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PHARMACY POLICY – 5.01.534

Multiple Receptor Tyrosine Kinase Inhibitors

Effective Date:	May 1, 2026
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Replaces:	N/A

RELATED MEDICAL POLICIES:

5.01.517	Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Treatment
5.01.518	BCR-ABL Kinase Inhibitors
5.01.544	Prostate Cancer Targeted Therapies
5.01.589	BRAF and MEK Inhibitors
5.01.591	Immune Checkpoint Inhibitors
5.01.603	Epidermal Growth Factor Receptor (EGFR) Inhibitors

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POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

An enzyme is a chemical messenger. Tyrosine kinases are enzymes within cells. They serve as on/off switches for many of the cells' functions. One of their most important roles is to help send signals telling a cell to grow. If there is a genetic change that leaves the switch permanently on, cells grow without stopping and tumors form. Multiple tyrosine kinase inhibitors block the "grow" signal in specific types of tumors. This policy discusses when multiple receptor tyrosine kinase inhibitors 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: Initial approval period for oral drugs listed below will be 3 months. Continued approval beyond the first 3 months will require documentation showing objective response to therapy.

Drug	Medical Necessity
Oral Drugs	

Augtyro (repotrectinib)	**Augtyro (repotrectinib) may be considered medically necessary for the treatment of adult individuals with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC) when ALL the following are met:**
	• The individual is aged 18 years or older
	AND
	• Has been diagnosed with locally advanced or metastatic *ROS1*-positive NSCLC
	AND
	• Dose is limited to 160 mg twice daily
	
	Augtyro (repotrectinib) may be considered medically necessary for the treatment of individuals with solid tumors when ALL the following are met:
	• The individual is aged 12 years or older
	AND
	• Has been diagnosed with a solid tumor that meets ALL of the following:
	  ○ Has a neurotrophic tyrosine receptor kinase (NTRK) gene fusion
	  ○ Is locally advanced or metastatic or surgical resection is likely to result in severe morbidity
	  ○ Has progressed following treatment or has no satisfactory alternative therapy
	AND
	• Dose is limited to 160 mg twice daily

Ayvakit (avapritinib)	**Ayvakit (avapritinib) may be considered medically necessary when ALL the following are met:** • The individual is aged 18 years or older **AND** • Meets one of the following:

Drug	Medical Necessity
Oral Drugs	
	○ Treatment of adult individuals with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations ○ Treatment of adult individuals with advanced systemic mastocytosis (AdvSM). AdvSM includes individuals with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SMAHN), and mast cell leukemia (MCL) ○ Treatment of adult individuals with indolent systemic mastocytosis (ISM)
Cabometyx (cabozantinib)	**Cabometyx (cabozantinib) may be considered medically necessary for the treatment of one of the following:** • Advanced renal cell carcinoma (RCC) in adults • Advanced RCC in adults as a first-line treatment in combination with Opdivo (nivolumab) • Hepatocellular carcinoma (HCC) in adults who have been previously treated with sorafenib • Locally advanced or metastatic differentiated thyroid cancer (DTC) in adult and pediatric individuals aged 12 years and older that has progressed following prior VEGFR-targeted therapy (e.g., Lenvima [lenvatinib], Nexavar [sorafenib], etc.) and who are radioactive iodine-refractory or ineligible • Unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET) in adult and pediatric individuals aged 12 years and older that have been previously treated with everolimus, sunitinib, or Lutathera (lutetium Lu 177 dotatate) • Unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET) in adult and pediatric individuals aged 12 years and older that have been previously treated with everolimus or Lutathera (lutetium Lu 177 dotatate)
Caprelsa (vandetanib)	**Caprelsa (vandetanib) may be considered medically necessary for:**

Drug	Medical Necessity
Oral Drugs	
	• Treatment of individuals with symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancers
Cometriq (cabozantinib)	**Cometriq (cabozantinib) may be considered medically necessary for:** • Treatment of adults with progressive, metastatic medullary thyroid cancer
Fotivda (tivozanib)	**Fotivda (tivozanib) may be considered medically necessary for the treatment of adult individuals with relapsed or refractory advanced renal cell carcinoma (RCC) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has received prior treatment with 2 or more systemic therapies **AND** • Dose is limited to 1.34 mg per day for 21 days on treatment followed by 7 days off treatment for a 28-day cycle **AND** • The quantity is limited to 21 capsules per 28 days
Ibtrozi (taletrectinib)	**Ibtrozi (taletrectinib) may be considered medically necessary for the treatment of adults with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC) when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with locally advanced or metastatic *ROS1*-positive NSCLC **AND** • Dose is limited to 600 mg daily
Inlyta (axitinib)	**Inlyta (axitinib) may be considered medically necessary for the treatment of one of the following:** • First-line treatment of individuals with advanced renal cell carcinoma (RCC) in combination with Bavencio (avelumab) • First-line treatment of individuals with advanced RCC in combination with Keytruda (pembrolizumab)

Drug	Medical Necessity
Oral Drugs	
	• Treatment of advanced RCC after failure of one prior systemic therapy when used as a single agent
Lenvima (lenvatinib)	**Lenvima (lenvatinib) may be considered medically necessary for treatment of one of the following:** • The individuals with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer • First-line treatment of individuals with advanced renal cell carcinoma (RCC) in combination with Keytruda (pembrolizumab) • Has advanced RCC in combination with everolimus, following one prior anti-angiogenic therapy • First-line treatment of individuals with unresectable hepatocellular carcinoma (HCC) • Use in combination with pembrolizumab for the treatment of individuals with advanced endometrial carcinoma who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation

Nexavar (sorafenib)	**Nexavar (sorafenib) may be considered medically necessary when ALL the following are met:**
	• The individual is aged 18 years or older
	AND
	• Meets one of the following:
	  ○ Diagnosed with unresectable hepatocellular carcinoma
	  ○ Diagnosed with advanced renal cell carcinoma
	  ○ Diagnosed with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment
	  ○ Diagnosed with progressing desmoid tumors that require systemic treatment
	AND
	• Has had an inadequate response or intolerance to generic sorafenib

Generic pazopanib	**Generic pazopanib may be considered medically necessary when ALL the following are met:** • The individual is aged 18 years or older

Drug	Medical Necessity
Oral Drugs	

	AND
	• Meets one of the following:
	  ○ Treatment of adult individuals with advanced, relapsed or unresectable renal cell carcinoma (RCC)
	  ○ Treatment of adult individuals with advanced soft tissue sarcoma who have received prior chemotherapy
	
	Note: The efficacy of pazopanib for the treatment of individuals with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated.

Qinlock (ripretinib)	**Qinlock (ripretinib) may be considered medically necessary for the treatment of adult individuals with advanced gastrointestinal stromal tumor (GIST) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has received prior treatment with 3 or more kinase inhibitors, including imatinib **AND** • Dose is limited to 150 mg per day (taken as 150 mg once daily)

Generic sorafenib	**Generic sorafenib may be considered medically necessary when ALL the following are met:**
	• The individual is aged 18 years or older
	AND
	• Meets one of the following:
	  ○ Diagnosed with unresectable hepatocellular carcinoma
	  ○ Diagnosed with advanced renal cell carcinoma
	  ○ Diagnosed with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment
	  ○ Diagnosed with progressing desmoid tumors that require systemic treatment

Stivarga (regorafenib)	**Stivarga (regorafenib) may be considered medically necessary for:**

Drug	Medical Necessity
Oral Drugs	
	• Treatment of individuals with metastatic colorectal cancer who have been previously treated with all of the following: ○ Fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, **AND** if RAS wild type, an anti-EGFR therapy • Treatment of individuals with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib • Treatment of locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) in individuals who have been previously treated with imatinib mesylate and sunitinib malate

Generic sunitinib	**Generic sunitinib may be considered medically necessary when ALL the following are met:**
	• The individual is aged 18 years or older
	AND
	• Meets one of the following:
	  ○ Diagnosed with gastrointestinal stromal tumor (GIST) and has experienced disease progression on or has an intolerance to imatinib mesylate
	  ○ Diagnosed with advanced renal cell carcinoma (RCC)
	  ○ Requires adjuvant treatment with generic sunitinib and is at high risk of recurrent RCC following nephrectomy
	  ○ Diagnosed with progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) with unresectable locally advanced or metastatic disease

Sutent (sunitinib)	**Sutent (sunitinib) may be considered medically necessary when ALL the following are met:**
	• The individual is aged 18 years or older
	AND
	• Meets one of the following:
	  ○ Diagnosed with gastrointestinal stromal tumor (GIST) and has experienced disease progression on or has an intolerance to imatinib mesylate
	  ○ Diagnosed with advanced renal cell carcinoma (RCC)

Drug	Medical Necessity
Oral Drugs	
	○ Requires adjuvant treatment with Sutent (sunitinib) and is at high risk of recurrent RCC following nephrectomy ○ Diagnosed with progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) with unresectable locally advanced or metastatic disease **AND** • Has had an inadequate response or intolerance to generic sunitinib
Tabrecta (capmatinib)	**Tabrecta (capmatinib) may be considered medically necessary for the treatment of adult individuals with metastatic non-small cell lung cancer (NSCLC) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as confirmed by a stand-alone test for MET exon 14 skipping (e.g., NeoGenomics MET Exon 14 Deletion Analysis) or a targeted panel appropriate for individuals with metastatic NSCLC which includes MET exon 14 skipping (e.g., NeoTYPE Lung Tumor Profile) **AND** • Dose is limited to 800 mg per day (taken as 400 mg twice daily)
Tepmetko (tepotinib)	**Tepmetko (tepotinib) may be considered medically necessary for the treatment of adult individuals with metastatic non-small cell lung cancer (NSCLC) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has a mutation that leads to MET exon 14 skipping as confirmed by a stand-alone test for MET exon 14 skipping (e.g., NeoGenomics MET Exon 14 Deletion Analysis) or a targeted panel appropriate for individuals with metastatic NSCLC which includes MET exon 14 skipping (e.g., NeoTYPE Lung Tumor Profile) **AND** • The dose is limited to 450 mg per day **AND**

Drug	Medical Necessity
Oral Drugs	
	• The quantity is limited to 60 tablets per 30 days
Turalio (pexidartinib)	**Turalio (pexidartinib) may be considered medically necessary for the treatment of adult individuals with symptomatic tenosynovial giant cell tumor (TGCT) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Tenosynovial giant cell tumor (TGCT) is associated with severe morbidity or functional limitations **AND** • TGCT is not amenable to improvement with surgery
Vanflyta (quizartinib)	**Vanflyta (quizartinib) may be considered medical necessary for the treatment of adult individuals with newly diagnosed acute myeloid leukemia (AML) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Is newly diagnosed with acute myeloid leukemia (AML) **AND** • Is FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD)-positive as detected by an FDA-approved test **AND** • Vanflyta (quizartinib) will be used in combination with cytarabine and anthracycline induction and cytarabine consolidation

Votrient (pazopanib)	**Votrient (pazopanib) may be considered medically necessary when ALL the following are met:**
	• The individual is aged 18 years or older
	AND
	• Meets one of the following:
	  ○ Treatment of adult individuals with advanced, relapsed or unresectable renal cell carcinoma (RCC)
	  ○ Treatment of adult individuals with advanced soft tissue sarcoma who have received prior chemotherapy
	AND

Drug	Medical Necessity
Oral Drugs	
	• Has had an inadequate response or intolerance to generic pazopanib **Note:** The efficacy of Votrient for the treatment of individuals with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated.
Xospata (gilteritinib)	**Xospata (gilteritinib) may be considered medically necessary for the treatment of adult individuals with relapsed or refractory acute myeloid leukemia (AML) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has relapsed or refractory acute myeloid leukemia (AML) **AND** • Has an FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test **Note:** The LeukoStrat CDx FLT3 Mutation Assay is the FDA-approved test.

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	**Non-formulary exception reviews for all drugs listed in this policy may be approved up to 12 months.** **All other reviews for all drugs listed in this policy may be approved up to 6 months.**

Length of Approval	
Approval	**Criteria**
Reauthorization	**Non-formulary exception reviews and all other reviews for all drugs listed in this 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

Child-Pugh Score

Child Pugh Score is a scoring system used to measure the severity of chronic liver disease (including cirrhosis). The purpose of this scoring system is to allow clinicians to objectively describe liver function.

The score is composed of the following components:

- Total bilirubin (mg/dL):
  - <34: 1 point
  - 34 to 50: 2 points
  - >50: 3 points
- Serum albumin (g/L):
  - >35: 1 point
  - 28 to 35: 2 points
  - <28: 3 points
- INR:
  - <1.7: 1 point
  - 1.7 to 2.3: 2 points
  - >2.3: 3 points
- Presence/absence of ascites:
  - None: 1 point
  - Mild: 2 points
  - Moderate to severe: 3 points

Child-Pugh Score

- Presence/absence of hepatic encephalopathy:
  - None: 1 point
  - Grades I to II (or suppressed with medication): 2 points
  - Grades III to IV (or refractory): 3 points
- Then the point scores are added together and classified as follows:
  - Class A: 5 to 6 points (well-compensated disease)
  - Class B: 7 to 9 points (significant functional compromise)
  - Class C: 10 to 15 points (decompensated disease)
- If individual has primary biliary cirrhosis or sclerosing cholangitis, then bilirubin is classified differently:
  - <68: 1 point
  - 68 to 170: 2 points
  - >170: 3 points

Coding

N/A

Related Information

Benefit Application

This policy is managed through the pharmacy benefit.

Evidence Review

Description

Cancer is characterized by the uncontrolled growth and spread of malignant cells. Nearly 1.8 million Americans will be diagnosed with cancer this year, and approximately 613,000 will die of

the disease. As of 2023, the cancer death rate for men and women combined had fallen 14% since 2013.

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 these drugs 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" are the newest therapeutic approach. This category includes the multiple receptor tyrosine kinase inhibitors, or multikinase inhibitors, which are small molecule agents that have been designed to interfere with more than one tyrosine kinase protein. These tyrosine kinases are molecular targets located on the cell membrane that contain extracellular and intracellular binding sites. When the external receptor binds to its specific signaling molecule, a conformational change takes place which activates the intracellular tyrosine kinase binding site. This in turn triggers intracellular signaling pathways when the kinase is activated. The target kinase proteins are preferentially expressed in tumor cells, so the kinase inhibitors inhibit growth of these cells more than the cells found in normal tissues. The promise of these agents is that 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.

The multikinase inhibitors currently available are as follows:

Table 1. Currently Available Multikinase Inhibitors

Drug Name	Targets	FDA-Approved Uses
Avapritinib (Ayvakit)	PDGFRA, PDGFRA D842 mutants, KIT exon 11, 11/17 and 17 mutants	GIST, AdvSM, ISM
Axitinib (Inlyta)	VEGFR 1-3	RCC
Cabozantinib (Cabometyx)	VEGFR 1-3, AXL, FLT3, KIT, MER, RET, ROS1, TIE-2, TRKB, TYRO3	DTC, RCC, HCC, PNET
Cabozantinib (Cometriq)	VEGFR 1-3, AXL, FLT3, KIT, MER, RET, ROS1, TIE-2, TRKB, TYRO3	MTC
Capmatinib (Tabrecta)	MET	NSCLC
Gilteritinib (Xospata)	FLT3	AML

Drug Name	Targets	FDA-Approved Uses
Lenvatinib (Lenvima)	VEGFR 1-3, FGF-R 1-4, PDGFR-α, KIT, RET	DTC, RCC, HCC, EC
Pazopanib (Votrient)	VEGFR 1-3, PDGFR α + β, FGFR 1,3, c-Kit, Itk, Lck, c-Fms	RCC, STS
Pexidartinib (Turalio)	CSF1R, KIT, FLT3	TGCT
Quizartinib (Vanflyta)	FLT3	AML
Regorafenib (Stivarga)	VEGFR 1-3, TEK, KIT, RET, RAF1, BRAF and $BRAF^{V600E}$	CRC, GIST, HCC
Repotrectinib (Augtyro)	ROS1	NSCLC
Ripretinib (Qinlock)	KIT, PDGFRA, DGFRB, TIE2, VEGFR2, BRAF	GIST
Sorafenib (Nexavar)	VEGFR 1-3, PDGFR α + β, c-Kit, Flt3, CSF-1R, RET	DTC, RCC, HCC
Sunitinib (Sutent)	VEGFR 1-3, PDGFR α + β, c-Kit, Flt3, CSF-1R, RET	RCC, GIST refractory to imatinib, PNET
Taletrectinib (Ibtrozi)	ROS1	NSCLC
Tepotinib (Tepmetko)	MET	NSCLC
Tivozanib (Fotivda)	VEGFR 1-3, c-Kit, PDGFR β	RCC
Vandetanib (Caprelsa)	EGFR, VEGF-R, RET	MTC

AdvSM = Advanced Systemic Mastocytosis; AML = Acute Myeloid Leukemia; CLL = Chronic lymphocytic leukemia; CRC = Colorectal Cancer; DCT = Differentiated Thyroid Cancer; EC = Endometrial Carcinoma; GIST = Gastrointestinal stromal tumor; HCC = Hepatocellular carcinoma; MCC = Metastatic colorectal cancer; MCL = Mantle Cell Lymphoma; MTC = Medullary Thyroid Ca; MZL = Marginal Zone Lymphoma; PNET = Pancreatic Neuroendocrine Tumors; RCC = Renal Cell Carcinoma; STC = Soft Tissue Sarcoma; TGCT = Tenosynovial Giant Cell Tumor; WM =Waldenstrom Macroglobulinemia.

Avapritinib is a tyrosine kinase inhibitor that targets PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC50s) less than 25 nM. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumor cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1. In *in vitro* cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V, mutants associated with resistance to approved kinase inhibitors, with IC50 of 4 nM and 30 nM, respectively. Avapritinib also had anti-tumor activity in mice implanted with an imatinib-resistant individual derived xenograft model of human GIST with activating KIT exon 11/17 mutations. Avapritinib was studied in an unpublished, single-arm, open-label, Phase 1 study in 237 individuals with unresectable GIST and other solid tumors without an available treatment. The primary outcome measures were adverse events (AEs) and overall response rate (ORR). The prescribing information (PI) reported the ORR in individuals with GIST and the D842V

mutation as 89% (95% confidence interval [CI] 75-79) (n=38). Additionally, the PI reported an ORR of 84% (95% CI 69-93) for all individuals with an exon 18 mutation including D842V (n=43). The study investigators reported ORR for all individuals receiving fourth-line treatment for GIST regardless of mutation status as 22% (95% CI 14.4-30.4) (n=121). Avapritinib was also evaluated in a randomized, double-blind, placebo-controlled trial involving adult individuals diagnosed with indolent systemic mastocytosis (ISM). Participants were randomized to receive 25 mg avapritinib once daily or placebo over a period of 24 weeks. The primary efficacy endpoint focused on assessing the change in the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS), as well as percentage of individuals achieving > 50% reduction from baseline through week 24 in the treatment group vs placebo group. The results demonstrated that the absolute mean change in ISM-SAF TSS from baseline to week 24 was -15.33 in the treatment group, whereas it was -9.64 in the placebo group (2-sided p-value = 0.012). Moreover, a higher proportion of individuals in the treatment group (25%) achieved at least 50% of reduction in the ISM-SAF TSS, in contrast to the placebo group (10%) (2-sided p value = 0.009).

Axitinib is a tyrosine kinase inhibitor targeting VEGFR 1, 2, and 3. It is used in the second-line treatment of metastatic renal cell carcinoma (mRCC) of clear-cell histology. Efficacy was first demonstrated in the phase III AXIS trial, which directly compared axitinib with sorafenib, another tyrosine kinase inhibitor that targets VEGFR. Out of 723 individuals enrolled in the study, 361 individuals taking axitinib achieved a median progression-free survival (PFS) of 6.7 months versus 362 individuals taking sorafenib reaching a medial PFS of 4.7 months ($p<0.0001$). Secondary endpoints included median overall survival, objective response rate and median duration of response.

Cabozantinib is a potent inhibitor of provinvasive receptor tyrosine kinase that induces apoptosis of cancer cells and suppress tumor growth, metastasis and angiogenesis. A literature search was conducted from January 2013 to June 4, 2014. A Phase III trial (N=330) compared cabozantinib (140mg) with placebo in individuals with radiographically progressive metastatic medullary thyroid cancer. This study showed a significant increase in the primary endpoint of progression-free survival, when comparing cabozantinib (140mg) with placebo (11.2 months vs. 4.0 months, HR 0.28; $P< 0.001$). Adverse events leading to treatment discontinuation occurred more frequently in individuals receiving cabozantinib than placebo (8% vs 16%). A Phase II trial in individuals with castration-resistant prostate cancer halted random assignment early due to a substantial increase in median progression-free survival when comparing cabozantinib (100mg) with placebo (23.9 weeks vs. 5.9 weeks, HR 0.12; $P < 0.001$).

Capmatinib is a kinase inhibitor that targets MET, including the mutant variant produced by exon 14 skipping. MET exon 14 skipping results in a protein with a missing regulatory domain

that reduces its negative regulation leading to increased downstream MET signaling. Capmatinib inhibited cancer cell growth driven by a mutant MET variant lacking exon 14 at clinically achievable concentrations and demonstrated anti-tumor activity in murine tumor xenograft models derived from human lung tumors with either a mutation leading to MET exon 14 skipping or MET amplification. Capmatinib inhibited the phosphorylation of MET triggered by binding of hepatocyte growth factor or by MET amplification, as well as MET-mediated phosphorylation of downstream signaling proteins and proliferation and survival of MET-dependent cancer cells.

Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3). Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.

Lenvatinib is a multi-target tyrosine kinase inhibitor (TKI) that inhibits the kinase activities of VEGF-R 1-3, FGF-R 1-4. PDGFR-α, KIT, and RET. Lenvatinib was approved for the treatment of individuals with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DCT). Individuals in the SELECT trial showed a significant difference in PFS (18.3 vs. 3.6 months). Individual characteristics were largely similar. Notably, the only subgroup that had any significant efficacy difference was those who had received a dose of a TKI previously (18.7 vs.15.1 months). Safety data clearly show a common incidence of side effects in treatment vs. placebo (97% vs. 60%), but this is comparable to sorafenib (99 % vs. 88%), and to be expected among most chemotherapeutic agents.

Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR-1, VEGFR-2, VEGFR-3), platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR-β receptors. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

Pexidartinib is a small molecule tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation. Overexpression of the CSF1R ligand promotes cell proliferation and accumulation in the synovium. In vitro, pexidartinib inhibited proliferation of cell lines dependent on CSF1R and ligand-induced

autophosphorylation of CSF1R. Pexidartinib also inhibited the proliferation of a CSF1R dependent cell line in vivo.

Quizartinib is a small molecule inhibitor of the receptor tyrosine kinase FMS-like tyrosine kinase 3 (FLT3). Quizartinib and its major active metabolite AC886 bind to the adenosine triphosphate (ATP) binding domain of FLT3 with comparable affinity, and both had 10-fold lower affinity towards FLT3-ITD mutation compared to FLT3 in a binding assay. Quizartinib and AC886 inhibited FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting downstream FLT3 receptor signaling and blocking FLT3- ITD-dependent cell proliferation. Quizartinib showed antitumor activity in a mouse model of FLT3-ITD-dependent leukemia.

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC.

Ripretinib is a tyrosine kinase inhibitor that inhibits KIT and platelet derived growth factor receptor A (PDGFRA) kinase, including wild type, primary, and secondary mutations. Ripretinib also inhibits other kinases in vitro, such as PDGFRB, TIE2, VEGFR2, and BRAF.

Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human xenografts in athymic mice. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-beta). Several of these kinases are thought to be involved in angiogenesis.

The efficacy of **regorafenib** for the third-line treatment of mCRC was established in a single Grade 1, Phase III RCT. Results demonstrated regorafenib plus best supportive care modestly but significantly increased overall survival versus best supportive care (BSC) alone. PFS and disease control rate (DCR) were also significantly improved. Efficacy for metastatic or unresectable GIST after second progression is supported by one Grade 1 phase III trial showing improved PFS versus placebo. However, the secondary endpoint of OS was not met. This was likely due to confounding by crossover of placebo individuals after progression. DCR also highly favored regorafenib. Results from a small, Grade 3, phase II trial also supports these results.

The clinical efficacy and safety of STIVARGA were evaluated in an international, multicenter, randomized (2:1), double blind, placebo-controlled trial [Study "REgorafenib after SORafenib in individuals with hepatoCEllular carcinoma" (RESORCE); NCT 01774344]. The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer Stage Category B or C hepatocellular carcinoma, with documented disease progression following sorafenib. The median duration of previous sorafenib treatment was 7.8 months; individuals who permanently discontinued sorafenib due to toxicity or were unable to tolerate sorafenib doses of 400 mg once daily were ineligible. Individuals were randomized to receive 160 mg regorafenib orally once daily plus best

supportive care (BSC) or matching placebo plus BSC for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographical region (Asia vs rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), alphafetoprotein levels (<400 ng/mL vs ≥400 ng/mL), extrahepatic disease (presence vs absence), and macrovascular invasion (presence vs absence). The major efficacy outcome measure was overall survival (OS). Additional outcome measures were PFS, ORR and duration of response as assessed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and using modified RECIST (mRECIST) for HCC. Individuals continued therapy with STIVARGA until clinical or radiological disease progression or unacceptable toxicity. The characteristics of the study population were a median age of 63 years (range 19 to 85 years); 88% male; 41% Asian, 36% White, and 21% not reported; 66% had ECOG performance status (PS) of 0 and 34% had ECOG PS of 1; 98% had Child-Pugh A and 2% had Child-Pugh B. Risk factors for underlying cirrhosis included hepatitis B (38%), alcohol use (25%), hepatitis C (21%), and non-alcoholic steatohepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of individuals. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of individuals. All individuals received prior sorafenib and 61% received prior loco-regional transarterial embolization or chemo infusion procedures.

Sunitinib is an oral multi-kinase inhibitor that targets several receptor tyrosine kinases (RTK). It inhibits multiple RTKs, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib is an inhibitor of platelet-derived growth factor receptors (PDGFR- α and PDGFR-β), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

Teletrectinib is a kinase inhibitor that targets ROS1. Approval of Ibtrozi is supported by pooled data from the pivotal phase II TRUST-I and TRUST-II studies showing a confirmed objective response rate (cORR) in 89% of individuals who were TKI-naïve and in 56% of TKI-pretreated individuals. As much as 40% of ROS1+ NSCLC metastasizes to the brain and is the leading cause of disease progression and mortality. The pooled studies showed an intracranial response was achieved in 73% of TKI- naïve individuals and 63% of TKI-pretreated individuals. Common adverse effects that occurred in clinical trials included diarrhea, nausea, vomiting, dizziness, rash, constipation and fatigue.

Tepotinib is a kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF)-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations. *In vitro*,

tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells. In mice implanted with tumor cell lines with oncogenic activation of MET, including METex14 skipping alterations, tepotinib inhibited tumor growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases. The efficacy of tepotinib was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible individuals were required to have advanced or metastatic NSCLC harboring METex14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by RECIST version 1.1, and ECOG PS of 0 to 1.

Tivozanib inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2 and VEGFR-3 and inhibits other kinases including c-kit and PDGFR β at clinically relevant concentrations. In tumor xenograft models in mice and rats, tivozanib inhibited angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human renal cell carcinoma. The efficacy of tivozanib was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open-label, multicenter trial of tivozanib versus sorafenib in individuals with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib.

Vandetanib inhibits several tyrosine kinases, including EGFR, VEGF-R and the RET (Rearranged during Transfection) proto-oncogene. In vitro, it inhibits endothelial cell migration, proliferation, survival, and angiogenesis. Vandetanib efficacy in treating metastatic medullary thyroid cancer (MTC) was demonstrated by the Phase III ZETA trial, involving 331 individuals with unresectable, measurable, locally advanced, or metastatic medullary thyroid cancer.

Vemurafenib: In BRIM-3, 675 individuals, all with a positive test for the BRAFV600E mutation using the co-developed Cobas 4800 BRAF V600 Mutation Test, and all with previously untreated metastatic melanoma (stage IIIc or IV) were enrolled. Individuals ranged in age from 17 to 86 years and had ECOG PS of 0 or 1 (restricted physically but ambulatory and able to perform light housework or office work). Fifty-eight percent of the cohort had serum lactate dehydrogenase (LDH) levels above the upper limit of normal, and 65% were stage IV, M1c (distant visceral metastases). Individuals were randomized to receive Zelboraf (vemurafenib) 960 mg orally twice daily or dacarbazine 1000 mg/m^2 of body surface area every 3 weeks. Treatment continued until unacceptable toxicity or disease progression. Six-month overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group, with a hazard ratio of 0.37 (95% confidence interval [CI]: 0.26, 0.55). Median progression-free survival (evaluated in 549 individuals) was 5.3 months and 1.6 months in the vemurafenib and dacarbazine groups, respectively. Resistance to therapy could not be addressed in this study because of the short duration of follow-up (3.8 months for vemurafenib and 2.3 months for dacarbazine); it is under

study, however. Data presented are the planned interim analyses; the data and safety monitoring committee halted the trial and allowed crossover of dacarbazine-treated individuals to the vemurafenib group due to the magnitude of effect.

National Comprehensive Cancer Network (NCCN) 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.

Thyroid Cancer

Vandetanib efficacy in treating metastatic medullary thyroid cancer (MTC) was demonstrated by the Phase III ZETA trial. In this study, 331 individuals with unresectable, measurable, locally advanced, or metastatic MTC were randomized to receive either vandetanib 300 mg p.o. qd or placebo. Individuals that progressed were offered open-label vandetanib. The primary endpoint was PFS, as determined by independent central modified RECIST assessments. Secondary endpoints included OS, objective response (OR), stable disease and changes in serum calcitonin and CEA levels.

In the "intention to treat" analysis, vandetanib reduced the risk of progression by 54% as compared to placebo (HR: 0.46; 95% CI: 0.31, 0.69; $p<0.0001$). Median PFS was 19.3 months in the placebo group; median PFS on vandetanib was not reached at 30 months. Partial OR rates

were 44.6% for vandetanib and 13% for placebo. Unfortunately, the design of this study makes it unlikely that OS results will be meaningful, due to the extent of crossover from placebo to active drug, and the fact that the trial was not powered for this endpoint to begin with.

Lenvatinib individuals in the SELECT trial showed a significant difference in PFS (18.3 vs. 3.6 months). Individual characteristics were largely similar. Notably, the only subgroup that had any significant efficacy difference was those who had previously received a dose of a TKI (18.7 vs.15.1 months). Safety data clearly show a common incidence of side effects in treatment vs. placebo (97% vs. 60%), but this is comparable to sorafenib (99 % vs. 88%), and to be expected among most chemotherapeutic agents.

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 for 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.

Approval of Nexavar (sorafenib) for the treatment of individuals with advanced renal cell carcinoma was based on two randomized, controlled clinical trials. The first study was a phase III, multicenter, randomized, double-blind, placebo-controlled trial in 769 individuals with advanced RCC who had received one prior systemic therapy. Individuals were randomized to receive sorafenib 400 mg twice daily (N=384) or placebo (N=385). Primary study endpoints included overall survival and progression-free survival, defined as the time from randomization to progression or death from any cause. Tumor response was a secondary endpoint. The median progression-free survival for individuals treated with sorafenib was 167 days compared to 84 days for individuals treated with placebo (HR 0.44, 95% CI: 0.35-0.55).

At the time of the planned interim survival analysis, based on 220 deaths, OS was longer for individuals in the sorafenib treatment group than the placebo treatment group with a hazard ratio of 0.72. However, this analysis did not meet the pre-specified criteria for statistical

significance. Additional analyses are planned as the survival data mature. Of 672 individuals evaluable for tumor response, seven sorafenib-treated individuals (1%) and zero placebo-treated individuals (0%) had a confirmed partial response.

The second study was a Phase II randomized discontinuation study in individuals with RCC. Individuals initially received sorafenib 400 mg twice daily during an open-label run-in period. After 12 weeks, individuals with <25% change in bi-dimensional tumor measurements from baseline were randomized to sorafenib or placebo for an additional 12 weeks. Individuals with >25% tumor shrinkage continued open-label sorafenib, whereas individuals with tumor growth >25% discontinued treatment. The primary study endpoint was the percentage of randomized individuals remaining progression-free at 24 weeks. Secondary endpoints included progression-free survival.

Of the 202 individuals treated during the 12-week run-in period, 73 individuals had tumor shrinkage of >25% and continued open-label treatment with sorafenib. Sixty-five individuals with stable disease were randomized to receive sorafenib (N=32) or placebo (N=33). After an additional 12 weeks, at week 24, for the 65 randomized individuals, the progression-free rate was significantly higher in individuals randomized to sorafenib (16/32, 50%) than in individuals randomized to placebo (6/33, 18%) (P=.0077). Median progression-free survival from randomization was significantly longer in individuals treated with sorafenib (163 days) than individuals treated with placebo (41 days) (P=.0087).

Approval of Sutent (sunitinib) for the treatment of advanced RCC is based on uncontrolled partial response rates and duration of response rates. There are no randomized controlled trials of sunitinib demonstrating clinical benefit for outcomes such as increased survival or improvement in disease-related symptoms in individuals with advanced RCC.

The activity of sunitinib in advanced RCC has been studied in two unpublished, single-arm, multicenter, phase II trials as second-line therapy in individuals with advanced RCC. These individuals were either intolerant of or had experienced disease progression during or following treatment with one prior cytokine-based therapy. One study enrolled only individuals with clear cell RCC while the second study enrolled individuals with any RCC histology. Study One also required prior nephrectomy and radiographic documentation of progression. Individuals were treated with repeat cycles of sunitinib 50 mg daily for four consecutive weeks followed by two weeks off. Treatment was continued until disease progression or intolerability.

In the first study (N=106), objective response rate (complete response, partial response) was 25.5% (95% CI: 17.5-34.9) with a median time to tumor progression of 34.0 weeks (95% CI: 24.1-36.0). The median duration of response could not be estimated because of the 27 responses experienced during the study, 23 were ongoing at the time of the report.

In the second study (N=63), there were 23 partial responses, as assessed by the investigators, for an objective response rate of 36.5% (95% CI: 24.7-49.6). Median duration of tumor response in Study Two was 42 weeks. Overall, the median time to treatment failure was 33.7 weeks (95% CI: 18.3-37.9) and the median time to tumor progression was 37.7 weeks (95% CI: 24.0-46.4).

Pfizer completed a randomized, multicenter, Phase III trial comparing the safety and efficacy of sunitinib to interferon-alpha as first-line therapy in individuals with advanced RCC. A total of 335 individuals with measurable clear cell kidney cancer were assigned to receive sunitinib subcutaneous injections of nine million units three times a week and 327 individuals to receive interferon alfa in six-week cycles. The median time to progression for individuals on sunitinib was significantly greater (11 months) compared with five months for interferon alfa (P <.000001). Also, 31% of individuals on sunitinib achieved an objective clinical response compared with 6% of individuals on the interferon regimen (103 individuals versus 20 individuals). Another 160 individuals on sunitinib and 160 on interferon achieved disease stabilization.

There was significantly more diarrhea, hypertension and hand-foot syndrome observed in sunitinib-treated individuals and significantly more fatigue among interferon-treated individuals.

Soft Tissue Sarcoma

The safety of Votrient has been evaluated in 382 individuals with advanced soft tissue sarcoma, with a median duration of treatment of 3.6 months (range: 0 to 53). The most commonly observed adverse reactions (≥20%) in the 382 individuals were fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, and skin hypopigmentation.

The data described reflect the safety profile of Votrient in 240 individuals who participated in a randomized, double-blind, placebo-controlled trial. The median duration of treatment was 4.5 months (range: 0 to 24) for individuals who received Votrient and 1.9 months (range: 0 to 24) for the placebo arm. Fifty-eight percent of individuals on Votrient required a dose interruption. Thirty-eight percent of individuals on Votrient had their dose reduced. Seventeen percent of individuals who received Votrient discontinued therapy due to adverse reactions.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide. Surgical resection and liver transplantation are the only cures for HCC, but they benefit only 15% of individuals. Most cases are fatal within one year of diagnosis. Soratenib is the only pharmacotherapy option available for advanced, inoperable HCC.

One Phase II study, N=137 individuals, looked at the safety and efficacy of four-week cycles of soratenib 400 mg given twice daily to individuals with inoperable HCC, no prior systemic treatment and Child-Pugh A or B scores. After independent assessment, three individuals (2.2%) had a partial response, eight individuals (5.8%) had minor response and 46 individuals (33.6%) had stable disease for at least 16 weeks. The median time to progression was 4.2 months and median overall survival was 9.2 months. Adverse events included fatigue, diarrhea, and hand-foot skin reaction.

One Phase III study (N=602) looked at the efficacy and safety of 400 mg of soratenib given twice daily compared to placebo in individuals with advanced HCC. These individuals had no prior systemic treatment, ECOG 0-2 and were Child-Pugh Class A. Primary endpoints were median OS and time to symptomatic progression (TTSP). The hazard ratio for OS was 0.69 for sorafenib versus placebo which represented 44% improvement in OS. This was the basis for early stopping criteria. The median overall survival advantage was 10.7 months for sorafenib versus 7.9 months for placebo. The hazard ratio for TTSP was 0.58 and median TTP was 5.5 months for sorafenib vs 2.8 months for placebo. Rates of adverse events were similar between the two groups; however, there were more serious adverse events of diarrhea and hand-foot skin reactions in the sorafenib group.

K-Ras Mutations and Their Impact on the Clinical Effectiveness Epidermal Growth Factor Receptor Inhibitors

Many retrospective observational studies during 2008 were performed to evaluate the contribution of mutations downstream of the epithelial growth factor receptor (EGFR) on the efficacy of the anti-EGFR tyrosine kinase inhibitor oncology therapies such as cetuximab, panitumumab, and gefitinib. Studies differ in design, individual demographics, and therapeutic regimens. The majority of studies evaluating the association of K-Ras mutation with treatment resistance conclude that wild type status is associated with a more favorable response to treatment. Higher efficacy is often seen among tumors with wild-type K-Ras, including a higher percent and degree of response, overall survival, and time-to-progression. However, no single outcome is consistently statistically significant among all studies. Currently available evidence

suggests that K-Ras mutation is associated with poor response to TKI therapy, with the most evidence being for cetuximab. At this time, K-Ras mutation status neither predicts resistance to therapy, nor does the presence of wild-type allele predict good efficacy.

A statistically significant difference in overall response was seen in 10 of 13 studies in which response was an outcome. Response rates among K-Ras mutants ranged from 0% to 33%. Only five of 13 studies that measured response reported any response to TKI treatment, ranging from 9.5% to 33%. No studies assessing response to panitumumab reported any response to therapy in the K-Ras mutant group. In general, the presence of K-Ras mutation is associated with decreased response to TKI treatment. However, studies presenting response rates of approximately 10-30% suggest that the existence of K-Ras mutation is not the sole determinant of treatment response. In addition, the percent of K-Ras wild-type subjects with partial or complete response is still relatively low, ranging from 26-68%. This suggests that while K-Ras likely contributes the TKI resistance, other factors are involved.

Seven of 15 studies assessed overall survival as an outcome. Three of these found no statistically significant difference, and one found a difference in overall survival only among individuals taking combination therapy of cetuximab with irinotecan, while no difference in overall survival was seen in the same individuals taking cetuximab monotherapy. The remaining three found statistically significant differences in overall survival between K-Ras mutants and K-Ras wild-type. All three assessed response to cetuximab. Comparison of the overall survival of mutants versus wild-type found an overall median response rate of 6.9 months and 16.3 months, respectively ($p<0.001$), 27.3 weeks versus 44.7 weeks, respectively ($p=0.003$), and 10.1 months versus 14.3 months, respectively ($p=0.026$). Overall, half of the studies that measured overall survival as an outcome reported a difference between K-Ras mutants and K-Ras wild type. The largest study performed with overall survival as an outcome, consisting of 427 individuals, found that there was no difference in overall survival between K-Ras mutants and K-Ras wild type after treatment with panitumumab.

Eleven of 15 studies assessed PFS or time-to-progression (TTP). Three of these directly compared TTP or PFS between K-Ras mutants and K-Ras wild type after treatment with cetuximab and found no statistically significant difference. However, six studies directly comparing them confirmed that there was a difference. After treatment with cetuximab, TTP for K-Ras mutants and K-Ras wild type were 10.1 weeks [95% CI:, 8 to 16 weeks] and 31.4 weeks [95% CI:, 19.4 to 36 weeks], respectively. PFS was 6.9 months versus 16.3 months for mutants and wild-type, respectively ($p=0.016$). One study found a statistically significant difference in progression-free survival only with cetuximab combined with irinotecan (12 weeks versus 34 weeks, $p=0.016$), but not for cetuximab monotherapy. When randomized to best supportive care or best supportive care and panitumumab, subjects with K-Ras mutations showed no difference

in PFS between the two treatment arms. In K-Ras wild-type individuals, a statistically significant difference in PFS was seen (HR 0.45, 95% CI: -.34-0.59). One study with individuals taking either cetuximab or panitumumab reported difference in PFS of 8.6 weeks in K-Ras mutants versus 32 weeks in K-Ras wild type ($p<0.001$). Two abstracts presented at the American Society of Clinical Oncology (ASCO) 2008 Annual Meeting evaluated the benefit of cetuximab as adjunct therapy to the standard regimen for metastatic colorectal cancer, FOLFIRI. Both studies found that the addition of cetuximab to standard therapy only resulted in increased median PFS in K-Ras wild-type individuals. K-Ras mutants showed no improvement in PFS. Overall, the evidence shows that K-Ras mutation is associated with shorter TTP and PFS after treatment with TKI than K-Ras wild type. However, K-Ras mutation has been independently associated with disease progression and this may contribute to differences in disease progression regardless of therapy.

Karapetis et al. published a study that used tissue samples from the CO.17 trial of cetuximab versus supportive care in treating refractory advanced stage metastatic colorectal cancer individuals. Five hundred seventy-two individuals were enrolled in the original clinical trial, of which tissue samples were examined for 394 individuals (69%). The remainder was unavailable for logistic reasons, or due to lack of consent. The authors observed a five-month improvement in median overall survival (9.5 months in the cetuximab group versus 4.8 months with supportive care) for individuals with wild type K-Ras. There was no difference in survival between cetuximab and supportive care groups for individuals with K-Ras mutations.

2014 Update

A Phase II trial assessed dabrafenib (150mg BID) in BRAF (V600E/K) mutation positive stage-IV metastatic melanoma (N=92). The primary endpoint in this trial was investigator-assessed overall response rate. In individuals with the V600E mutation (N=76), 59% of individuals had a confirmed response and 7% had a complete response. In individuals with the V600K mutation (N=15), 13% had a confirmed partial response. Secondary endpoints were similar between subjects with V600E/K with respect to median progression free survival (6.3 vs. 4.5 months) and median overall survival (13.1 vs. 12.9 months). Individuals with the BRAF-V600K mutation may still benefit from treatment with dabrafenib, indicated by comparable median overall survival to individuals with the BRAF-V600E mutation.

A Phase III trial (N=1110) compared pazopanib (800mg daily, continuously) vs. sunitinib (50mg daily x 4wks followed by 2 weeks of no treatment) in subjects with clear-cell, metastatic renal-cell carcinoma. Pazopanib was found to be non-inferior to sunitinib, with respect to the primary endpoint of progression-free survival (HR [death from any cause] 1.05). Final analysis of this study also showed a similar death-rate (60 vs. 61%, HR = 0.92; P=0.24) and median overall

survival (28.3 vs. 29.1 months) when comparing treatment with pazopanib and sunitinib. Individuals treated with sunitinib had a higher incidence of fatigue (63% vs. 55%), hand–foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%), while individuals treated with pazopanib had a higher incidence of increased alanine aminotransferase (60%, vs. 43%). The mean change from baseline in 11 of 14 health-related quality-of-life domains favored pazopanib ($P<0.05$ for all 11 comparisons).

A Phase II trial assessed pazopanib (800g daily) in individuals with metastatic gastroenteropancreatic neuroendocrine tumors (pancreatic or colorectal, N=37), with a primary endpoint of objective response rate according to the RECIST. The objective response rate and disease control rate with pazopanib were found to be 18.9%, and 75.7%, respectively.

A Phase III trial in subjects (N=199) with metastatic or unresectable gastrointestinal stromal tumors (GIST) previously treated with and failed sunitinib and imatinib were randomized to receive either regorafenib (160mg daily) or placebo. The primary endpoint assessed progression-free survival with median values substantially longer for regorafenib vs placebo (4.8 vs. 0.9 months, HR 0.27; $p < 0.0001$). The most common ≥ grade 3 adverse events related to regorafenib treatment were hypertension (23.5%), hand–foot skin reaction (19.7%), and diarrhea (5.3%).

A Phase III trial in subjects with metastatic colorectal cancer (N=760) and with progression during or within the past 3 months after the last standard therapy were treated with regorafenib (160mg for the first 3 weeks of a 4-week cycle) or placebo. The primary endpoint in this study, overall median survival, was significantly longer when comparing regorafenib to placebo (6.4 vs. 5.0 months, HR 0.7; one-sided $p=0.052$). The most common ≥ grade 3 adverse events with regorafenib treatment were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%).

A Phase III trial (N=1074) comparing sunitinib (37.5mg daily) with sorafenib (400mg twice daily) in individuals with advanced hepatocellular carcinoma found significantly increased median overall survival (primary outcome) with sorafenib (7.9 vs. 10.2 months, HR 1.3; $P=0.0014$), as well as a substantially increased median overall survival in the subset of hepatitis C infected individuals who were treated with sorafenib (9.2 vs. 17.6 months, HR 1.52). Discontinuation due to adverse events occurred with similar frequency between sunitinib and sorafenib groups (13.3% vs. 12.7%) and the trial was terminated early due to futility.

Due to the positive response to vemurafenib in the initial portion of the BRIM-3 study, many of the individuals initially randomly assigned to dacarbazine (83 (25%) of 338) crossed over to vemurafenib for continued treatment of their metastatic melanoma. An extended follow-up analysis of this trial found that median overall survival (13.6 vs. 9.7 months, HR 0.70; $p=0.0008$)

and median progression-free survival (6.9 vs. 1.6 months, HR 0.38; p<0.0001) were both significantly longer in vemurafenib treated subjects. The majority of subjects (598 (91%)) in the study had a BRAF (V600E) mutation and in this subset, both the median overall survival (13.3 vs. 10.0 months, HR 0.75; p=0.0085) and median progression-free survival (6.9 vs. 1.6 months, HR 0.39; p<0·0001) were longer in the vemurafenib treated cohort. For the 57 (9%) individuals with a BRAF V600K mutation, median overall survival (14.5 vs. 7.6 months, HR 0.43; p=0.024) and median progression-free survival (5.9 vs. 1.7 months, HR 0.30; p<0.0001) were also both significantly longer in the vemurafenib cohorts. Frequent grade 3-4 adverse events in the trial included cutaneous squamous cell carcinoma (19%), keratoacanthomas (10%), rash (9%), and abnormal liver function tests (11%) in the vemurafenib treated group and neutropenia (9%) in the dacarbazine treated group. The incidence of grade 5 adverse events was similar between the two groups.

A Phase III trial (N=288), with a primary endpoint of progression-free survival, compared axitinib (5mg twice daily) with sorafenib (400mg twice daily) in treatment-naïve subjects with clear cell, metastatic renal cell carcinoma. The study found no significant differences in median progression-free survival when comparing axitinib with sorafenib (10.1 vs. 6.5 months, stratified HR = 0.77). Serious adverse events were reported in 64 (34%) of 189 individuals receiving axitinib, and 24 (25%) of 96 individuals receiving sorafenib.

A Phase III trial (N=723), with a primary endpoint of progression free survival, compared axitinib (5mg twice daily) with sorafenib (400mg twice daily) as second-line treatment for clear cell, metastatic renal cell carcinoma. The study found that median investigator assessed progression-free survival was significantly longer for axitinib compared with sorafenib (8.3 vs. 5.7 months, HR 0.656; one-sided p<0.0001). However, median overall survival was similar between the treatment groups (20.1 vs. 19.2 months, HR = 0.969; one-sided p=0.3744). It is also notable that a post-hoc analysis found significant differences in outcomes depending on the subject's diastolic blood pressure. Median overall survival was longer in individuals with a diastolic blood pressure ≥ 90 mm Hg compared with ≤ 90mm Hg for both axitinib (20.7 vs. 12.9 months; p=0·0116) and sorafenib groups (20.2 vs. 14.8 months; one-sided p=0·0020).

2015 Update

Updated to include criteria for ibrutinib to treat mantle cell lymphoma and chronic lymphocytic leukemia. Mantle cell lymphoma (MCL) is a B-cell malignancy classified as an aggressive form of non-Hodgkin lymphoma (NHL). MCL is characterized by lymph node involvement, as well as spleen, blood, and bone marrow. In most cases of MCL, chromosomal translocation t(11:14)(q13;q32) results in aberrant expression of cyclin D1, which is not typically expressed in

normal lymphocytes,[7] leading to cell cycle dysregulation. Many signaling pathways are constitutively activated and/or deregulated in MCL, including the B-cell receptor (BCR) signaling pathway, BAFF-R, mTOR, WNT, and NOTCH1 signaling, as well as pathways that promote the cell cycle and inhibit apoptosis. Bruton's tyrosine kinase (BTK) has been identified as an essential component of the BCR signaling pathway.

Updated to include indication for Lenvima to treat locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Also, updated to include new indication for Votrient to treat soft tissue sarcoma. See designated section(s) for more detail.

Updated in October 2015 to add new FDA-approved indications and NCCN Compendium recommendations for the above agents.

2017 Update

Updated indications for Imbruvica (ibrutinib) per label.

2018 Update

Updated description and multikinase inhibitor table. Added Cotellic safety and efficacy study. Added reauthorization criteria statement and documentation requirements. Literature search and indication update through May 2018 did not require other changes.

2019 Update

Reviewed prescribing information for all drugs and updated Lenvima (lenvatinib) coverage criteria. No new evidence was identified that would require changes to other drugs listed in this this policy. Added coverage criteria for a new drug Turalio (pexidartinib).

2020 Update

Reviewed prescribing information for all drugs and updated Inlyta (axitinib) coverage criteria. Added two new indications identified which are for first-line treatment of individuals with advanced RCC in combination with Bavencio (avelumab) or first-line treatment of individuals

with advanced RCC in combination with Keytruda (pembrolizumab). No new evidence was identified that would require changes to other drugs listed in this this policy.

2021 Update

Reviewed prescribing information for all drugs and updated Ayvakit (avapritinib) adding coverage for the treatment of adult individuals with advanced systemic mastocytosis (AdvSM). No new evidence was identified that would require changes to other drugs listed in this this policy.

2022 Update

Reviewed prescribing information for all drugs in the policy. No new evidence was identified that would require changes to any drugs listed in this this policy.

2023 Update

Reviewed prescribing information for all drugs in the policy. Updated Lenvima criteria by removing the reference to MSI-H and dMMR. Changed "patient" to "individual" for the process of standardization. Updated coverage criteria of Ayvakit to include the indication of treatment of adult individuals with indolent systemic mastocytosis (ISM). Added coverage criteria for Vanflyta (quizartinib) for the treatment of adults with newly diagnosed acute myeloid leukemia that is FLT3 internal tandem duplication (ITD)-positive.

2024 Update

Reviewed prescribing information for all drugs in the policy. Added coverage criteria for Augtyro (repotrectinib) and generic pazopanib. Updated Votrient (pazopanib) criteria to require trial with the generic first. Updated coverage criteria for Sutent (sunitinib) to clarify that use for gastrointestinal stromal tumor, renal cell carcinoma, and pancreatic neuroendocrine tumors is medically necessary in adults only per the FDA label. Added coverage criteria for generic sorafenib. Updated coverage criteria for Nexavar (sorafenib) to clarify that use is considered medically necessary in adults only per the FDA prescribing information. Update Nexavar (sorafenib) coverage criteria to include treatment of certain individuals with desmoid tumors.

Update Nexavar (sorafenib) coverage criteria to require trial with the generic first. Added coverage criteria for generic sunitinib. Updated Sutent (sunitinib) coverage criteria to require trial with the generic first. Updated Augtyro (repotrectinib) coverage criteria to include treatment of certain individuals with solid tumors. Clarified that Lenvima (lenvatinib) can be used as first-line treatment for individuals with unresectable hepatocellular carcinoma (HCC).

2025 Update

Reviewed prescribing information for all drugs in the policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated Cabometyx (cabozantinib) criteria to include coverage for the treatment of pancreatic neuroendocrine tumors (pNET) and extra-pancreatic neuroendocrine tumors (epNET). Added coverage criteria for Ibtrozi (taletrectinib).

2026 Update

Reviewed prescribing information for all drugs in the policy. Updated coverage criteria for Fotivda (tivozanib) adding a prescribed quantity limit per 28 days. Updated coverage criteria for Tepmetko (tepotinib) adding a prescribed quantity limit per 30 days.

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33. Augtyro (repotrectinib) Prescribing Information. Bristol-Myers Squibb. Princeton, NJ. Revised June 2024.

34. Ibtrozi (taletrectinib). Prescribing Information. Nuvation Bio. Burlington, MA. Revised June 2025.

History

Date	Comments
05/10/11	Add to Prescription Drug Section - New Pharmacy Policy.
02/14/12	Replace Policy – Policy updated with literature review. Policy section updated with two new medically necessary indications for *Vandetanib (Caprelsa);* one for unresectable locally advanced or metastatic medullary thyroid cancer; and the other unresectable or metastatic melanoma with BRAFV600E. Reviewed by P&T on January 24, 2012. Related Policy added.
09/21/12	Update Related Policy – 2.04.77 changed to 12.04.77.
04/09/13	Replace policy. New drug added the policy section. New policy statement added: Regorafenib (Stivarga) may be considered medically necessary for treatment of individuals with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and, if KRAS wild type, an anti-EGFR therapy; or metastatic or unresectable GIST and prior failure or intolerance to imatinib and sunitinib. Policy Guidelines additionally update.
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member's pharmacy benefit; this is now listed in the header and within the coding section.
08/12/13	Replace policy. Policy statement added indicating cabozantinib (Cometriq) as medically necessary for the treatment of metastatic medullary thyroid cancer.
10/14/13	Replace policy. Policy section updated with the addition of dabrafenib (Tafinlar) as medically necessary to treat unresectable or metastatic melanoma with BRAFV600 mutations and trametinib (Mekinist) as medically necessary as monotherapy to treat unresectable or metastatic melanoma with BRAFV600 mutations when BRAF inhibitor therapy has failed or is not tolerated. Clarification made on vemurafenib (Zelboraf) to treat unresectable or metastatic melanoma with BRAFV600E mutations with the addition of "for whom treatment with dabrafenib would not be appropriate". Policy Guidelines and Rationale sections updated to support changes to policy statements. References 23 – 31 added.
12/06/13	Update Related Policies. Add 5.01.544.
12/18/13	Update Related Policies. Edit title to 5.01.603.
07/31/14	Annual review. Policy updated with literature review. No change in policy statements. References 34 – 45 added.
03/10/15	Annual Review. Policy updated with literature review. New policy statement added: Trametinib (Mekinist) may be considered medically necessary in combination with dabrafenib for the treatment of individuals with unresectable or metastatic melanoma with BRAFV600 mutations. (Testing will be covered whenever use of trametinib is contemplated.) Policy statements added for Inlyta (axitinib) to policy for RCC; and Imbruvica (ibrutinib) to policy for MCL and

Date	Comments
	CLL. The following updates were made to the existing drugs on policy: Mekinist (trametinib) to allow combination therapy with dabrafenib for unresectable or metastatic melanoma with BRAFV600E mutation.
07/14/15	Interim Update. Addition of a new indication for Votrient (pazopanib): treatment of Soft Tissue Sarcoma and Lenvima (lenvatinib): treatment of Differentiated Thyroid Cancer to the policy section.
10/13/15	Interim Update. Medically necessary statements updated to reflect NCCN guidelines and new FDA labeling indications for: Inlyta, Imbruvica, Votrient, Stivarga, Nexavar and Sutent and Zelboraf. Definition of the "Child-Pugh Scoring System" has been added to the "Policy" section of the document.
12/08/15	Interim Update. Unresectable or metastatic hepatocellular carcinoma removed from the list of medically necessary indications for Nexavar.
01/12/16	Interim Update minor update. Information from Policy Guidelines section moved into Policy section. No other changes.
05/01/16	Annual Review, approved April 12, 2016. Removal of outdated information from the criteria for Imbruvica and Zelboraf.
06/01/16	Interim Update, approved May 24, 2016. Updated Related Policies. Remove 12.04.77 as it is archived.
07/01/16	Interim Update, approved June 14, 2016. Inclusion of cabozantinib brand name agent, Cabometyx for RCC, per P&T's recommendation: PA to label.
10/01/16	Interim Update, approved September 13, 2016. Inclusion of a new indication for Lenvima and Imbruvica.
01/01/17	Minor correction, approved December 13, 2016. Vemurafenib was inadvertently referenced in Tafinlar (dabrafenib) testing for BRAFv600 mutations. Corrected to dabrafenib.
03/01/17	Annual Review, approved February 14, 2017. Updated indications for ibrutinib per label.
06/01/17	Interim Review, approved May 16, 2017. A statement outlining the length of therapy for initial approval has been added to the policy. Addition of a new indication for regorafenib (HCC).
06/29/17	Updated criteria for Zelboraf to include combination treatment with Cotellic.
12/01/17	Interim Review, approved November 21, 2017. Added Calquence.
01/01/18	Interim Review, approved December 20, 2017. Updated Calquence criteria.
02/01/18	Interim Review, approved January 30, 2018. Added Cotellic criteria.
05/01/18	Interim Review, approved April 18, 2018. Updated criteria for Cabometyx – removed requirement to try antiangiogenic therapy first prior to Cabometyx.
07/01/18	Annual Review, approved June 22, 2018. Updated description and multikinase inhibitor table. Added Cotellic safety and efficacy study. Added reauthorization criteria statement and documentation requirements. Literature search through May 2018.

Date	Comments
11/01/18	Interim Review, approved October 9, 2018. Added new label indication for Lenvima for HCC. Added encorafenib and binimetinib for BRAF V600 mutated melanoma. Moved all BRAF and MEK inhibitors to new policy 5.01.589. Moved Bruton's Kinase Inhibitors (ibrutinib, acalabrutinib) to new policy 5.01.590. Reorganized policy and updated all indications per product labeling.
03/01/19	Interim Review, approved February 12, 2019. Added new indication for Cabometyx.
06/01/19	Interim Review, approved May 14, 2019. Added criteria for Xospata (gilteritinib).
12/01/19	Annual Review, approved November 12, 2019. Added criteria for Turalio (pexidartinib). Updated criteria for Lenvima (lenvatinib).
04/01/20	Interim Review, approved March 10, 2020. Added criteria for Ayvakit (avapritinib) for the treatment of GIST.
07/01/20	Interim Review, approved June 9, 2020. Added criteria for Qinlock (ripretinib) for the treatment of GIST.
08/01/20	Annual Review, approved July 23, 2020. Added two new indications to Inlyta (axitinib) for treatment of RCC in combination with Bavencio (avelumab) or treatment of RCC in combination with Keytruda (pembrolizumab).
10/01/20	Interim Review, approved September 8, 2020. Added criteria for Tabrecta (capmatinib) for the treatment of metastatic NSCLC.
03/01/21	Interim Review, approved February 18, 2021. Added a new indication to Cabometyx (cabozantinib) for the treatment of advanced RCC in combination with nivolumab.
05/01/21	Interim Review, approved April 13, 2021. Added criteria for Fotivda (tivozanib) for the treatment of individuals with RCC. Added criteria for Tepmetko (tepotinib) for the treatment of metastatic NSCLC.
08/01/21	Annual Review, approved July 9, 2021. Added a new indication to Ayvakit (avapritinib) for the treatment of adult individuals with advanced systemic mastocytosis (AdvSM).
10/01/21	Interim Review, approved September 14, 2021. Added a new indication to Lenvima (lenvatinib) for the treatment of RCC in combination with pembrolizumab.
11/01/21	Interim Review, approved October 12, 2021. Added a new indication to Cabometyx (cabozantinib) for the treatment of locally advanced or metastatic DTC in adult and pediatric individuals 12 years of age and older.
04/01/22	Annual Review, approved March 7, 2022. No changes to policy statements.
06/01/23	Annual Review, approved May 22, 2023. Reviewed prescribing information for all drugs in the policy. No new evidence was identified that would require changes to any drugs listed in this this policy. Updated Lenvima criteria by removing the reference to MSI-H and dMMR. Changed "patient" to "individual" for the process of standardization.
08/01/23	Interim Review, approved July 11, 2023. Updated coverage criteria of Ayvakit to include the indication of treatment of adult individuals with indolent systemic mastocytosis (ISM).

Date	Comments
01/01/24	Interim Review, approved December 12, 2023. Added coverage criteria for Vanflyta (quizartinib) for the treatment of adults with newly diagnosed acute myeloid leukemia that is FLT3 internal tandem duplication (ITD)-positive.
02/01/24	Annual Review, approved January 9, 2024. Added coverage criteria for Augtyro (repotrectinib) and generic pazopanib. Updated Votrient (pazopanib) criteria to require trial with the generic first and limit use to adults. Updated coverage criteria for Sutent (sunitinib) to clarify that use for gastrointestinal stromal tumor, renal cell carcinoma, and pancreatic neuroendocrine tumors is medically necessary in adults only per the prescribing information.
06/01/24	Interim Review, approved May 14, 2024. Added coverage criteria for generic sorafenib. Updated coverage criteria for Nexavar (sorafenib) to clarify that use is considered medically necessary in adults only per the FDA prescribing information. Update Nexavar (sorafenib) coverage criteria to include treatment of certain individuals with desmoid tumors. Update Nexavar (sorafenib) coverage criteria to require trial with the generic first. Added coverage criteria for generic sunitinib. Updated Sutent (sunitinib) coverage criteria to require trial with the generic first.
12/01/24	Interim Review, approved November 12, 2024. Updated Augtyro (repotrectinib) coverage criteria to include treatment of certain individuals with solid tumors. Clarified that Lenvima (lenvatinib) can be used as first-line treatment for individuals with unresectable hepatocellular carcinoma (HCC).
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
07/01/25	Interim Review, approved June 10, 2025. Updated Cabometyx (cabozantinib) criteria to include coverage for the treatment of pancreatic neuroendocrine tumors (pNET) and extra-pancreatic neuroendocrine tumors (epNET).
08/01/25	Interim Review, approved July 8, 2025. Added coverage criteria for Ibtrozi (taletrectinib).
02/01/26	Annual Review, approved January 26, 2026. Updated coverage criteria for Fotivda (tivozanib) adding a prescribed quantity limit per 28 days. Updated coverage criteria for Tepmetko (tepotinib) adding a prescribed quantity limit per 30 days.
05/01/26	Interim Review, approved April 13, 2026. Updated initial authorization for all other reviews for all drugs listed in the policy from 3 months to 6 months.

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. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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