goal of the trial was 53 individuals. The study closed to accrual after the first 44 individuals because of a gastrointestinal perforation rate of 11.4% (5/44 individuals). One of these perforations was fatal. Perforations did not appear to correlate with response. On October 4, 2005, the National Cancer Institute (NCI) alerted investigators of the perforation risk with bevacizumab. Gastrointestinal perforation appeared to be associated with gastrointestinal tumor involvement, specifically bowel obstruction and bowel wall thickening.

In a third trial, NCI trial 5789, recurrent ovarian cancer individuals with up to two prior regimens were treated with bevacizumab 10 mg/kg IV every two weeks in combination with metronomic oral cyclophosphamide (50 mg daily). Forty-two percent were platinum-sensitive. Overall

response rate of 28% with 57% of individuals being progression-free at six months was noted. Two individuals (3%) experienced gastrointestinal perforation.

A retrospective case series of 32 individuals treated with bevacizumab at 15 mg/kg IV every three weeks was reported. Individuals had had a median of five prior regimens. The majority were treated with bevacizumab alone, although 10 individuals received bevacizumab with chemotherapy or had chemotherapy added during the course of treatment. The response rate was 16%. One enterocutaneous fistula was noted.

The results of these studies clearly show that bevacizumab has single agent activity in individuals with metastatic ovarian disease that is refractory to numerous prior regimens; however, the response rates are very modest, and are offset by a worrisome incidence of bowel perforations in this population. While it has been suggested that individuals with bowel involvement of the tumor are at higher risk, there is to date insufficient evidence to confidently predict this. Given the very modest benefit and considerable risk, bevacizumab should be considered a potentially promising therapy for this population, and in need of further research to confirm that the benefits outweigh risk and to identify the population most suitable for treatment.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) usually occurs in adults between the ages of 50 and 70 and is the most common cancer of the kidney, accounting for 3% of all human cancers and over 90% of malignant kidney tumors. Between 25 and 30% of individuals have metastases at the time of diagnosis. RCC is classified into five subtypes, but most individuals (70-80%) have the clear cell type.

Treatment of RCC depends on disease staging and the individual's overall physical health. Surgery is typically performed in earlier/lower stages of the disease, and systemic therapy is reserved when there is recurrence or spread of the cancer. Unfortunately, RCC tends to be very resistant to chemotherapy. Consequently, various types of immunotherapy (e.g., interferon alpha and interleukin-2) are currently preferred. However, immunotherapies have only resulted in modest improvements in median survival; therefore, new treatment options are needed.

In a randomized, double-blind, placebo-controlled Phase II trial, 116 individuals with immunotherapy refractory RCC received bevacizumab 3 or 10 mg/kg every two weeks or placebo (Yang et al, 2003). Crossover from placebo to bevacizumab 3 mg/kg ± thalidomide was permitted at progression. The two primary endpoints were time to progression (TTP) and response. OS was only a secondary endpoint because crossover therapy at progression was allowed. The trial was closed early because progression-free survival was significantly longer in

individuals treated with bevacizumab 10 mg/kg than in those receiving placebo (HR=2.55, P<0.001). There were no life-threatening adverse events or deaths related to bevacizumab therapy. The most common adverse events reported were hypertension and proteinuria.

Two large Phase III clinical trials are also underway to investigate the use of bevacizumab in combination with immunotherapy in individuals with metastatic RCC.

2008 Update

Glioblastoma

Fifty four individuals with recurrent high grade glioma received therapy with bevacizumab at 10 mg/kg every two weeks for four doses in an eight week cycle along with Irinotecan at 125 mg/m^2. The survival was calculated from the time of starting bevacizumab-based therapy. The median PFS and OS were 5 (95% confidence interval, 1.0-6.9) and 9 (95% confidence interval, 7.5-10.5) months respectively. Radiological responses following therapy were noted in 72.2% of cases. The individuals who received less than two cycles of bevacizumab-based therapy had a PFS and OS of seven and 11 months compared to 3.5 and five months for the individuals who received less than two cycles of therapy (p=0.02 and P<0.0001) respectively. Neither the grade of the tumor nor the surgical resection prior to therapy had an impact on survival.

2009 Update

Ovarian Cancer

Azad and colleagues stated that CA125 is an accepted indicator of epithelial ovarian cancer (EOC) response and is used to monitor individuals treated with cytotoxic chemotherapy. However, it is uncertain how CA125 is affected by molecularly targeted drugs and so the authors analyzed the utility of CA125 to predict disease behavior in individuals who were receiving sorafenib, a Raf-kinase/VEGFR2 inhibitor, and bevacizumab, an anti-VEGF monoclonal antibody. Fifteen of 42 individuals had recurrent EOC. Individuals received sorafenib 200 mg orally twice daily or D1-5 of seven and bevacizumab 5 mg/kg to 10 mg/kg intravenously every two weeks for 28-day cycles. Computed tomography (CT) scans were performed every two cycles for restaging, and CA125 was measured monthly. CA125 concentrations were retrospectively analyzed as a function of clinical behavior. They found that fourteen of 15 individuals had abnormal CA125 concentrations at study entry. Seven (47%) individuals had partial response by

imaging criteria. Five of these seven individuals had partial response by CA125 criteria (71% sensitivity). Eight (53%) individuals would have had partial responses if CA125 criteria were used; only 5 were confirmed by CT (63 % specificity). Imaging and CA125 criteria combined yielded a higher total response rate of 10 of 15 (67%). Three individuals with objective partial response by imaging lasting >20, >22, and >24 cycles would have terminated treatment prematurely if CA125 had been used. They concluded that CA125 changes may not correspond to imaging response criteria for EOC individuals who are receiving sorafenib and bevacizumab. They stated that caution is recommended when using CA125 as a response criterion of molecularly targeted agents until prospective studies validate CA125 changes with objective imaging response results.

National Comprehensive Cancer Network Drug Compendium

The NCCN (April 2009) Drugs and Biologics Compendium states that bevacizumab is recommended for use as recurrence therapy for ovarian cancer as a single agent for the following indications:

- Recurrence as evidenced by serially rising CA125 in individuals who have received prior chemotherapy (2B category of evidence);
- Progressive or stable disease on primary therapy (2A category of evidence);
- Relapse after being in complete remission following primary chemotherapy (2B category of evidence); and
- Stage II to IV disease showing partial response to primary treatment (2A category of evidence).

The Company recognizes indications and uses of bevacizumab listed in the NCCN Drugs and Biologics Compendium with Categories of Evidence and Consensus of 1and 2A as proven and Categories of Evidence and Consensus of 2B and 3 as unproven. However, Category 2B uses may be considered for coverage if they are substantiated by provider submission of significant peer-reviewed phase 2 or phase 3 studies demonstrating treatment effectiveness.

2010 Update

Avastin (bevacizumab) and Advanced Adenocarcinoma of the Pancreas

This summary is adapted from a 2009 Technology Evaluation Center (TEC) Assessment. The objective of the Assessment was to evaluate the use of bevacizumab in advanced adenocarcinoma of the pancreas to identify any incremental benefit of using bevacizumab in these individuals taking into account potential increases in survival and quality of life as well as the effects of adverse events caused by the treatment.

Because VEGF appears to play a role in pancreatic cancer, bevacizumab was considered a promising therapy and results of two of the phase 2 trials seemed to indicate potential benefit as well. About 89–93% of pancreatic individuals have a VEGF mutation, which is associated with early recurrence after surgery, liver metastases, and poor prognosis. Finding VEGF in tumors is also correlated with tumor size.

Five studies were identified for review as part of the Assessment that tested the use of bevacizumab in individuals with advanced adenocarcinoma. These studies consisted of two phase 3 trials, two phase 2 trials and one phase 1 trial. In all trials, bevacizumab was added to gemcitabine which is considered the current standard of care. Some trials also included other agents as well including cisplatin and erlotinib.

The two Phase III studies, one by Kindler et al. and the second by van Cutsem et al., provided the strongest evidence because of their design. Neither study demonstrated that the addition of bevacizumab resulted in a statistically significant difference in the primary outcome of overall survival. For the secondary outcome of progression-free survival, the van Cutsem study appeared to show benefit while the Kindler study did not.

Kindler et al. randomized 590 individuals with advanced cancer (local or metastatic) to gemcitabine with or without bevacizumab. The trial was stopped early when it was determined that the combination of gemcitabine plus bevacizumab could not achieve longer survival than the gemcitabine alone arm of the trial. The results have not been published in a peer-reviewed journal; however they were presented at the American Society for Clinical Oncology (ASCO) annual meeting in 2007.

Van Cutsem et al. randomized 607 individuals with metastatic adenocarcinoma of the pancreas to gemcitabine plus erlotinib with or without bevacizumab. There was no statistically significant difference between the two groups in the primary outcome of overall survival. The median survival was 7.1 months for the treatment group and 6.0 months for the control group (hazard ratio=0.73; 95% confidence interval 0.74–1.07; p=0.21). The study reported a statistically

significant difference in progression-free survival of 4.6 months in the treatment arm and 3.6 months in the control group. Although this secondary outcome was significant, there were few details given regarding the methods used to assess progression-free survival, which may be subject to greater measurement error than overall survival.

It was anticipated that bevacizumab may offer benefit in advanced adenocarcinoma of the pancreas because the drug targets VEGF, which is thought to play an important role in pancreatic cancer, and because of an apparently positive effect in a phase 2 clinical trial. Unfortunately, the results of two phase 3 trials, one of which was stopped early because of lack of overall survival benefit, and the second recently released trial also showed no incremental benefit in overall survival.

Treatment of advanced adenocarcinoma of the pancreas with bevacizumab is not an FDA-approved indication. The available evidence does not clearly demonstrate that addition of bevacizumab to chemotherapy regimens for advanced adenocarcinoma of the pancreas improves the net health outcome of those individuals. Therefore, bevacizumab for individuals with advanced adenocarcinoma of the pancreas is considered investigational.

Avastin (bevacizumab) and Revlimid (lenalidomide)

As a result of NCCN Drug Compendium revisions, policy statements were revised to reflect additional medically necessary statements for bevacizumab and lenalidomide.

2011 Update

Avastin

The FDA posted the following information on their website on December 16, 2010: "FDA is proposing that the breast cancer indication for Avastin be removed based on results from required clinical studies of the drug, including the AVADO and RIBBON1 studies, which established the following:

- The addition of Avastin to chemotherapy resulted in only a small delay in tumor growth (i.e., progression-free survival, PFS), and the average time it took for tumors to progress seen in these trials was much shorter than had been expected based on the data from an earlier trial that led to accelerated approval.

- The addition of Avastin to chemotherapy did not prolong the lives of women with breast cancer (i.e., overall survival, OS).

The addition of Avastin to various chemotherapies leads to an increase in incidence of serious adverse events from Avastin, as well as the serious side effects related to chemotherapy. Serious adverse events are toxicities that are severe or life-threatening, require medical intervention, hospitalization, or even result in death.

Considering all information from these clinical trials, FDA concluded that the risks of this drug outweigh its benefits in the treatment of individuals with metastatic breast cancer. Under the accelerated approval process, the agency must provide the company with the chance to request a hearing by issuing a Notice of Opportunity for a Hearing (NOOH). The agency issued the NOOH today. Genentech will have 15 days to request a hearing in writing. If Genentech does not request a hearing, the indication will be removed from the label. If Genentech requests a hearing, it must, within 30 days of receiving the NOOH, submit to FDA the data and information upon which it intends to rely at a hearing. If a hearing is requested and granted, it will be open to the public."

Genentech has requested a hearing. The hearing is scheduled for June 28-29, 2011.

2012 Update

Avastin

Clarified grade requirement for bevacizumab treatment of gliomas. A literature search and review of NCCN compendium listings failed to identify other new information that would change these policy requirements.

Although FDA has withdrawn the indication of bevacizumab for treatment of breast cancer it remains as an option in NCCN guidelines; therefore, the Plan will continue to approve off-label use for this indication as medically necessary.

Zaltrap

Added this newly approved agent for treatment of metastatic colorectal cancer. Efficacy of ziv-aflibercept for the treatment of metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen was demonstrated in the Phase III multinational trial (VELOUR). The 1,226 individuals were randomized (1:1) to receive ziv-

aflibercept 4 mg/kg (n=612) or placebo (n=614) by intravenous (IV) infusion every 2 weeks in conjunction with the standard FOLFIRI regimen. Baseline characteristics were balanced between treatment groups at. The majority of individuals were from Western and Eastern Europe. Approximately 11% were in the US Approximately 30% had prior treatment with bevacizumab. Median follow-up was 22.3 months. Median OS was significantly higher in the ziv-aflibercept group than in the placebo group (13.5 versus 12.1 months; hazard ratio [HR] 0.82 [95.3% confidence interval (CI): 0.71, 0.94]; p=0.003). The ziv-aflibercept group also had greater median PFS (6.9 versus 4.7 months, HR 0.76 [95% CI: 0.66, 0.87]; p<0.001). Response rate was also higher in the ziv-aflibercept group.

2013 Update

Updated to include indication for recurrent or metastatic cervical cancer, based on a recent abstract of a Phase 3 trial by Tewari et al., and NCCN Category 2A recommendation. A literature search from 01/01/2012 to 04/30/2013 and review of NCCN compendium listings failed to identify new information that would change these policy requirements. Clarified policy by adding ependymoma as a specific example of coverage for gliomas.

2014 Update

Updated with new indications per NCCN compendium listings: bevacizumab for anaplastic glioma and endometrial carcinoma and lenalidomide for AIDS-related B-cell lymphoma, CLL/SLL and Hodgkin lymphoma. A literature search from 01/01/13 to 10/28/14 failed to identify other new information that would change these policy requirements.

2015 Update

Updated with new indications per FDA approval and NCCN compendium listings: bevacizumab for second line treatment of mCRC, mesothelioma and rectal cancer; and lenalidomide for mantle cell lymphoma, non-Hodgkin lymphoma; and lenalidomide or pomalidomide for systemic light chain amyloidosis. A literature search from 01/01/14 to 8/31/15 failed to identify other new information that would change these policy requirements.

2018 Update

Updated with new labeled indications. A literature search from 05/01/17 to 05/31/18 failed to identify additional new information that would change the policy criteria.

2019 Update

Reviewed prescribing information for all drugs and updated criteria for Avastin (bevacizumab) for metastatic colorectal cancer and epithelial ovarian, fallopian tube, or primary peritoneal cancer.

2020 Update

Reviewed prescribing information for all drugs and updated criteria for Pomalyst (pomalidomide) to include the treatment of adult individuals with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in individuals with KS who are HIV-negative. Updated criteria for Avastin (bevacizumab) and the biosimilars Mvasi (bevacizumab-awwb) and Zirabev (bevacizumab-bvzr) to include coverage for hepatocellular carcinoma (HCC) in combination with Tecentriq (atezolizumab) for the treatment of individuals with unresectable or metastatic HCC who have not received prior systemic therapy.

2021 Update

Reviewed prescribing information for all drugs and no new indications were identified. Updated criteria for Pomalyst (pomalidomide) adding a daily dose limit for multiple myeloma and Kaposi sarcoma following dosing limits in the prescribing information.

2022 Update

Reviewed prescribing information for all drugs and no new indications were identified. Updated background on cancer statistics and NCCN recommended preferred treatment for individuals with advanced NSCLC who have an EGFR exon 19 deletion or an L858R mutation. Added generic lenalidomide to policy with identical coverage criteria as brand Revlimid (lenalidomide).

2023 Update

Reviewed prescribing information for all drugs and no new indications were identified. No changes to the policy statements.

2024 Update

Reviewed prescribing information for all drugs. Removed requirement from bevacizumab products to have tried two prior chemotherapy regimens for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer when used in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan for platinum-resistant recurrent disease. Added Avzivi (bevacizumab-tnjn) as a non-preferred bevacizumab product. Updated bevacizumab product criteria to include the treatment of metastatic colorectal cancer in combination with Lonsurf (trifluridine and tipiracil) who have been previously treated with fluoropyrimidine-. oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. Added coverage for Fruzaqla (fruquintinib) for the treatment of certain adult individuals with metastatic colorectal cancer. Removed ECOG requirement from the policy.

2026 Update

Reviewed prescribing information for all drugs. Updated initial authorization for all other reviews for oral drugs listed in the policy from 3 months to 6 months. Added coverage criteria for generic pomalidomide. Updated criteria for Pomalyst (pomalidomide) to require an inadequate response or intolerance to generic pomalidomide. Added 5.01.591 Immune Checkpoint Inhibitors to related medical policies.

References

1. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst. 1990; 82:4-6.
2. Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003; 21:60-65.
3. Chen HX. Expanding the clinical development of bevacizumab. Oncologist. 2004; 9(Suppl 1):27-35.

4. Yang JC, Haworth L, Sherry RM et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003; 349:427-434.

5. Johnson DH, Fehrenbacher L, Novotny WF et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004; 22:2184-2191.

6. National Cancer Institute (NCI). Colon Cancer (PDQ): Treatment 2022. Available at: **http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional** Accessed March 16, 2026.

7. American Cancer Society. Cancer Reference Information – Detailed Guide: Colorectal Cancer. Available at: **http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_colon_and_rectum_cancer_staged.asp?sitearea** Accessed March 16, 2026.

8. August DA, Ottow RT, Sugarbaker PH. Clinical perspective of human colorectal cancer metastasis. Cancer Metastasis Rev 1994; 3:303-324.

9. Coutinho AK, Rocha Lima CMS. Metastatic colorectal cancer: systemic treatment in the new millennium. Cancer Control. 2003; 10:224-238.

10. Van Cutsem E, Verslype C. Integration of new cytotoxic agents in the management of advanced colorectal cancer: where are we now and where do we go? American Society of Clinoidal Oncology Educational Book 2002; 240-247.

11. Saltz LB, Cox JV, Blanke C et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2000; 343:905-914.

12. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000; 18:2938-2947.

13. Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. Lancet 2000; 355:1041-1047.

14. Goldberg RM, Morton RF, Sargent DJ et al. N9741: oxaliplatin (Oxal) or CPT-11 + 5-fluororacil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Updated efficacy and quality of life (QOL) data from an intergroup study. Proc Am Soc Clin Oncol 2003; 22:252.

15. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350:2335-2342.

16. Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. Nature Medicine 2003; 9:669-676.

17. Coutinho AK, Rocha Lima CMS. Metastatic colorectal cancer: systemic treatment in the new millennium. Cancer Control 2003; 10:224-238.

18. Johnson DH, Fehrenbacher L, Novotny WF et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004; 22:2184-2191.

19. Yang JC, Haworth L, Sherry RM et al. A randomized trial of bevacizumab, and anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003; 349:427-434.

20. Miller KD, Rugo HS, Cobleigh MA et al. Phase III trial of capecitabine (Xeloda) plus bevacizumab (Avastin) versus capecigtabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane. Breast Cancer Res Treat. 2002; 79:abstract 36.

21. Miller KD, Wang M, Gralow J et al. E2100: a randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Presented at the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO), May 13-17, 2005; Orlando, FL.

22. de Gramont A, Van Cutsem E. Investigating the potential of bevacizumab in other indications: metastatic renal cell, non-small cell lung, pancreatic and breast cancer. Oncology. 2005; 69(suppl 3):46-56.

23. Herbst RS, Bajorin DF, Bleiberg H et al. Clinical cancer advances 2005: Major research advances in cancer treatment, prevention, and screening—A report from the American Society of Clinical Oncology. J Clin Oncology. Published ahead of print on 12/02/05.

24. Motzer RJ, Murphy BA, Bacik J et al. Phase III trial of interferon alfa-2a with or without 13-cis-reinoic acid for patients with advanced RCC. J Clin Oncol. 2000;18:2972-2980.

25. Aghajanian C. The role of bevacizumab in ovarian cancer-An evolving story. Gynecol Oncol 2006 Aug;102(2):131-3.

26. R.A. Burger, M. Sill, B.J. Monk, B. Greer, J. Sorosky, Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC): a Gynecologic Oncology Group (GOG) study. J Clin Oncol, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005:5009.

27. S.A. Cannistra, U. Matulonis, R. Penson et al. Bevacizumab in patients with advanced platinum-resistant ovarian cancer. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings. Vol 24, No. 18S, Part I of II (June 20 Suppl), 2006:5006.

28. A.A. Garcia, A.M. Oza, H. Hirte et al. Interim report of a phase II clinical trial of bevacizumab (Bev) and low dose metronomic oral cyclophosphamide (mCTX) in recurrent ovarian (OC) and primary peritoneal carcinoma: A California Cancer Consortium Trial. J Clin Oncol, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Suppl), 2005:5000.

29. Monk BJ, Han E, Josephs-Cowan CA et al. Salvage bevacizumab (rhuMAB VEGF)-based therapy after multiple prior cytotoxic regimens in advanced refractory epithelial ovarian cancer. Gynecol Oncol 2006 ;102(2):140–4.

30. Narayana A, Raza S, Golfinos JG et al. Bevacizumab therapy in recurrent high grade glioma: Impact on local control and survival. J Clin Oncol 26: 2008 (May 20 suppl; abstr 13000).

31. Azad NS, Annunziata CM, Steinberg SM, Minasian L et al. Lack of reliability of CA125 response criteria with anti-VEGF molecularly targeted therapy. Cancer 2008;112(8):1726-32.

32. Habermann TM, Lossos IS, Justice G et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol. 2009 May;145(3):344-9.

33. Tempescul A, Ianotto JC, Morel F et al. Lenalidomide, as a single agent, induces complete remission in a refractory mantle cell lymphoma. Ann Hematol. 2009 Sep;88(9):921-2.

34. National Comprehensive Cancer Network (NCCN). The NCCN Drugs and Biologics Compendium. Available at: **https://www.nccn.org/login?code=fef9ba0e6cba315acaec4c3c830a66a1** Accessed March 16, 2026.

35. Centers for Medicare & Medicaid Services (CMS). CMS Manual System. Pub 100-02 Medicare Benefit Policy. Transmittal 96; Date: October 24, 2008. Available at: **http://www.cms.hhs.gov/transmittals/downloads/R96BP.pdf** Accessed March 16, 2026.

36. Noridian Administrative Services (NAS). Medicare Part B News. Issue # 251, January 21, 2009. Available at: **https://www.noridianmedicare.com/p-medb/fees/medicare_participation_cd/docs/bulletins/medicare_b_news_issue_251_january_21_2009.pdf** Accessed March 16, 2026.

37. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). "Off-Label Use of Bevacizumab: Advanced Adenocarcinoma of the Pancreas". TEC Assessments. Volume 24, No. 4; October 2009.

38. Ko AH, Tempero MA. Treatment of metastatic pancreatic cancer. J Natl Compr Canc Netw 2005; 3(5):627-36.

39. Ducreux M, Boige V, Malka D. Treatment of advanced pancreatic cancer. Semin Oncol 2007; 34(Suppl 1):S25-30

40. Borja-Cacho D, Jensen EH, Saluja AK et al. Molecular targeted therapies for pancreatic cancer. Am J Surg 2008; 196(3):430-41.

41. Kindler HD, Niedzwiecki D, Hollis D et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis of Cancer and Leukemia Group B (CALGB) 80303. Abstract and slide presentation from the American Society of Clinical Oncology (ASCO) 2007 Gastrointestinal Cancers Symposium. Available at: **http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.4508** Accessed March 16, 2026.

42. Van Cutsem E, Vervenne WL, Bennouna I et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib for patients with metastatic pancreatic cancer. J Clin Oncol 2009; 27(13):2231-7.
43. Kindler HD, Friberg G, Singh DA et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2005; 23(31):8033-40.
44. US Food and Drug Administration (FDA). Postmarket Drug and Safety Information for Patients and Providers. Questions and Answers about Avastin. Online; December 16, 2010. Available at: **http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm237095.htm** Accessed March 16, 2026.
45. Tewari KS, Sill M, Long HJ, et al. Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A phase III randomized trial of the Gynecologic Oncology Group [abstract]. J Clin Oncol 2013;31:Abstract 3.
46. Alymsys (bevacizumab-maly). Prescribing information. Amneal Pharmaceuticals LLC; Bridgewater, NJ. Updated April 2022.
47. Avastin (bevacizumab). Prescribing information. Genentech Inc.; South San Francisco, CA. Updated September 2022.
48. Mvasi (bevacizumab-awwb). Prescribing information. Amgen; Thousand Oaks, CA. Updated February 2023.
49. Vegzelma (bevacizumab-adcd). Prescribing information. Celltrion Inc.; Incheon, 22014, Republic of Korea. Updated February 2023.
50. Zirabev (bevacizumab-bvzr). Prescribing information. Pfizer Inc.; New York, NY. Updated August 2024.
51. Cyramza (ramucirumab). Prescribing information. Eli Lilly and Company; Indianapolis, IN. Updated August 2025.
52. Zaltrap (ziv-aflibercept). Prescribing information. Sanofi-Aventis LLC; Bridgewater, NJ. Updated December 2023.
53. Pomalyst (pomalidomide). Prescribing information. Celgene Corporation; Summit, NJ. Updated February 2025.
54. Revlimid (lenalidomide). Prescribing information. Celgene Corporation; Summit, NJ. Updated March 2023.
55. Avzivi (bevacizumab-tnjn). Prescribing information. Bio-Thera Solution, Ltd; Guangzhou, 510530, China. Updated December 2023.
56. Jobevne (bevacizumab-nwgd). Prescribing information. Biocon Biologics Inc.; Cambridge, MA. Updated April 2025.
57. Fruzaqla (fruquintinib). Prescribing information. Takeda Pharmaceuticals America, Inc; Lexington, MA. Updated February 2025.

History

Date	Comments
08/12/08	Add to Prescription Drug Section - New PR Policy.
12/16/08	Updated Rationale Section - No other changes.
05/12/09	Replace Policy - Policy updated with literature search. Policy statement regarding ovarian cancer revised to reflect change from investigational to medically necessary for certain uses. NCCN categories of evidence added to Description and Rationale. References added.
10/13/09	Replace Policy - Policy statement revised for Avastin to allow as either first or second line treatment for kidney cancer and deleted requirement of combo therapy with Irinotecan for CNS cancer. Revisions for Revlimid: In multiple myeloma, deleted

Date	Comments
	requirement for concurrent dexamethasone or needing one prior therapy. In myelodysplastic syndrome, added requirement for no chromosomal abnormality. In NHL/mantle cell lymphoma, changed from investigational to medically necessary.
01/12/10	Replace Policy - Policy updated with literature search. Policy statement revised to change carboplatin to "carboplatin-like agent". Policy statement also now specifically indicates that Avastin for advanced adenocarcinoma of the pancreas is investigational, incorporating data from BC.5.01.18. Rationale and References revised.
09/14/10	Replace Policy - Policy statement on Avastin revised to add capecitabine-based regimen as medically necessary for CRC, add continuous maintenance therapy as medically necessary for NSCLS, and angiosarcoma and solitary fibrous tumor/hemangiopericytoma as medically necessary. Guidelines on Avastin revised to add unresected or stage IV disease and no untreated CNS metastasis. Policy statement and Guidelines on Revlimid revised to add seven types of lymphoma as medically necessary.
12/14/10	Replace Policy - Policy guidelines updated with medically necessary indications for Avastin in the treatment of ovarian cancer recurrence as a single therapy agent.
05/10/11	Replace Policy - Reviewed and recommended by OAP on February 17, 2011. Rationale updated with FDA information regarding their action to remove Breast Cancer as a labeled indication for Avastin.
04/10/12	Replace policy. Policy updated with clarification on grade requirements for bevacizumab treatment of gliomas.
12/11/12	Replace policy. Policy statement updated: ziv-aflibercept (Zaltrap) in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI) may be considered medically necessary for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen; investigational for all other uses. Reviewed by P&T on 11/27/12. HCPCS code J1725 added to the policy. Add Related Policy 5.01.01.
05/28/13	Replace policy. Policy reviewed with literature search; no change to policy statements. Clarified policy by adding ependymoma as a specific example of coverage for gliomas.
08/12/13	Replace policy. Policy statement added indicating Pomalidomide (Pomalyst™) may be medically necessary for the treatment of multiple myeloma when criteria are met. Policy Guidelines section also updated. Policy statement for Avastin® updated to include indication for recurrent or metastatic cervical cancer.
11/20/13	Update Related Policies. Delete 5.01.01 and replace it with 5.01.549, add 5.01.544.
11/20/14	Annual Review. Policy section updated with new medically necessary indications per NCCN compendium listings: bevacizumab for anaplastic glioma and endometrial carcinoma and lenalidomide for AIDS-related B-cell lymphoma, CLL/SLL and Hodgkin lymphoma. HCPCS code J9400 added to the policy; this is a new code.

Date	Comments
01/13/15	Minor update. Clarification made to the medically necessary policy statement for Avastin in the treatment of ovarian cancer; the word "recurrence" was removed.
10/13/15	Annual Review. Updated policy with new NCCN guidelines and indications from updated FDA labels.
12/08/15	Interim Update. Relapsed or refractory mantle cell lymphoma now requires step-therapy when treated with Revlimid. Pomalyst may be considered medically necessary to treat systemic light chain amyloidosis. Approved by P&T on November 19, 2015.
01/04/16	Minor edit. Formatting change to list of indications for off-label use of lenalidomide (Revlimid®).
10/01/16	Annual Review, approved September 13, 2016. Updating indication and criteria for bevacizumab.
12/09/16	Minor edit. Formatting correction to indicate that treatment of endometrial carcinoma is a standalone criterion for use of Avastin, not a subset of ovarian carcinoma.
06/01/17	Annual Review, approved May 16, 2017. Policy moved into new format. A statement outlining the length of therapy for initial approval has been added to the policy. Note added to confirm that eye-related injections do not require a review; these are standard of care.
06/01/18	Annual Review, approved May 3, 2018. A literature search from 05/01/17 to 05/31/18 failed to identify additional new information that would change the policy criteria. Updated per labeled indications.
06/15/18	Minor edit, reformatted the Avastin medical necessity criteria but statements were unchanged.
11/01/18	Interim Review, approved October 9, 2018. Updated Avastin criteria for ovarian cancer per label revised (6/13/18). Removed HCPCS codes J8499 and J8999.
01/01/19	Coding update, added new HCPCS code Q5107 (new code effective 1/1/19).
05/01/19	Annual Review, approved April 9, 2019. Updated Avastin criteria for metastatic colorectal cancer and epithelial ovarian, fallopian tube, or primary peritoneal cancer.
07/01/19	Interim Review, approved June 11, 2019. Added criteria for Mvasi (bevacizumab-awwb) which is a biosimilar to Avastin (bevacizumab).
09/01/19	Interim Review, approved August 13, 2019. Added criteria for Zirabev (bevacizumab-bvzr) which is a biosimilar to Avastin (bevacizumab). Updated criteria for Revlimid (lenalidomide). Added HCPCS code Q5118 (new code effective 10/1/19).
01/01/20	Interim Review, approved December 17, 2019, effective for dates of service on or after April 3, 2020, following provider notification. Updated criteria for Mvasi (bevacizumab-awwb) to require use of Avastin (bevacizumab) or Zirabev (bevacizumab-bvzr) first.
04/03/20	Minor update. Policy title changed from "Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Patients" to

Date	Comments
	"Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Treatment".
07/01/20	Annual Review, approved June 9, 2020. Updated coverage criteria for Pomalyst (pomalidomide) to include the treatment of Kaposi sarcoma. Updated criteria for Avastin (bevacizumab), Mvasi (bevacizumab-awwb) and Zirabev (bevacizumab-bvzr) to include coverage for hepatocellular carcinoma.
09/01/20	Interim Review, approved August 11, 2020. Added Cyramza (ramucirumab) to policy with coverage criteria for gastric/GEJ, NSCLC, CRC, and HCC effective for dates of service on or after December 3, 2020, after provider notification. Separated Mvasi (bevacizumab-awwb) from Avastin (bevacizumab) and Zirabev (bevacizumab-bvzr) within policy. No change to coverage criteria for Mvasi, Avastin and Zirabev. Added HCPCS code J9308.
11/01/20	Interim Review, approved October 22, 2020. Updated criteria for Avastin (bevacizumab), Mvasi (bevacizumab-awwb), Zirabev (bevacizumab-bvzr), and Zaltrap (ziv-aflibercept) for the treatment of mCRC to include an equivalent drug to 5-fluorouracil (e.g., capecitabine, floxuridine).
05/01/21	Annual Review, approved April 22, 2021. Updated Pomalyst (pomalidomide) criteria adding a daily dose limit for multiple myeloma and Kaposi sarcoma indications.
10/01/21	Interim Review, approved September 23, 2021. Added a new indication to Pomalyst (pomalidomide) for the treatment of adult patients with multiple myeloma in combination with Darzalex Faspro (daratumumab and hyaluronidase-fihj) and dexamethasone. Updated Pomalyst criteria for the treatment of multiple myeloma to adult patients.
05/01/22	Annual Review, approved April 25, 2022. Added generic lenalidomide to policy with identical coverage criteria as brand Revlimid (lenalidomide).
12/01/22	Interim Review, approved November 8, 2022. Added the biosimilars Alymsys (bevacizumab-maly) and Vegzelma (bevacizumab-adcd) to policy with requirement for individual to have an inadequate response or intolerance to Avastin or Zirabev first. Changed the wording from "patient" to "individual" throughout the policy for standardization. Added HCPC code C9142 for Alymsys®. Added HCPC code J3590 Vegzelma®.
01/01/23	Coding update. Added code term date to HCPCS code C9142 and added HCPCS code Q5126.
04/01/23	Coding update. Added new HCPCS code Q5129. Removed HCPCS codes J3590 andC9142.
07/01/23	Annual Review, approved June 26, 2023. No changes to the policy statements.
03/01/24	Annual Review, approved February 13, 2024. Removed requirement from bevacizumab products to have tried two prior chemotherapy regimens for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer when used in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan for

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	platinum-resistant recurrent disease. Added Avzivi (bevacizumab-tnjn) as a non-preferred bevacizumab product. Updated bevacizumab product criteria to include the treatment of metastatic colorectal cancer in combination with Lonsurf (trifluridine and tipiracil) who have been previously treated with fluoropyrimidine-. oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. Added coverage for Fruzaqla (fruquintinib) for the treatment of certain adult individuals with metastatic colorectal cancer. Added HCPC code J9999 for Avzivi. Removed ECOG requirement from the policy.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Changed Mvasi (bevacizumab-awwb) to a preferred product and changed Avastin (bevacizumab) to a non-preferred product. Updated coverage criteria for Alymsys (bevacizumab-maly), Avastin, Avzivi (bevacizumab-tnjn) and Vegzelma (bevacizumab-adcd) to require the individual has had an adequate trial and failure with Mvasi or Zirabev.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.
09/01/25	Interim Review, approved August 12, 2025. Added Jobevne (bevacizumab-nwgd) as a non-preferred bevacizumab product. Added HCPCS code C9399 for Jobevne. Jobevne also added to parenthetical of J9999.
01/01/26	Interim Review, approved December 9, 2025. Updated coverage criteria for Revlimid (lenalidomide) for all indications to require the individual has tried and had an inadequate response or intolerance to generic lenalidomide. Added new HCPCS code Q5160 effective January 1, 2026.
05/01/26	Annual Review, approved April 14, 2026. Updated initial authorization for all other reviews for oral drugs listed in the policy from 3 months to 6 months. Added coverage criteria for generic pomalidomide. Updated criteria for Pomalyst (pomalidomide) to require an inadequate response or intolerance to generic pomalidomide. Added 5.01.591 Immune Checkpoint Inhibitors to related medical policies.
10/01/26	Interim Review approved September 8, 2026. Updated Vegzelma (bevacizumab-adcd) from a non-preferred product to a preferred product. Updated criteria for Alymsys, Avastin, Avzivi, and Jobevne adding Vegzelma (bevacizumab-adcd) to list of preferred alternatives. Removed reference to non-formulary exception reviews. Removed HCPCS code C9399. The following policy changes are effective January 1, 2027, following 90-day provider notification. Updated criteria for Alymsys, Avastin, Avzivi, and Jobevne to require trial of all preferred bevacizumab products.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review

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