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PHARMACY / MEDICAL POLICY – 5.01.650

Bispecific Antibodies

Effective Date:	May 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 8, 2025	N/A
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

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Introduction

Bispecific antibody drugs are a type of immunotherapy. Immunotherapy drugs work with the immune system and make it stronger. These drugs help the cells in the immune system find and kill cancer cells more effectively. This policy describes when certain bispecific antibody 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

Drug	Medical Necessity
Bizengri (zenocutuzumab-zbco) IV	**Bizengri (zenocutuzumab-zbco) may be considered medically necessary for the treatment of adults when all the following are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity
	• Has been diagnosed with advanced, unresectable, or metastatic pancreatic adenocarcinoma **OR** • Has been diagnosed with advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) **AND** • Is harboring a neuregulin 1 (*NRG1*) gene fusion **AND** • Bizengri (zenocutuzumab-zbco) will be administered as monotherapy **AND** • Has an Eastern Cooperate Oncology Group (ECOG) performance status of 0 or 1 **AND** • Has experienced disease progression on or after prior systemic therapy **AND** • Dose is limited to 750 mg every 2 weeks

Blincyto (blinatumomab) IV	**Blincyto (blinatumomab) may be considered medically necessary for the treatment of individuals when all the following are met:**
	• The individual is aged one month or older
	AND
	• Meets one of the following:
	  ○ CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
	  OR
	  ○ Relapsed or refractory CD-19-positive B-cell precursor ALL
	  OR
	  ○ CD19-positive Philadelphia chromosome-negative B-cell precursor ALL in the consolidation phase of multiphase chemotherapy
	  OR
	  ○ Standard or high-risk B-cell ALL in individuals aged less than 18 years

Drug	Medical Necessity
Columvi (glofitamab-gxbm) IV	**Columvi (glofitamab-gxbm) may be considered medically necessary for the treatment of relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma when all the following criteria are met:** • The individual is aged 18 years and older **AND** • Two or more lines of systemic therapy have been tried and failed **AND** • Documentation of pretreatment with a single 1,000mg dose of obinutuzumab intravenously 7 days before initiation of Columvi
Elrexfio (elranatamab-bcmm) SC	**Elrexfio (elranatamab-bcmm) may be considered medically necessary for the treatment of relapsed or refractory multiple myeloma when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has received at least four prior therapies including a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib), an immunomodulatory agent (e.g., lenalidomide, pomalidomide, thalidomide), and an anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab-irfc)
Epkinly (epcoritamab-bysp) SC	**Epkinly (epcoritamab-bysp) may be considered medically necessary for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) when all the following criteria are met:** • The individual is aged 18 years and older **AND** • Has relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy **Epkinly (epcoritamab-bysp) may be considered medically necessary for the treatment of relapsed and refractory follicular lymphoma (FL) when all the following criteria are met:**

Drug	Medical Necessity
	• The individual is aged 18 years and older **AND** • Two or more lines of systemic therapy have been tried and failed
Imdelltra (tarlatamab-dlle) IV	**Imdelltra (tarlatamab-dlle) may be considered medically necessary for the treatment of adults with extensive stage small cell lung cancer (ES-SCLC) when all the following are met:** • The individual is aged 18 years or older **AND** • Has relapsed or refractory ES-SCLC **AND** • Has had progression on or after treatment with platinum-based chemotherapy (e.g., cisplatin and carboplatin) **AND** • Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 **AND** • Imdelltra (tarlatamab-dlle) is prescribed by or in consultation with an oncologist
Lunsumio (mosunetuzumab-axgb) IV	**Lunsumio (mosunetuzumab-axgb) may be considered medically necessary for the treatment of relapsed or refractory follicular lymphoma (FL) when all the following criteria are met:** • The individual is aged 18 years and older **AND** • Had an inadequate response or intolerance to two or more lines of systemic therapy
Rybrevant (amivantamab-vmjw) IV	**Rybrevant (amivantamab-vmjw) may be considered medically necessary for non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations **AND**

Drug	Medical Necessity

	• Meets one of the following:
	  ○ Disease has progressed on or after platinum-based (eg, cisplatin, carboplatin, oxaliplatin) chemotherapy
	  ○ Rybrevant (amivantamab-vmjw) will be first-line treatment used in combination with carboplatin and pemetrexed
	AND
	• The maintenance dose is limited to 1,400 mg every 2 weeks if given as a single agent OR 2,100 mg every 3 weeks if given in combination with chemotherapy
	
	Rybrevant (amivantamab-vmjw) may be considered medically necessary for non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations when all the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Has been diagnosed with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations
	AND
	• Meets one of the following:
	  ○ Disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor and Rybrevant (amivantamab-vmjw) will be used in combination with carboplatin and pemetrexed
	  ○ Rybrevant (amivantamab-vmjw) will be used as first-line treatment in combination with Lazcluze (lazertinib)
	AND
	• The maintenance dose is limited to 1,400 mg every 2 weeks if given in combination with Lazcluze (lazertinib) OR 2,100 mg every 3 weeks if given in combination with chemotherapy

Talvey (talquetamab-tgvs) SC	**Talvey (talquetamab-tgvs) may be considered medically necessary for the treatment of relapsed or refractory multiple myeloma when all the following criteria are met:** • The individual is aged 18 years or older

Drug	Medical Necessity
	AND • Has received at least four prior therapies including a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib), an immunomodulatory agent (e.g., lenalidomide, pomalidomide, thalidomide), and an anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab-irfc)
Tecvayli (teclistamab-cqyv) SC	**Tecvayli (teclistamab-cqyv) may be considered medically necessary for the treatment of adult individuals with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib), an immunomodulatory agent (e.g., lenalidomide, pomalidomide, thalidomide), and an anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab-irfc).**
Ziihera (zanidatamab-hrii) IV	**Ziihera (zanidatamab-hrii) may be considered medically necessary for the treatment of adults with biliary tract cancer (BTC) when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with unresectable or metastatic HER2-positive (IHC 3+) BTC **AND** • Has been previously treated **AND** • Ziihera (zanidatamab-hrii) will be administered as monotherapy **AND** • Has an Eastern Cooperate Oncology Group (ECOG) performance status of 0 or 1 **AND** • Ziihera (zanidatamab-hrii) is prescribed by or in consultation with an oncologist **AND** • Dose is limited to 20 mg/kg every 2 weeks

Drug	Investigational
As listed	**Use of Rybrevant (amivantamab-vmjw) to treat other types of solid tumors and hematological malignancies not listed above is considered investigational.** **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	**Non-formulary exception reviews for all the drugs listed in the policy may be approved up to 12 months.** **All other reviews for all drugs listed in the policy may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in the policy 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	
J1323	Injection, elranatamab-bcmm (Elrexfio), 1 mg
J3055	Injection, talquetamab-tgvs (Talvey), 0.25 mg
J9026	Injection, tarlatamab-dlle (Imdelltra), 1 mg (new code effective 01/01/25)
J9039	Injection, blinatumomab (Blincyto), 1 mcg
J9061	Injection, amivantamab-vmjw, (Rybrevant) 2 mg
J9286	Injection, glofitamab-gxbm (Columvi), 2.5 mg
J9321	Injection, epcoritamab-bysp (Epkinly), 0.16 mg
J9350	Injection, mosunetuzumab-axgb (Lunsumio), 1 mg
J9380	Injection, teclistamab-cqyv (Tecvayli), 0.5 mg
J9999	Not otherwise classified, antineoplastic drugs (use to report: Bizengri, Ziihera)

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

Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

Benefit Application

The drugs in this policy are managed through the medical benefit.

Evidence Review

Bizengri (zenocutuzumab-zbco)

Bizengri's approval is supported by results from the Phase 1/2 eNRGy trial (NCT02912949), a multicenter, open-label study that included 64 individuals with NRG1+ non-small cell lung cancer (NSCLC) and 30 individuals with NRG1+ PDAC. All study participants had disease progression following standard-of-care (SOC) treatment. Trial results demonstrated a 33% overall response rate (ORR) in individuals with NSCLC and 40% in individuals with pancreatic adenocarcinoma (PDAC), with a median duration of response (DOR) of 7.4 months in NSCLC and a range of 3.7 to 16.6 months in PDAC. In the pooled safety population, the most common adverse reactions (ARs) (≥10%) were diarrhea, musculoskeletal pain, fatigue, nausea, infusion-related reactions, dyspnea, rash, constipation, vomiting, abdominal pain, and edema. The most common Grade 3 or 4 laboratory abnormalities (≥10%) were increased gamma-glutamyl transferase, decreased hemoglobin, decreased sodium, and decreased platelets. The prescribing information includes a Boxed Warning for embryo-fetal toxicity.

Columvi (glofitamab-gxbm)

The efficacy of Columvi (glofitamab-gxbm) was evaluated in an open-label, multicenter, multicohort, single-arm clinical trial which included 132 individuals with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The inclusion criteria required individuals to have ECOG performance status of 0 or 1, absolute neutrophil count greater than or equal to 1500/µL, platelet count greater than or equal to 75,000 /µL independent of transfusion, serum creatinine less than or equal to 1.5 x ULN or CLcr greater than or equal to 50 ml/min, hepatic transaminases less than or equal to 3 x ULN. The individuals required to have pretreatment with Obinutuzumab on Cycle 1 Day 1.

The primary efficacy endpoint was objective response rate (ORR) and duration of response (DOR). The overall response rate was 56% for the Columvi group, where 43% individuals had complete response and 13% individuals had partial response. Out of 74 individuals with overall response, median duration of response was 18.4 months.

The most common adverse effects included cytokine release syndrome, musculoskeletal pain, rash and fatigue. The most common Grade 3 to 4 laboratory abnormalities are reduced lymphocyte counts, reduced phosphate level, reduced neutrophil count, increased uric acid and reduced fibrinogen. Treatment related adverse events which led to permanent discontinuation in the Columvi group included infection, delirium, neutropenia, and CRS. Also, adverse events which led to dose interruption included neutropenia and thrombocytopenia.

Elrexfio (elranatamab-bcmm)

Elrexfio is an antibody that binds bispecific B-cell maturation antigen (BCMA) on plasma cells, plasmablasts, multiple myeloma (MM) cells, and CD3 on T-cells leading to proinflammatory cytokine release and eventually cytolysis of the BCMA-expressing cells.

The efficacy of Elrexfio monotherapy was evaluated in an open-label, single-arm, multi-center study (MagnetisMM-3) with 123 individuals receiving Elrexfio once weekly post initial titration. After 24 weeks, individuals who achieved an IMWG response category of partial response or better for a duration of at least 2 months changed dosing interval from weekly to biweekly. The objective response rate, calculated as a total of stringent complete response, complete response, very good partial response, and partial response, was achieved in 57.7% (47.3-67.7%) of BCMA-directed therapy naïve individuals and 33.3% (22-46.3%) of individuals who had previously tried BCMA-directed therapy.

Serious adverse reactions occurred in 68% of individuals receiving Elrexfio, with those occurring in at least 2% of individuals being pneumonia (25%), sepsis (13%), cytokine release syndrome (CRS) (13%), upper respiratory tract infection (URTI) (4.4%), acute kidney injury (3.8%), urinary tract infection (3.3%), COVID-19 (3.3%), encephalopathy (3.3%), pyrexia (2.2%), and febrile neutropenia (2.2%). Fatal adverse reactions occurred in 10% of individuals, including pneumonia, sepsis, acute respiratory distress syndrome, cardio-respiratory arrest, cardiogenic shock, cardiopulmonary failure, COVID-19, failure to thrive, and pulmonary embolism. Permanent discontinuation of Elrexfio due to adverse reactions occurred in 17% of individuals and dosage interruptions due to adverse reactions occurred in 73% of individuals. The most common adverse events (at least 20%) were CRS, fatigue, injection site reaction, diarrhea, URTI, musculoskeletal pain, pneumonia, decreased appetite, rash, cough, nausea, and pyrexia. The most common Grade 3 to 4 laboratory abnormalities (at least 30%) were decreases in lymphocyte, neutrophil, hemoglobin, white blood cell, and platelet counts.

Epkinly (epcoritamab-bysp)

The Phase 1/2 EPCORE NHL-1/Study GCT3013-01 (NCT03625037) trial was an open-label, multicohort, multicenter, single-arm study involving individuals with relapsed or refractory (R/R) B-cell lymphoma. The efficacy population included 148 individuals with DLBCL, not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma. The study excluded individuals with central nervous system (CNS) involvement of

lymphoma, allogeneic hematopoietic stem cell transplant (HSCT) or solid organ transplant, or ongoing active infection, and any individuals with known impaired T-cell immunity. Individuals received Epkinly subcutaneously (SC) with Cycle 1 step-up dosing consisting of a 0.16 mg priming dose once on Day 1, followed by an 0.8 mg intermediate dose once on Day 8, and subsequent full 48 mg doses once on Day 15 and Day 22. Cycles were every 28 days. On Cycles 2 and 3, individuals received 48 mg on Days 1, 8, 15, and 22. On Cycles 4–9, individuals received 48 mg on Days 1 and 15. From Cycle 10 and beyond, individuals received 48 mg once every 28 days. Individuals continued to receive Epkinly until disease progression or unacceptable toxicity. In the setting of a suspected tumor flare reaction, continued treatment was permitted. The primary efficacy measure of the study was the overall response rate (ORR) assessed according to the Lugano 2014 criteria by an independent review committee. The ORR was determined to be 61% (95% CI: 53, 69), with 38% of individuals achieving complete responses. Among responders, with a median follow-up of 9.8 months, the estimated median duration of response (DOR) was 15.6 months (95% confidence interval [CI]: 9.7, not reached). The median time to response was 1.4 months (range: 1.0 to 8.4 months). Among responders, the median follow-up for DOR was 9.8 months (range: 0.0 to 17.3 months). The prescribing information has a Boxed Warning for serious or life-threatening cytokine release syndrome (CRS) and life-threatening or fatal immune effector cell-associated neurotoxicity syndrome (ICANS). Warnings and precautions include infections and cytopenias. In the full EPCORE NHL-1 clinical trial involving 157 individuals with R/R large B-cell lymphoma who received Epkinly at the recommended dose, CRS occurred in 51% of individuals, ICANS in 6%, and serious infections in 15%. It is emphasized that Epkinly should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and ICANS. Due to the risk of these reactions, individuals should be hospitalized for 24 hours following the Cycle 1, Day 15 dosage of 48 mg. The most frequently reported adverse reactions associated with Epkinly include CRS, fatigue, musculoskeletal pain, injection site reactions, fever, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities observed were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Imdelltra (tarlatamab-dlle)

The accelerated approval was based on overall response rate (ORR) and duration of response (DOR) observed in the Phase 2 DeLLphi-301 trial, which evaluated Imdelltra in individuals with small cell lung cancer (SCLC) who had failed two or more prior lines of treatment, and who had received the 10 mg every-2-weeks (Q2W) dosing regimen. Results from the DeLLphi-301 trial demonstrated an ORR of 40% and a median DOR of 9.7 months. The median overall survival

(OS) was 14.3 months. The prescribing information for Imdelltra includes a Boxed Warning regarding cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell–associated neurotoxicity syndrome (ICANS). Accordingly, the approved dosage of Imdelltra is based on a step-up dosing schedule to reduce the incidence of CRS.

Lunsumio (mosunetuzumab-axgb)

Lunsumio (mosunetuzumab-axgb) is a T-cell engaging bispecific antibody that binds to the CD3 receptor expressed on the surface of T-cells and CD20 expressed on the surface of lymphoma cells and some healthy B-lineage cells. In vitro, mosunetuzumab-axgb activated T-cells, caused the release of proinflammatory cytokines, and induced lysis of B-cells.

The efficacy of Lunsumio (mosunetuzumab-axgb) was evaluated in an open-label, multicenter, multi-cohort study (GO29781, NCT02500407) in individuals with relapsed or refractory follicular lymphoma (FL) who had received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The study excluded individuals with active infections, history of autoimmune disease, prior allogeneic transplant, or any history of CNS lymphoma or CNS disorders.

Individuals received step-up doses of 1 mg on Cycle 1 Day 1 and 2 mg on Cycle 1 Day 8, followed by 60 mg on Cycle 1 Day 15, and 60 mg on Cycle 2 Day 1, then 30 mg every 3 weeks in subsequent cycles. A treatment cycle was 21 days. Lunsumio was administered for 8 cycles unless individuals experienced progressive disease or unacceptable toxicity. After 8 cycles, individuals with a complete response discontinued therapy; individuals with a partial response or stable disease continued treatment up to 17 cycles, unless individuals experienced progressive disease or unacceptable toxicity.

Among the 90 individuals with relapsed or refractory FL, the median age was 60 years (range: 29 to 90 years), 33% were 65 years of age or older, 61% were male, 82% were White, 9% were Asian, 4% were Black or African American, and 8% were Hispanic or Latino. A total of 77% of individuals had Stage III-IV disease, 34% had bulky disease, and all individuals had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies, and 31% receiving more than 3 prior therapies.

Seventy-nine percent of individuals were refractory to prior anti-CD20 monoclonal antibody therapy, 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 9% received prior rituximab plus lenalidomide therapy, 21% received prior autologous stem cell

transplant, and 3% received prior CAR T therapy. Fifty-two percent of individuals had progression of disease within 24 months of first systemic therapy.

Efficacy was established on the basis of objective response rate (ORR) and duration of response (DOR) as assessed by an independent review facility according to standard criteria for NHL (Cheson 2007). The median follow-up for DOR was 14.9 months. The ORR was achieved in 80% (95% CI: 70%, 88%) of individuals and the median DOR was 22.8 months (95% CI: 10 months, not reached).

Rybrevant (amivantamab-vmjw)

Rybrevant (amivantamab-vmjw) is a bispecific antibody that binds to the extracellular domains of EGFR and MET. In in vitro and in vivo studies amivantamab-vmjw was able to disrupt EGFR and MET signaling functions through blocking ligand binding and, in exon 20 insertion mutation models, degradation of EGFR and MET. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

The efficacy of Rybrevant was evaluated in individuals with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in a multicenter, open-label, multi-cohort clinical trial (CHRYSALIS, NCT02609776). The study included individuals with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Individuals with untreated brain metastases and individuals with a history of interstitial lung disease requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study.

In the efficacy population, EGFR exon 20 insertion mutation status was determined by prospective local testing using tissue (94%) and/or plasma (6%) samples. Of the 81 individuals with EGFR exon 20 insertion mutations, plasma samples from 96% of individuals were tested retrospectively using Guardant360 CDx. While 76% of individuals had an EGFR exon 20 insertion mutation identified in plasma specimen, 20% did not have an EGFR exon 20 insertion mutation identified in plasma specimen, and 3.7% did not have plasma samples for testing. The overall response rate was 40% with 3.7% of participants having a complete response and 36% of participants with a partial response.

The efficacy of Rybrevant in combination with carboplatin and pemetrexed was evaluated in individuals with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858 that progressed after receiving treatment with Tagrisso (osimertinib) in a randomized,

open-label, multicenter trial (MARIPOSA-1). Individuals with asymptomatic or previously treated and stable intracranial metastases were eligible to enroll. A total of 394 individuals were randomized between the two arms, 131 to the Rybrevant in combination with carboplatin and pemetrexed arm and 263 to the carboplatin and pemetrexed arm.

In the efficacy population, 45% had history of brain metastasis, and 99.7% had Stage IV cancer at study enrollment. The trial demonstrated a statistically significant improvement in PFS for Rybrevant in combination with carboplatin and pemetrexed compared to carboplatin and pemetrexed. HR (95% CI); p-value: 0.48 (036,0.64); p<0.0001.

The efficacy of Rybrevant in combination with Lazcluze (lazertinib) was evaluated in individuals with untreated locally advanced or metastatic NSCLC with either exon 19 deletions or exon 21 L858R substitution EGFR mutations was evaluated in a multicenter, randomized, active-controlled trial (MARIPOSA-2). The study also included individuals with asymptomatic or previously treated and stable intracranial metastases. A total of 858 individuals were randomized between the two study arms, 429 to the Rybrevant in combination with Lazertinib and 429 to the Osimertinib monotherapy arm.

In the efficacy population, 60% of individuals had tumors harboring exon 19 deletions and the remaining 40% had exon 21 L858R substitution mutations, 41% had prior brain metastases; and 89% had Stage IV cancer at initial diagnosis. The trial demonstrated a statistically significant improvement in progression-free survival (PFS) for Rybrevant in combination with lazertinib compared to Osimertinib. HR (95% CI); p-value: 0.70 (0.58, 0.85); p=0.0002.

Talvey (talquetamab-tgvs)

Talvey binds to the CD3 receptor expressed on the surface of T-cells and G protein-coupled receptor class C group 5 member D (GPRC5D) expressed on the surface of multiple myeloma (MM) cells and non-malignant plasma cells, causing the release of proinflammatory cytokines that leads to the lysis of multiple myeloma cells.

The efficacy of Talvey monotherapy was evaluated in an open-label, single-arm, multicenter study (MonumenTAL-1) with 100 individuals receiving Talvey weekly (0.4 mg/kg) and 87 individuals receiving Talvey biweekly (0.8 mg/kg) until disease progression or unacceptable toxicity. Overall response rate, calculated as a total of stringent complete response, complete response, very good partial response, and partial response, was observed in 73% (63.2-81.4%) of the weekly dosing group and 73.6% (63-82.4%) of the biweekly dosing group. The duration of exposure for each group was 5.9 months and 3.7 months, accordingly.

Serious adverse reactions were reported in 47% of individuals who received Talvey, with those occurring in at least 2% of individuals being cytokine release syndrome (CRS) (13%), bacterial infection (8%), pyrexia (4.7%), immune effector cell-associated neurotoxicity syndrome (ICAN) (3.8%), COVID-19 (2.7%), neutropenia (2.1%), and upper respiratory tract infection (URTI) (2.1%). Fatal adverse reactions occurred in 3.2% of individuals, including COVID-19, dyspnea, general health deterioration, bacterial infection, basilar artery occlusion, fungal infection, infection, and pulmonary embolism. Permanent discontinuation of Talvey occurred in 9% of individuals and dosage interruptions due to adverse reactions occurred in 56% of individuals. Most common adverse reactions (> 20%) were pyrexia, CRS, dysgeusia, nail disorder, musculoskeletal pain, skin disorder, rash, fatigue, weight loss, dry mouth, xerosis, dysphagia, URTI, diarrhea, hypotension, and headache. The most common Grade 3 or 4 laboratory abnormalities (at least 30%) were decreases in lymphocyte, neutrophil, white blood cell, and hemoglobin counts.

Ziihera (zanidatamab-hrii)

The FDA approval of Ziihera is based on results from the Phase 2b HERIZON-BTC-01 (NCT04466891) trial, which evaluated the drug as a single agent in previously treated, HER2-positive BTC (as determined by Roche Diagnostics' PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody companion diagnostic). The trial achieved its primary endpoint of confirmed ORR (cORR) by independent central review (ICR). Individuals with HER2-amplified, locally advanced unresectable or metastatic BTC (including GBC, ICC, and ECC) were enrolled and assigned into cohorts based on tumor IHC score by central assessment: Cohort 1 included individuals who were IHC 2+ or 3+ (HER2 positive) and Cohort 2 included individuals who were IHC 0 or 1+ (HER2 negative and HER2 low, respectively). The trial evaluated Ziihera at a dose of 20 mg/kg, administered intravenously every 2 weeks in individuals who had received at least one prior gemcitabine-based systemic chemotherapy regimen and had adequate cardiac function (defined as left ventricular ejection fraction [LVEF] ≥50%). No responses were observed in Cohort 2 (IHC 0 or 1+), while significant clinical benefit was demonstrated in Cohort 1. Among the 62 individuals evaluated with HER2-positive (IHC 3+) BTC, Ziihera demonstrated an ORR of 52% (95% CI: 39, 65) with an estimated median DOR of 14.9 months (95% CI: 7.4−not estimable) by ICR. The safety profile of Ziihera was evaluated in 80 individuals in the HERIZON-BTC-01 trial. Serious adverse reactions (SARs) occurred in 53% of individuals who received Ziihera. The most common adverse reactions (ARs) in individuals who received Ziihera (≥20%) were diarrhea, infusion-related reaction (IRR), abdominal pain, and fatigue. SARs in >2% of individuals included biliary obstruction (15%), biliary tract infection (8%), sepsis (8%), pneumonia (5%), diarrhea (3.8%), gastric obstruction (3.8%), and fatigue (2.5%). A fatal adverse reaction of hepatic failure

occurred in one individual who received Ziihera. Permanent discontinuation due to an adverse reaction occurred in 2.5% of patients who received Ziihera.

References

1. Rybrevant (amivantamab-vmjw) [package insert]. Horsham, PA: Janssen Biotech, Inc; Revised September 2024.
2. Columvi (glofitamab-gxbm). Prescribing Information. South San Francisco, CA; Genentech, Inc. Revised June 2023.
3. Epkinly (epcoritamab-bysp). Prescribing Information. Plainsboro, NJ; Genmab US, Inc. Revised August 2024.
4. Lunsumio (mosunetuzumab-axgb). Prescribing Information. South San Francisco, CA. Genentech, Inc. Revised November 2024.
5. Blincyto (blinatumomab) [prescribing information]. Thousand Oaks, CA; Amgen Inc. Revised December 2024.
6. Elrexfio (elranatamab-bcmm) [prescribing information]. New York, NY; Pfizer Inc. Revised August 2023.
7. Imdelltra (tarlatamab-dlle) [prescribing information]. Thousand Oaks, CA; Amgen, Inc. Revised May 2024.
8. Epkinly (epcoritamab-bysp). [prescribing information]. Plainsboro, NJ; Genmab US, Inc. Revised August 2024.
9. Talvey (talquetamab-tgvs) [prescribing information]. Horsham, PA; Janssen Biotech. Revised August 2023.
10. Tecvayli (teclistamab-cqyv) [prescribing information]. Horsham, PA; Janssen Biotech, Inc. Revised November 2024.
11. Bizengri (zenocutuzumab-zbco) [prescribing information]. Lexington, MA; Partner Therapeutics, Inc. Revised March 2025.
12. Ziihera (zanidatamab-hrii) [prescribing information]. Palo Alto, CA; Jazz Pharmaceuticals, Inc. Revised November 2024.

History

Date	Comments
05/01/25	New policy, approved April 8, 2025. Moved Rybrevant (amivantamab-vmjw) from policy 5.01.603 Epidermal Growth Factor Receptor (EGFR) Inhibitors to policy 5.01.650 Bispecific Antibodies. Moved Columvi (glofitamab-gxbm), Epkinly (epcoritamab-bysp), Lunsumio (mosunetuzumab-axgb) from policy 2.03.502 Monoclonal Antibodies for the Treatment of Lymphoma to policy 5.01.650 Bispecific Antibodies. Moved Blincyto (blinatumomab), Elrexfio (elranatamab-bcmm), Imdelltra (tarlatamab-dlle), Talvey (talquetamab-tgvs), and Tecvayli (teclistamab-cqyv) from policy 5.01.540 Miscellaneous Oncology Drugs to policy 5.01.650 Bispecific Antibodies. Added coverage criteria for Bizengri (zenocutuzumab-zbco). Added coverage criteria for Ziihera (zanidatamab-hrii). Updated Blincyto (blinatumomab) coverage criteria to include treatment of standard or high-risk B-cell ALL in pediatric individuals. Added HCPCS codes J1323, J3055, J9026, J9039, J9061, J9286, J9321, J9350, J9380, J9999.

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 and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.