

# Bevacizumab

ACG: A-0491 (AC)  
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## Clinical Indications

- Bevacizumab may be indicated when **1 or more** of the following are present:
  - Intravitreal administration needed, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Eye condition appropriate for bevacizumab treatment, as indicated by **1 or more** of the following:
      - Diabetic macular edema(54)(55)(56)(57)(58)(59)[N](#)
      - Macular edema following retinal vein occlusion(67)(68)(69)[N](#)
      - Myopic choroidal neovascularization[N](#)
      - Neovascular age-related macular degeneration(56)(81)(82)(83)[N](#)
      - Ocular histoplasmosis<sup>[A]</sup> with choroidal neovascularization(97)[N](#)
    - No concurrent ocular or periocular infection
  - Systemic administration needed, as indicated by **ALL** of the following(1)(101)(102):
    - Age 18 years or older
    - Malignancy appropriate for bevacizumab treatment, as indicated by **1 or more** of the following:
      - Cervical cancer and **ALL** of the following(103)(104)(105)(106)(107):[N](#)
        - Administered in combination with other agents (eg, atezolizumab, carboplatin, paclitaxel, and topotecan; paclitaxel and cisplatin with or without pembrolizumab)
        - Persistent, recurrent, or metastatic disease
      - Colon or rectal cancer (metastatic) and **ALL** of the following(112)(113)(114)(115)(116):[N](#)
        - Metastatic disease(124)
        - Treatment scenario includes **1 or more** of the following:
          - First-line therapy and administered in combination with other agents (eg, intravenous 5-fluorouracil-based, irinotecan-based, or oxaliplatin-based chemotherapy)(125)(126)
          - Subsequent therapy and administered in combination with other agents (eg, irinotecan-based chemotherapy, oxaliplatin-based chemotherapy, trifluridine-tipiracil)
        - No coadministration of cetuximab or panitumumab(112)(127)
      - Hepatocellular carcinoma and **ALL** of the following(128)(129)(130)(131)(132):[N](#)
        - Administered in combination with atezolizumab(139)(140)
        - Metastatic or unresectable disease
        - Previously untreated disease



afibercept monotherapy and found, at 2-year follow-up, no difference in change in visual acuity or retinal central subfield thickness between groups, with higher adverse event rates in the aflibercept group compared with the step-therapy group.(62) **(EG 1)** A meta-analysis of studies comparing efficacy and safety of intravitreal triamcinolone vs intravitreal bevacizumab for diabetic macular edema found evidence that triamcinolone may be more effective, but the authors indicated that additional randomized studies are needed to determine and confirm which patients might benefit the most from either drug.(63) **(EG 1)** A randomized study of 660 adults with diabetic macular edema who received either intravitreal aflibercept, ranibizumab, or bevacizumab found that, after 1 year, visual acuity improvement was comparable with all 3 drugs in those with mild initial visual acuity loss.(64) **(EG 1)** A follow-up study for up to 2 years found that all 3 groups showed continuing improvement in visual acuity, with similar improvement across all 3 drugs in eyes with better baseline acuity.(65) **(EG 1)** A systematic review and meta-analysis of 8 randomized controlled trials (817 eyes) evaluating the efficacy of intravitreal ranibizumab or bevacizumab combined with intravitreal steroids for the treatment of diabetic macular edema found no difference in both the mean change in visual acuity and central macular thickness at 6-month to 2-year follow-up compared with vascular endothelial growth factor inhibitor therapy alone. Additionally, combination therapy was associated with an increased rate of cataract development and raised intraocular pressure.(66) **(EG 1)**

For macular edema following retinal vein occlusion, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Meta-analyses and systematic reviews have confirmed the efficacy and safety of vascular endothelial growth factor inhibitors for treatment of central retinal vein occlusion for up to 26 to 52 weeks.(70)(71)(72)(73) **(EG 1)** A meta-analysis found randomized controlled studies that indicate that patients with branch retinal vein occlusion experience a significant benefit with intravitreal bevacizumab, as compared with placebo, in terms of improvement in both central foveal thickness and visual acuity over periods of up to 24 months.(74) **(EG 1)** A randomized study assigned 52 eyes of 52 patients with branch retinal vein occlusion to monotherapy with either intravitreal triamcinolone or bevacizumab, or to both. After 6 months, the group receiving bevacizumab alone had better visual acuity than the other 2 groups.(68) **(EG 1)** A randomized noninferiority trial of 463 patients with macular edema due to central retinal vein occlusion compared treatment with bevacizumab, aflibercept, or ranibizumab and found, at 100-week follow-up, mean gains in best-corrected visual acuity letter scores of 9.8, 15.1, and 12.5 in patients treated with bevacizumab, aflibercept, and ranibizumab, respectively. The authors found that bevacizumab was not noninferior compared with ranibizumab.(75) **(EG 1)** A randomized controlled trial of 98 patients with either central or branch retinal vein occlusion found that intravitreal bevacizumab and ranibizumab had similar efficacy in improving both macular thickness and visual acuity after 6 months.(76) **(EG 1)** Specialty society guidelines state that bevacizumab is an effective treatment for macular edema due to retinal vein occlusion.(77)(78) **(EG 2)**

For myopic choroidal neovascularization, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A meta-analysis and systematic review of 6 randomized studies of 594 patients with myopic choroidal neovascularization found low to moderate evidence that bevacizumab and ranibizumab are effective in treating this condition for up to a period of 1 to 2 years.(79) **(EG 1)** A specialty society consensus statement recommends that vascular endothelial growth factor inhibitor therapy should be the first-line treatment for patients with myopic choroidal neovascularization.(80) **(EG 2)**

For neovascular age-related macular degeneration, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A randomized controlled trial of 131 patients receiving either intravitreal bevacizumab, standard care at the time of study (verteporfin or pegaptanib), or sham injection found significant improvement in visual acuity and contrast sensitivity in the bevacizumab group after 1 year.(84)(85) **(EG 1)** In a multicenter randomized single-blind trial, 1208 patients with neovascular age-related macular degeneration were assigned to receive intravitreal injections of either bevacizumab or ranibizumab, either monthly or as needed with monthly evaluation. After 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule.(86) **(EG 1)** These results were maintained at 2-year follow-up.(87)(88)(89) **(EG 1)** Randomized trials (of 610, 501, 441, and 327 patients with neovascular age-related macular edema) reported equivalent outcomes with either ranibizumab or bevacizumab at 1-year follow-up.(83)(90)(91)(92) **(EG 1)** A meta-analysis of randomized studies (with a total of 2686 patients receiving either bevacizumab or ranibizumab for neovascular age-related macular edema) confirmed that bevacizumab and ranibizumab had comparable positive effects on visual acuity after 1 year, but bevacizumab was associated with a higher risk of serious systemic adverse events.(93) **(EG 1)** Specialty society and international practice guidelines recommend bevacizumab as a management option for patients with age-related neovascular macular degeneration.(94)(95) **(EG 2)**

For ocular histoplasmosis with choroidal neovascularization, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A retrospective chart review of 54 eyes with ocular histoplasmosis treated with either intravitreal bevacizumab or ranibizumab found, at 26.8-month follow-up, that treatment with either agent was associated with improved visual acuity.(98) **(EG 2)** A retrospective case series of 140 patients (150 eyes) with ocular histoplasmosis treated with intravitreal bevacizumab alone or combined with verteporfin photodynamic therapy found, at a mean follow-up of 21.1 months, that both treatments resulted in visual stabilization in most patients, with no difference between the groups. The authors recommended further randomized trials.(99) **(EG 2)** A review article notes that bevacizumab has been evaluated for treatment of ocular histoplasmosis only in case series, with good results.(100) **(EG 2)** A narrative review notes that both verteporfin and anti-vascular endothelial growth factor injections are treatment options for patients with ocular histoplasmosis with choroidal neovascularization.(96) **(EG 2)**

For cervical cancer (recurrent, persistent, or metastatic), evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A randomized controlled study of 452 patients with recurrent, persistent, or metastatic cervical cancer assigned patients to the standard chemotherapy regimens of cisplatin plus paclitaxel or topotecan plus paclitaxel, with or without bevacizumab. The addition of bevacizumab to any regimen was associated with significant improvement in median overall survival (16.8 months vs

13.3 months), median progression-free survival (8.2 months vs 6.0 months), and response rate (49% vs 36%) without significant deterioration in health-related quality of life.(108)(109)(110)(111) **(EG 1)**

For colon or rectal cancer (metastatic), evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review and meta-analysis of 7 randomized controlled trials (3588 patients) evaluating the efficacy of bevacizumab for first-line treatment of metastatic colorectal cancer found that bevacizumab in combination with 5-fluorouracil-based chemotherapy was associated with prolonged progression-free and overall survival.(117) **(EG 1)** A systematic review and meta-analysis identified 8 studies and found that FOLFOXIRI-Bev (ie, fluorouracil, oxaliplatin, and irinotecan plus bevacizumab) therapy resulted in a pooled overall and curative resection rate of liver metastases of 39.1% and 28.1%, respectively, and a median overall survival of 30.2 months in patients previously diagnosed with unresectable metastatic colorectal cancer.(118) **(EG 1)** An open-label phase III trial of 820 patients with unresectable metastatic colorectal cancer that progressed after discontinuing first-line bevacizumab plus chemotherapy randomized patients to second-line chemotherapy (oxaliplatin-based or irinotecan-based) with or without bevacizumab; the addition of bevacizumab in second-line therapy was associated with an improvement in median overall survival (11.2 months vs 9.8 months) and median progression-free survival (5.7 months vs 4.1 months).(119) **(EG 1)** A phase III trial of 492 patients with metastatic colorectal cancer (94.7% of whom had failed 2 or more prior chemotherapy regimens) treated patients with trifluridine-tipiracil and either bevacizumab or placebo and found, at a median follow-up of 14.2 months (combination therapy group) and 13.6 months (trifluridine-tipiracil group), that median overall survival was longer in the combination therapy group compared with trifluridine-tipiracil treatment alone.(120) **(EG 1)** A meta-analysis (including 13 randomized studies) found that administration of the anti-epidermal growth factor antibody drugs (cetuximab or panitumumab) plus chemotherapy was associated with a likely survival benefit compared with administration of bevacizumab plus chemotherapy in patients with left-sided origination of colorectal cancer, while patients with right-sided disease had improved progression-free survival and overall survival associated with treatment with bevacizumab plus chemotherapy.(121) **(EG 1)** A phase III trial of 823 patients with RAS wild-type, unresectable, metastatic colorectal cancer (802 of whom received treatment and were included in the analysis) compared treatment with chemotherapy (fluorouracil, levoleucovorin, and oxaliplatin) combined with either panitumumab or bevacizumab and found, at a median follow-up of 61 months, that panitumumab was associated with longer overall survival in patients with left-sided tumors and in the overall population compared with bevacizumab.(122) **(EG 1)** An open-label phase III study of 530 patients with initially unresectable colorectal cancer liver metastases compared treatment with bevacizumab plus either combination folinic acid, fluorouracil, and oxaliplatin or irinotecan (FOLFOX/FOLFIRI) or combination folinic acid, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) and found, at a median follow-up of 51 months, that bevacizumab plus FOLFOXIRI was associated with longer progression-free survival compared with bevacizumab plus FOLFOX or FOLFIRI for patients with right-sided primary tumors.(123) **(EG 1)**

For hepatocellular carcinoma, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** An open-label phase III trial of 501 patients with metastatic or unresectable hepatocellular carcinoma (all of whom had Child-Pugh class A liver disease, and none of whom had received prior systemic therapy) compared treatment with either combination atezolizumab plus bevacizumab or sorafenib and found, at a median follow-up of 8.6 months, that atezolizumab plus bevacizumab was associated with longer overall and progression-free survival compared with sorafenib.(128) **(EG 1)** An open-label phase III trial of 668 patients with high-risk surgically resected or ablated hepatocellular carcinoma (all of whom had Child-Pugh class A liver disease) compared further treatment with either bevacizumab plus atezolizumab or active surveillance and found, at a median follow-up of 17.4 months, that bevacizumab plus atezolizumab was associated with improved recurrence-free survival compared with surveillance. The authors noted that the short follow-up and lack of overall survival data limited the results.(133) **(EG 1)** A meta-analysis of 8 studies (342 patients) evaluating the efficacy of bevacizumab combined with erlotinib for advanced hepatocellular carcinoma found pooled objective response and disease control rates of 12.6% and 60.3%, respectively, a 16-week progression-free survival rate of 50.2%, and 6-month and 12-month overall survival rates of 74% and 43.7%, respectively. However, the authors noted that 7 of the included studies lacked a comparator arm, and there was high heterogeneity among the studies; further high-quality trials were recommended.(134) **(EG 1)** Specialty society guidelines note that bevacizumab combined with atezolizumab may be considered as a first-line treatment option for patients with advanced hepatocellular carcinoma.(135)(136)(137) **(EG 2)** A specialty society guideline states that adjuvant or neoadjuvant therapy including bevacizumab with atezolizumab should not be administered to patients after tumor resection or tumor ablation due to a lack of sustained survival benefit. (138) **(EG 2)**

For malignant glioma, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review and meta-analysis of 11 randomized trials (3743 patients) evaluating the efficacy of anti-angiogenic therapy for high-grade glioma found evidence that bevacizumab prolongs progression-free survival in newly diagnosed and recurrent glioblastoma; however, the impact on quality of life remains uncertain.(146) **(EG 1)** A randomized controlled study of 921 newly diagnosed patients found that the addition of bevacizumab to initial therapy had no effect upon quality of life during the progression-free period.(147) **(EG 1)** In a randomized controlled study of 921 patients with supratentorial glioblastoma, bevacizumab or placebo was added to a universal regimen of radiotherapy plus temozolomide. While bevacizumab significantly improved progression-free survival and maintenance of baseline health-related quality of life and performance status, overall survival did not improve, and significantly more adverse events were noted with bevacizumab.(148) **(EG 1)** Another randomized study of 978 patients with newly diagnosed central glioblastoma found no improvement in overall survival with bevacizumab added to radiotherapy plus temozolomide, although progression-free survival improved from 7.3 months to 10.7 months. (149)(150) **(EG 1)** A phase III randomized trial of 369 patients with recurrent glioblastoma (all of whom had been treated with temozolomide and radiation) compared further treatment with nivolumab or bevacizumab and found, at a median follow-up of 9.5 months, that bevacizumab was associated with longer progression-free survival, with no difference in overall survival seen between the groups; investigator-assessed objective response was higher with bevacizumab as compared with nivolumab (23.1% and 7.8%,

respectively).(151) **(EG 1)** A phase III randomized controlled trial of 437 patients with progressive glioblastoma after chemoradiation found that treatment with lomustine plus bevacizumab was associated with improved median progression-free survival compared with lomustine monotherapy (4.2 months vs 1.5 months, respectively); however, there was no difference in overall survival between the treatment groups. Combination therapy was associated with increased grade 3 to 5 adverse effects, including pulmonary embolism and arterial hypertension.(152) **(EG 1)**

For pleural mesothelioma, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** An open-label phase III randomized trial of 448 patients with unresectable pleural mesothelioma compared treatment with cisplatin plus pemetrexed with and without bevacizumab and found that treatment with bevacizumab was associated with prolonged overall and progression-free survival.(156) **(EG 1)** Specialty society practice guidelines and an expert consensus guideline recommend bevacizumab combined with pemetrexed and cisplatin(159) or carboplatin for first-line therapy of unresectable pleural mesothelioma.(157)(158) **(EG 2)**

For non-small cell lung cancer, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Meta-analyses of randomized controlled trials reported that bevacizumab is effective in improving response rate as well as progression-free(165) and overall survival in selected patients with advanced disease.(166)(167)(168) **(EG 1)** However, some authors feel that improvement in overall survival is debatable.(169) **(EG 2)** An open-label phase III randomized trial of 228 patients with advanced (stage IIIB or IV) or recurrent, EGFR-positive, nonsquamous non-small cell lung cancer compared treatment with erlotinib with and without bevacizumab and found, at 12.4-month follow-up, that bevacizumab was associated with prolonged progression-free survival.(170) **(EG 1)** Oncology practice guidelines recommend bevacizumab for advanced or metastatic non-small cell lung cancer as part of a combination chemotherapy regimen or as monotherapy maintenance; bevacizumab is not recommended for patients with squamous cell non-small cell lung cancer.(35)(161)(162) **(EG 2)**

For ovarian (epithelial), fallopian tube, or primary peritoneal cancer, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** An open-label randomized study of 361 patients with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within 6 months of completion of platinum-based therapy found that the addition of bevacizumab to chemotherapy was associated with a statistically significant improvement in median progression-free survival (6.7 months vs 3.4 months) and a significantly higher objective response rate (27.3% vs 11.8%).(171) **(EG 1)** For patients with platinum-sensitive recurrent ovarian cancer, a randomized study of 484 patients found, at a median follow-up of 24 months, that patients treated with bevacizumab plus gemcitabine had improved progression-free survival compared with patients treated with gemcitabine plus placebo (12.4 months vs 8.4 months, respectively); however, at a median follow-up of 58.2 months, the 2 groups had comparable overall survival.(175)(176) **(EG 1)** A randomized study of 674 patients with recurrent platinum-sensitive epithelial ovarian, primary peritoneal, or fallopian tube cancer assigned patients to treatment with chemotherapy (consisting of carboplatin and paclitaxel) with or without bevacizumab; a secondary intervention assessing the role of cytoreduction was also studied but has not yet been reported. At a median follow-up of 49.6 months, intention-to-treat analysis showed that the chemotherapy-plus-bevacizumab group was associated with improved median survival as compared with the chemotherapy-alone group (42.2 months vs 37.3 months, respectively), but the difference was not statistically significant. However, the authors identified an error in treatment-free interval stratification data for 7% of patients, and sensitivity analysis did reveal a difference between treatment groups that was statistically significant.(177) **(EG 1)** A double-blind phase III trial randomly assigned 1873 women who had undergone debulking surgery for newly diagnosed stage III or stage IV epithelial ovarian cancer to either chemotherapy alone (ie, carboplatin plus paclitaxel), chemotherapy plus 5 cycles of bevacizumab, or chemotherapy plus 21 cycles of bevacizumab; median progression-free survival rates in the 3 groups were 10.3 months, 11.2 months, and 14.1 months, respectively.(178) **(EG 1)** Oncology practice guidelines and a narrative review recommend bevacizumab as a part of treatment strategies for recurrent platinum-resistant or platinum-sensitive epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.(174)(179)(180)(181) **(EG 2)** An open-label phase III trial of 406 patients with stage IIIB or IV ovarian cancer (all of whom had recurrent disease after treatment with platinum chemotherapy combined with bevacizumab) compared further treatment with chemotherapy (carboplatin plus paclitaxel, gemcitabine, or liposomal doxorubicin) alone or combined with bevacizumab and found, at a median follow-up of 20.1 months, that bevacizumab was associated with longer median progression-free survival compared with chemotherapy alone.(182) **(EG 1)** An open-label phase III trial of 682 patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer compared further treatment with bevacizumab combined with either carboplatin plus gemcitabine or carboplatin plus liposomal doxorubicin and found that carboplatin plus liposomal doxorubicin was associated with longer progression-free and overall survival compared with carboplatin plus gemcitabine.(183) **(EG 1)** A phase III trial of 806 patients with advanced ovarian cancer (International Federation of Gynecology and Obstetrics (FIGO) stage III or IV) who had a complete or partial response to first-line treatment with platinum-based chemotherapy plus bevacizumab compared maintenance therapy with bevacizumab combined with either olaparib or placebo and found, at a median follow-up of 62 months, no difference in overall survival between groups. A subgroup analysis found that, among patients with a homologous recombination deficiency (defined as BRCA mutation and/or genomic instability), treatment with olaparib led to longer overall survival compared with placebo.(184) **(EG 1)** A technology appraisal of maintenance therapy for advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer recommends treatment with olaparib with bevacizumab for advanced (FIGO stages III and IV) cancers that demonstrate homologous recombination deficiency.(185) **(EG 2)**

For renal cell carcinoma, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** An open-label phase III randomized trial of 915 patients with previously untreated, unresectable, locally advanced or metastatic renal cell carcinoma (all with clear cell or sarcomatoid histology) compared treatment with either the combination of atezolizumab plus bevacizumab or sunitinib monotherapy and found that combination therapy was associated with prolonged progression-free survival compared with sunitinib. However, no difference in overall

survival was seen between the groups, and longer-term follow-up was recommended.(193) **(EG 1)** A multicenter double-blind phase III trial of 649 previously untreated patients found that the combination of bevacizumab plus interferon alfa-2a produced a significantly higher objective tumor response rate and a longer mean duration of progression-free survival, but a statistically nonsignificant increase in overall survival, as compared with interferon given alone. However, more than half of patients in both study arms received at least one postprotocol antineoplastic therapy, which may have confounded the overall survival analysis.(194) **(EG 1)** A randomized double-blind phase II trial of 116 patients with metastatic clear cell renal cell carcinoma compared treatment with bevacizumab or placebo and found, at a median follow-up of 27 months, that bevacizumab was associated with longer progression-free survival and time to disease progression compared with placebo.(195) **(EG 1)** A phase II study of 39 patients with metastatic clear cell renal cell cancer (all of whom had failed first-line anti-vascular endothelial growth factor therapy) evaluating subsequent therapy with the combination of bevacizumab and temsirolimus found, at a median follow-up of 37 months, a 6-month progression-free survival rate of 50.9% and median overall survival of 18.2 months.(196) **(EG 2)** A phase II trial of 34 patients with metastatic or unresectable sarcomatoid renal cell cancer treated with the combination of capecitabine, gemcitabine, and bevacizumab found median progression-free survival of 5.5 months and median overall survival of 12 months.(197) **(EG 2)** Specialty society guidelines and a review article recommend bevacizumab plus interferon as first-line therapy for unresectable, metastatic, or relapsing predominantly clear cell renal carcinoma.(188)(192)(198) **(EG 2)**

## Inconclusive or Non-Supportive Evidence

For breast cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** Meta-analyses and systematic reviews of randomized controlled studies reported improvement in progression-free survival and overall response rate but no incremental improvement in overall survival.(3)(4)(5)(6) **(EG 1)** A randomized controlled trial of 4994 patients with HER2-negative breast cancer (all of whom had lymph node-positive or high-risk lymph node-negative disease) compared 4 cycles of adjuvant chemotherapy (doxorubicin and cyclophosphamide) combined with bevacizumab or placebo, followed by 12 cycles of paclitaxel with or without bevacizumab, and found no difference in 5-year overall or invasive disease-free survival among the groups.(7) **(EG 1)** A phase II clinical trial of 112 women with breast cancer metastatic to brain compared treatment with whole brain radiotherapy with and without combination bevacizumab, etoposide, and cisplatin (BEEP) and found that BEEP was associated with longer brain-specific progression-free survival compared with whole brain radiotherapy alone. Larger phase III trials were recommended.(8) **(EG 1)** An open-label randomized phase III trial of 800 patients with HER2-negative breast cancer randomized to receive standard chemotherapy (eg, docetaxel, fluorouracil, epirubicin, cyclophosphamide) with or without neoadjuvant bevacizumab found, at 3.5-year follow-up, that among patients with a pathologic complete response, the addition of neoadjuvant bevacizumab was not associated with improvement in disease-free survival and overall survival compared with standard chemotherapy.(9) **(EG 1)** A pooled analysis from 2 randomized trials with a total of 749 patients (all of whom had unresectable, locally advanced or metastatic, hormone receptor-positive, HER2-negative breast cancer) comparing treatment with endocrine therapy with and without bevacizumab found, at a median follow-up of 34 months, that bevacizumab was associated with longer progression-free survival and a higher overall response rate compared with endocrine therapy alone. However, the authors noted there was no difference in overall survival seen between the groups and that bevacizumab was associated with an increase in grade 3 and higher toxicities (eg, hypertension, proteinuria, cardiovascular events) leading to death.(10) **(EG 1)** A health technology appraisal and expert consensus guidelines note that bevacizumab may be considered in select cases of advanced breast cancer.(11)(12)(13) **(EG 2)**

For central serous chorioretinopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A network meta-analysis of interventions for central serous chorioretinopathy found no incremental difference in visual acuity after treatment with anti-vascular endothelial growth factor therapy.(14) **(EG 1)**

For choroidal neovascularization secondary to angioid streaks, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A retrospective case series of 52 eyes (39 patients) with choroidal neovascularization secondary to angioid streaks treated as needed with bevacizumab (13 eyes), ranibizumab (33 eyes), or a combination (6 eyes) found, at a mean follow-up of 33.8 months, that treatment slowed the progression of choroidal neovascularization but did not prevent progressive visual loss. Further prospective randomized studies were recommended.(15) **(EG 2)** A prospective case series of 18 patients with non-subfoveal choroidal neovascularization with angioid streaks treated with intravitreal bevacizumab found no change in best-corrected visual acuity at 12 months, with subsequent worsening at 24 and 36 months.(16) **(EG 2)** A retrospective review of 20 patients (23 eyes) with choroidal neovascularization due to angioid streaks treated with intravitreal bevacizumab found, at a mean follow-up of 23 months, that treatment stabilized vision in affected eyes. Prospective randomized trials were recommended.(17) **(EG 2)**

For corneal neovascularization, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of the effectiveness of bevacizumab for corneal neovascularization found 7 clinical studies, consisting primarily of small uncontrolled case series, suggesting efficacy, but the authors caution that larger, confirmatory, randomized controlled studies are necessary.(18) **(EG 2)**

For endometrial cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A phase II randomized trial of 108 patients with advanced or recurrent endometrial cancer compared treatment with chemotherapy (carboplatin and paclitaxel) with and without bevacizumab and found that patients treated with bevacizumab had longer progression-free and overall survival compared with patients treated with chemotherapy alone, though the differences did not reach statistical significance. However, the authors noted that the small number of included patients limited the results, and further studies were recommended.(19) **(EG 1)** An expert consensus guideline states that bevacizumab alone or

combined with carboplatin and paclitaxel is a treatment option for recurrent, metastatic, or high-risk disease, based on phase II and retrospective studies.(20) **(EG 2)**

For gastric or gastroesophageal cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A multicenter open-label randomized trial of 1063 patients with resectable esophagogastric adenocarcinoma compared perioperative treatment with the combination of epirubicin, cisplatin, and capecitabine with and without bevacizumab and found, at a median follow-up of 38.4 months, no difference in overall, progression-free, or disease-free survival between the groups; patients treated with bevacizumab had a higher incidence of wound healing complications and postoperative anastomotic leak (especially among those patients who underwent esophagogastrectomy).(21) **(EG 1)** A multinational randomized placebo-controlled trial of 774 patients with advanced gastric cancer reported that bevacizumab in combination with chemotherapy was associated with increased response rate and progression-free survival; however, the trial did not achieve its primary objective of a projected increase in overall survival.(22) **(EG 1)** An expert consensus guideline does not include bevacizumab as a treatment option for gastric or gastroesophageal cancer.(23)(24) **(EG 2)**

For head and neck cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A phase III randomized trial of 403 patients with recurrent or metastatic squamous cell cancer of the head and neck compared platinum-based chemotherapy with and without bevacizumab and found that bevacizumab was associated with longer progression-free survival and a higher overall response rate compared with chemotherapy alone, with no difference in overall survival seen between the groups. However, bevacizumab was associated with more grade 3 or higher toxicities compared with chemotherapy alone, and further trials were recommended.(25) **(EG 1)** An expert consensus guideline does not include bevacizumab as a treatment option for head and neck cancer.(26) **(EG 2)**

For melanoma, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A phase III trial of 1343 patients (all with American Joint Committee on Cancer (AJCC) stage IIB, IIC, or III cutaneous melanoma) compared postoperative adjuvant therapy with bevacizumab or surveillance and found, at a median follow-up of 6.4 years, that although bevacizumab was associated with improvement in 5-year disease-free interval, there was no difference in overall survival or distant metastasis-free interval between the groups; the authors concluded that bevacizumab could not be recommended as standard adjuvant therapy in patients at high risk of disease recurrence.(27) **(EG 1)** A randomized phase II study of 214 previously untreated patients with advanced disease reported that the addition of bevacizumab to carboplatin plus paclitaxel did not meet the primary study objective of a statistically significant improvement in progression-free survival.(28) **(EG 1)**

For neovascular glaucoma, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis and systematic review studying the subconjunctival use of ranibizumab or bevacizumab to inhibit scar formation after trabeculectomy for glaucoma found 5 randomized controlled trials involving 177 eyes; however, the studies were heterogeneous and of low quality, and the authors stated that the evidence was insufficient to refute or support the use of ranibizumab or bevacizumab for this indication.(29) **(EG 1)** A systematic review evaluating intravitreal anti-vascular endothelial growth factors for treatment of neovascular glaucoma (including 2 studies of bevacizumab) found inconsistent effects on post-treatment intraocular pressure and visual acuity; further studies were recommended.(30) **(EG 1)**

For neuroendocrine tumors, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A consensus guideline and a systematic review found evidence that bevacizumab may be associated with improved response and progression-free survival, but the authors indicated that larger studies are necessary and that bevacizumab should not be used for this indication outside of a clinical trial.(31)(32) **(EG 2)** A single-arm open-label phase II study of 54 patients with advanced, recurrent, or metastatic extrapancreatic neuroendocrine tumors treated with the combination of bevacizumab and temsirolimus found, at a median follow-up of 17.1 months, an objective response rate of 2%, a 6-month progression-free survival rate of 48%, and that 54% of patients discontinued treatment due to adverse events.(33) **(EG 1)**

For non-small cell lung cancer, adjuvant therapy for early-stage disease, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** An open-label, multicenter, randomized, phase III trial of 1501 patients with resected stage IB to IIIA non-small cell lung cancer found, at 50.3-month follow-up, that the addition of bevacizumab to 4 cycles of adjuvant cisplatin-based chemotherapy did not improve overall survival compared with chemotherapy alone and resulted in more reported high-grade toxicities. The authors concluded that bevacizumab should not be used in this setting. (34) **(EG 1)** An expert consensus guideline does not include bevacizumab as a recommended treatment option for adjuvant treatment of early disease.(35) **(EG 2)**

For pancreatic cancer, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of randomized controlled studies found that bevacizumab was associated with moderate improvement in overall response rate in patients with advanced pancreatic cancer but not in progression-free survival or overall survival.(36) **(EG 1)** A systematic review and network meta-analysis of various chemotherapy combinations for pancreatic cancer could not find significant incremental improvement from the addition of bevacizumab to any regimen.(37) **(EG 1)**

For proliferative diabetic retinopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis evaluating the efficacy of anti-vascular endothelial growth factors for the treatment of proliferative diabetic retinopathy included 12 randomized trials of bevacizumab and found that the addition of bevacizumab to panretinal photocoagulation did not result in a clinically meaningful improvement in visual

acuity.(38) **(EG 1)** A review article states that there is a lack of evidence to support the long-term efficacy of anti-vascular endothelial growth factors, including bevacizumab, for treatment of proliferative diabetic retinopathy and that further studies are needed.(39) **(EG 2)**

For pterygia, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of 18 randomized controlled trials (1045 eyes) evaluating the efficacy of bevacizumab for the treatment of pterygia found that treatment with bevacizumab was associated with reduced recurrence rates, especially in patients with a primary pterygium or those who received a conjunctival autograft. However, the authors noted that significant heterogeneity among the included studies limited the results, including different administration routes of the medication, different types of pterygia, and variable follow-up; the authors recommended further long-term studies.(40) **(EG 1)**

For radiation retinopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A retrospective cohort study of patients with ciliary body or choroidal melanoma treated with plaque radiotherapy compared outcomes in patients who received postradiation bevacizumab (1131 patients) with those who did not receive bevacizumab (117 patients) and found, at up to 48-month follow-up, that bevacizumab was associated with better median logMAR (Snellen equivalent) visual acuity compared with those who did not receive bevacizumab. However, the authors noted that the lack of a randomized control group limited the results, and further studies were recommended.(41) **(EG 2)** A retrospective case series of 78 patients with radiation maculopathy compared intravitreal bevacizumab, triamcinolone, and dexamethasone implant and found no difference between the groups in central foveal thickness or visual improvement. The authors recommended further prospective randomized studies.(42) **(EG 2)** A retrospective review of 120 patients with radiation retinopathy treated with intravitreal bevacizumab or ranibizumab found, at a mean treatment interval of 38 months, that 80% of patients who received 3 or more injections remained within 2 lines of their initial visual acuity or better, with few acute or long-term side effects noted. However, due to the uncontrolled nature of the review, the authors noted that outcome assessments were limited.(43) **(EG 2)** A retrospective study of 418 patients compared intravitreal bevacizumab with no injection for prevention of macular edema and found, at 2-year follow-up, that bevacizumab was associated with less macular edema, vision loss, and poor visual acuity compared with no intervention; further controlled prospective studies were recommended.(44) **(EG 2)**

For retinal angiomatous proliferation, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized study assigned 50 patients with early or moderate disease to either intravitreal bevacizumab or ranibizumab; each group demonstrated comparable significant improvement after 1 year. However, there was no untreated control group, and the authors indicated that large randomized studies are needed.(45) **(EG 1)**

For retinopathy of prematurity, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** Meta-analyses and systematic reviews have found that the vast majority of published studies on the use of vascular endothelial growth factor inhibitors for retinopathy of prematurity consist of case series, retrospective cohort studies, and nonrandomized studies that show possible benefit; however, the authors stress that high-quality studies are needed to better assess and confirm appropriate dosing, timing, and longer-term adverse effects.(46)(47) **(EG 1)**

For vitreal hemorrhage prophylaxis after vitrectomy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 12 randomized controlled trials (654 eyes) found evidence to support the preoperative use of intravitreal bevacizumab to prevent the incidence of early (within 4 weeks), but not late (1 to 6 months), postoperative vitreal cavity hemorrhage.(48) **(EG 1)** For proliferative diabetic retinopathy treated with vitrectomy, a randomized controlled trial of 107 eyes in 91 patients reported that best-corrected visual acuity was no different between the control group and the groups treated with either preoperative or intraoperative intravitreal bevacizumab.(49) **(EG 1)** However, a subsequent randomized study of 156 patients undergoing pars plana vitrectomy for proliferative diabetic retinopathy suggested that those receiving bevacizumab 5 to 10 days preoperatively may fare better than those receiving it 1 to 3 days preoperatively in terms of visual acuity and postoperative complications. The authors recommended further studies to evaluate potential dosing and timing in relation to clinical outcomes in this population.(50) **(EG 1)** Meta-analyses have found that, while adjuvant intravitreal bevacizumab appeared to diminish intraoperative complications and early postoperative hemorrhage, additional studies are necessary to determine optimal doses and intervals for injection.(51)(52)(53) **(EG 1)**

## Rationale

Use of this MCG care guideline helps the clinician determine if a particular treatment, medication, or service might be appropriate for a specific patient, taking into account their unique health complexities.

Use of these evidence-based clinical criteria to support decision making benefits the patient by identifying patient-specific complex clinical factors and conditions, promoting personalized treatment. Utilizing evidence-based clinical criteria promotes patient safety by helping ensure that potential patient benefits outweigh the risks. In addition, the use of evidence-based guidelines can increase consistency in treatment thresholds, leading to less variation in care and promoting equitable treatment among patients.

## Related CMS Coverage Guidance

This guideline supplements but does not replace, modify, or supersede existing Medicare regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs).

**Code of Federal Regulations (CFR):** 42 CFR 419.22(199); 42 CFR 422.101(200)

**Internet-Only Manual (IOM) Citations:** CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(201); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(202); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(203)

**Medicare Coverage Determinations:** Medicare Coverage Database(204)

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## Footnotes

[A] Ocular histoplasmosis is a fungal infection of the chorioretinal region that is thought to be caused by *Histoplasma capsulatum*. The clinical diagnosis is defined as the absence of anterior or vitreous segment inflammation and 2 out of 3 of the following: multifocal chorioretinal scarring of the macular and midperiphery, chorioretinal peripapillary atrophy, or choroidal neovascularization.(96) [ A in Context Link 1 ]

[B] Salvage therapy may include treatment of symptoms due to radiation therapy necrosis, vasogenic edema, or mass effect.(145) [ B in Context Link 1 ]

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## Codes

**HCPCS: C9257, J9035, Q5129**

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