


## PHARMACY POLICY – 5.01.534

## Multiple Receptor Tyrosine Kinase Inhibitors

Effective Date:	May 1, 2018	RELATED MEDICAL POLICIES:
Last Revised:	April 18, 2018	5.01.517 Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Patients
Replaces:	N/A	5.01.518 Bcr-Abl Kinase Inhibitors
		5.01.544 Prostate Cancer Targeted Therapies
		5.01.603 Epidermal Growth Factor Receptor (EGFR) Inhibitors

Select a hyperlink below to be directed to that section.

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[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
<b>Oral Drugs</b>	
<b>Calquence® (acalabrutinib)</b>	<p><b>Calquence® (acalabrutinib) may be considered medically necessary for treatment of adult patients who meet all of the following criteria:</b></p> <ul style="list-style-type: none"> <li>• Bruton’s tyrosine kinase (BTK) inhibitor-naïve adult patients with relapsed or refractory mantle cell lymphoma</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Tried one prior chemotherapy regimen (rituximab alone or rituximab containing regimen, CHOP-based, cytarabine, bendamustine + rituximab, Hyper-CVAD, or stem-cell transplant)</li> </ul>
<b>Inlyta® (axitinib)</b>	<p><b>Inlyta® (axitinib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of unresectable, recurrent or metastatic renal cell carcinoma</li> <li>• Treatment of thyroid Carcinoma-Follicular Carcinoma, Hurthle Cell Carcinoma and Papillary Carcinoma</li> </ul>
<b>Cabometyx® (cabozantinib)</b>	<p><b>Cabometyx® (cabozantinib) may be considered medically necessary for treatment of adult patients with advanced renal cell carcinoma (RCC).</b></p>
<b>Cometriq® (cabozantinib)</b>	<p><b>Cometriq® (cabozantinib) may be considered medically necessary for treatment of adults with progressive, metastatic medullary thyroid cancer.</b></p>
<b>Tafinlar® (dabrafenib)</b>	<p><b>Tafinlar® (dabrafenib) may be considered medically necessary for treatment of patients with unresectable or metastatic melanoma with BRAF<sup>V600</sup> mutations. (Genetic testing will be covered whenever use of dabrafenib is contemplated.)</b></p>
<b>Imbruvica® (ibrutinib)</b>	<p><b>Imbruvica® (ibrutinib) may be considered medically necessary for treatment of the following hematologic malignancies:</b></p> <ul style="list-style-type: none"> <li>• Mantle cell lymphoma in patients who have received at least one prior therapy</li> <li>• Chronic lymphocytic leukemia/small lymphocytic lymphoma with or without 17p deletion</li> <li>• Waldenstrom macroglobulinemia</li> <li>• Marginal zone lymphoma (MZL) in patients who require systemic therapy and have received at least one prior anti-CD20-based therapy</li> </ul>



Drug	Medical Necessity
<b>Oral Drugs</b>	
<b>Lenvima® (lenvatinib)</b>	<p><b>Lenvima® (lenvatinib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer</li> <li>• Patients with advanced renal cell cancer (RCC) in combination with everolimus, following one prior anti-angiogenic therapy</li> </ul>
<b>Votrient® (pazopanib)</b>	<p><b>Votrient® (pazopanib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with advanced, relapsed or unresectable renal cell carcinoma (RCC)</li> <li>• Treatment of patients with thyroid carcinoma</li> <li>• Treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy</li> <li>• Metastatic non-melanoma skin cancers</li> </ul> <p><b>Note:</b> The efficacy of Votrient® for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated.</p>
<b>Stivarga® (regorafenib)</b>	<p><b>Stivarga® (regorafenib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with metastatic colorectal cancer who have been previously treated with all of the following: <ul style="list-style-type: none"> <li>○ fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, <b>AND</b> if KRAS wild type, an anti-EGFR therapy.</li> </ul> </li> <li>• Treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib</li> <li>• Metastatic or unresectable GIST and prior failure or intolerance to imatinib and sunitinib</li> <li>• Single agent therapy for unresectable advanced or metastatic rectal cancer not previously treated with regorafenib after <ul style="list-style-type: none"> <li>○ First progression (KRAS/NRAS mutant only) or second progression for disease previously treated with FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen with or without bevacizumab</li> </ul> </li> </ul>



Drug	Medical Necessity
<b>Oral Drugs</b>	
	<ul style="list-style-type: none"> <li>○ Second progression for disease previously treated with irinotecan-and oxaliplatin based regimens</li> <li>○ Progression of disease that progressed through all available regimens, including trifluridine and tipiracil</li> </ul>
<b>Nexavar® (sorafenib)</b>	<p><b>Nexavar® (sorafenib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with advanced renal cell carcinoma (RCC)</li> <li>• Treatment of patients with thyroid carcinoma</li> <li>• Treatment of patients with gastrointestinal stromal tumors, when the patient is no longer receiving benefit from Gleevec® (imatinib) or Sutent® (sunitinib)</li> <li>• Treatment of soft tissue sarcoma</li> <li>• Treatment of relapsed or refractory acute myeloid leukemia (AML) in combination with azacitidine or decitabine for patients with FLT3-ITD mutation-positive disease who cannot tolerate more aggressive regimens</li> <li>• Treatment of Hepatobiliary Cancers-Hepatocellular Carcinoma as a single agent for patients with <b>Child-Pugh</b> Class A or B* who are: <ul style="list-style-type: none"> <li>○ Non-transplant candidates with unresectable disease</li> <li>○ Inoperable by performance status or comorbidity (local disease or local disease with minimal extrahepatic disease only)</li> <li>○ Found to have extensive liver tumor burden or metastatic disease <ul style="list-style-type: none"> <li>▪ The dose is limited to 400 mg p.o. BID</li> </ul> </li> </ul> </li> </ul>
<b>Sutent® (sunitinib)</b>	<p><b>Sutent® (sunitinib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with advanced renal cell carcinoma (RCC)</li> <li>• Treatment of patients with Gleevec® (imatinib)-resistant or intolerant GIST/soft tissue sarcoma</li> <li>• Treatment of patients with clinically progressive or symptomatic metastatic thyroid carcinoma with non-radioiodine-responsive tumors at sites other than the central nervous system</li> </ul>



Drug	Medical Necessity
<b>Oral Drugs</b>	
	<ul style="list-style-type: none"> <li>• Treatment of disseminated symptomatic thyroid (medullary) carcinoma</li> <li>• Treatment of bone cancer as a single-agent therapy for recurrent disease</li> <li>• Treatment of neuroendocrine tumors of the pancreas or lung</li> <li>• Treatment of soft tissue angiosarcoma as a single agent</li> <li>• Second-line therapy treatment of thymomas and thymic carcinomas as a single agent <ul style="list-style-type: none"> <li>○ The dose is limited to 50 mg p.o. daily</li> </ul> </li> </ul>
<b>Mekinist® (trametinib)</b>	<p><b>Mekinist® (trametinib) may be considered medically necessary as monotherapy or in combination with dabrafenib (Tafinlar) for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutations (V600E or V600K), as detected by an FDA-approved test. (Genetic testing will be covered whenever use of trametinib is contemplated.)</b></p> <p><b>Treatment of patients that have progressed on BRAF inhibitor therapy is considered not medically necessary.</b></p>
<b>Caprelsa® (vandetanib)</b>	<p><b>Caprelsa® (vandetanib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancers</li> </ul>
<b>Zelboraf® (vemurafenib)</b>	<p><b>Zelboraf® (vemurafenib) may be considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutations (Genetic testing will be covered whenever use of vemurafenib is contemplated.)</li> <li>• Treatment of Hairy Cell Leukemia- as a single agent in patients with the indication for treatment for progression if non-responsive to purine analog</li> <li>• Treatment of NSCLC with BRAFV600 mutations</li> </ul> <p><b>Zelboraf® (vemurafenib) may be considered medically necessary in combination with Cotellic® (cobimetinib)for:</b></p> <ul style="list-style-type: none"> <li>• Treatment of patients with unresectable or metastatic</li> </ul>



Drug	Medical Necessity
<b>Oral Drugs</b>	
	melanoma with BRAF V600 mutations (V600E or V600K), as detected by an FDA-approved test
<b>Cotellic® (cobimetinib)</b>	<b>Cotellic® (cobimetinib) may be considered medically necessary in combination with Zelboraf® (vemurafenib) for: Treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations (V600E or V600K), as detected by an FDA-approved test</b>

**Investigational**  
**All other uses of the above-listed agents are considered investigational.**

**\*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
- Presence/absence of hepatic encephalopathy:



### \*Child-Pugh Score

- 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
  - Class B: 7 to 9 points
  - Class C: 10 to 15 points
- If patient 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 1.4 million Americans will be diagnosed with cancer this year, and approximately 570,000 will die of



the disease. The good news is survival rates for cancer are on the rise, increasing from 50% to 64% over the last 30 years.

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 (eg, 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:

Drug Name	Targets	FDA-Approved Uses
<b>Axitinib (Inlyta®)</b>	VEGFR 1-3	RCC
<b>Ibrutinib (Imbruvica®)</b>	Bruton’s Tyrosine Kinase (BTK)	MCL, CLL/SLL, WM, MZL
<b>Lenvatinib (Lenvima®)</b>	VEGFR 1-3, FGF-R 1-4, PDGFR- $\alpha$ , KIT, RET	DTC
<b>Pazopanib (Votrient®)</b>	VEGFR 1-3, PDGFR $\alpha + \beta$ , FGFR 1,3, c-Kit, Itk, Lck, c-Fms	RCC, STS
<b>Regorafenib (Stivarga®)</b>	VEGFR 1-3, TEK, KIT, RET, RAF1, BRAF and BRAF <sup>V600E</sup>	CRC, GIST, HCC
<b>Sorafenib (Nexavar®)</b>	VEGFR 1-3, PDGFR $\alpha + \beta$ , c-Kit, Flt3, CSF-1R, RET	RCC, HCC
<b>Sunitinib (Sutent®)</b>	VEGFR 1-3, PDGFR $\alpha + \beta$ , c-Kit, Flt3, CSF-1R, RET	RCC, Gist refractory to imatinib
<b>Vandetanib (Caprelsa®)</b>	EGFR, VEGF-R, RET	Medullary Thyroid Ca (MTC)
<b>Vemurafenib (Zelboraf®)</b>	V600-mutated BRAF	Melanoma
<b>Dabrafenib (Tafinlar®)</b>	V600-mutated BRAF	Melanoma
<b>Trametinib (Mekinist™)</b>	MEK in tumors that have V600-mutated BRAF	Melanoma





Drug Name	Targets	FDA-Approved Uses
<b>Cotellic® (cobimetinib)</b>	V600-mutated BRAF	Melanoma

RCC = Renal cell carcinoma; HCC = Hepatocellular carcinoma; GIST = Gastrointestinal stromal tumor; CLL = Chronic lymphocytic leukemia.

**Acalabrutinib** is a selective and irreversible second-generation Bruton's tyrosine kinase inhibitor. The efficacy was based upon Trial LY-004, which was an open-label phase 2 study with 124 patients with mantle cell lymphoma who had been on at least one prior therapy. The primary outcome was overall response rate (ORR). The study had 81 patients who had an overall response rate, 40 patients had a complete response, and 41 patients had a partial response.

**Axitinib** is a tyrosine kinase inhibitor targeting VEGFR 1, 2, and 3. It is used in the second-line treatment of 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 patients enrolled in the study, 361 patients taking axitinib achieved a median PFS of 6.7 months versus 362 patients taking sorafenib reaching a median PFS of 4.7 months ( $p < 0.0001$ ). Secondary endpoints included median overall survival, objective response rate and median duration of response.

**Ibrutinib** is a novel inhibitor of Bruton's Tyrosine Kinase (BTK) that is used to treat Mantle Cell Lymphoma. Patients ( $n = 111$ ) with confirmed relapsed or refractory mantle cell lymphoma (MCL) who had undergone at least 1, but no more than 5, prior treatment regimens were studied. These subjects were classified as either having been treated with bortezomib therapy ( $\geq 2$  cycles) or not ( $< 2$  complete cycles or no prior bortezomib therapy). The primary efficacy outcome was overall response rate (complete plus partial responses). Overall response rate (ORR) for all patients was 68%, with 48.6% of patients having a partial response and 17.1% having complete response (CR). Response to therapy did not differ by baseline characteristics or presence of risk factors associated with chemotherapy treatment failure.

Response rates were similar regardless of prior bortezomib therapy; 63% (17 of 27) patients previously treated with lenalidomide had a response to ibrutinib. For the 75 patients having a response at the time of data analysis, the estimated median response duration was 17.5 months (range: 0.0 to 19.6; 95% CI: 15.8, not reached).

Median overall survival (OS) for this study was not reached (estimated OS of 58% at 18 months).

Approval Chronic Lymphocytic Leukemia was based on one small open label trial of 48 previously treated patients with baseline ECOG scores of 0-1. Patients received ibrutinib 420mg per day. Median number of prior treatments was 4. ORR was 58.3%, all partial responses.



The safety and efficacy of IMBRUVICA in MZL were evaluated in an open-label, multi-center, single-arm trial of patients who received at least one prior therapy. The efficacy analysis included 63 patients with 3 sub-types of MZL: mucosa-associated lymphoid tissue (MALT; N=32), nodal (N=17); and splenic (N=14). The median age was 66 years (range, 30 to 92 years), 59% were female, and 84% were Caucasian. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had ECOG performance status 2. The median time since diagnosis was 3.8 years, and the median number of prior treatments was 2 (range, 1 to 9 treatments).

**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)- $\alpha$  and - $\beta$ , 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- $\beta$  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.

**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 patients 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 patients 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; patients who permanently discontinued sorafenib due to toxicity or were unable to tolerate sorafenib doses of 400 mg once daily were ineligible. Patients 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), 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 progression-free survival (PFS), overall tumor response rate (ORR) and duration of response as assessed by investigators using RECIST 1.1 and using modified RECIST (mRECIST) for HCC. Patients 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 steato hepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of patients. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of patients. All patients 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-  $\alpha$  and PDGFR- $\beta$ ), 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).

**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 patients with unresectable, measurable, locally advanced or metastatic medullary thyroid cancer.

**Dabrafenib** and **vemurafenib** are small molecule inhibitors of V600-mutated BRAF.

**Trametinib** is a small molecule inhibitor of MEK that is active in cancers with a BRAF V600 mutation.

**Lenvatinib** is a multi-target tyrosine kinase inhibitor (TKI) that inhibits the kinase activities of VEGF-R 1-3, FGF-R 1-4, PDGFR- $\alpha$ , KIT, and RET. Lenvatinib was approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory



differentiated thyroid cancer (DCT). Patients in the SELECT trial showed a significant difference in PFS (18.3 vs. 3.6 months). Patient 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.

## *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 (eg 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

A 2009 primary recommendation from National Comprehensive Cancer Network (NCCN) for thyroid cancer patients is to investigate a clinical trial. Data from clinical trials have shown that small molecule kinase inhibitors such as pazopanib, sorafenib and sunitinib can be effective. ClinicalTrials.gov lists several ongoing Phase II clinical trials (NCT00519896, NCT00668811, NCT00510640, etc.) that are studying how well sunitinib and sorafenib work in treating patients with certain types of thyroid cancer.



Vandetanib efficacy in treating metastatic medullary thyroid cancer (MTC) was demonstrated by the Phase III ZETA trial. In this study, 331 patients with unresectable, measurable, locally advanced or metastatic MTC were randomized to receive either vandetanib 300 mg p.o. qd or placebo. Patients that progressed were offered open-label vandetanib. The primary endpoint was progression free survival (PFS), as determined by independent central modified Response Evaluation Criteria in Solid Tumors (RECIST) assessments. Secondary endpoints included overall survival (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 patients in the SELECT trial showed a significant difference in PFS (18.3 vs. 3.6 months). Patient 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 patients have metastases at the time of diagnosis. RCC is classified into five subtypes, but most patients (70-80%) have the clear cell type.

Treatment of RCC depends on disease staging and the patient'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 (eg, 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 patients 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 patients with advanced RCC who had received one prior systemic therapy. Patients 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 patients treated with sorafenib was 167 days compared to 84 days for patients 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, overall survival was longer for patients 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 patients evaluable for tumor response, seven sorafenib-treated patients (1%) and zero placebo-treated patients (0%) had a confirmed partial response.

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

Of the 202 patients treated during the 12-week run-in period, 73 patients had tumor shrinkage of >25% and continued open-label treatment with sorafenib. Sixty-five patients 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 patients, the progression-free rate was significantly higher in patients randomized to sorafenib (16/32, 50%) than in patients randomized to placebo (6/33, 18%) (P=.0077). Median progression-free survival from randomization was significantly longer in patients treated with sorafenib (163 days) than patients 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 patients 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 patients with advanced RCC. These patients were either intolerant of or had experienced disease progression during or following treatment with one prior cytokine-based therapy. One study enrolled only patients with clear cell RCC while the second study enrolled patients with any RCC histology. Study One also required prior nephrectomy and radiographic documentation of progression. Patients 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 patients with advanced RCC. A total of 335 patients with measurable clear cell kidney cancer were assigned to receive sunitinib subcutaneous injections of nine million units three times a week and 327 patients to receive interferon alfa in six-week cycles. The median time to progression for patients on sunitinib was significantly greater (11 months) compared with five months for interferon alfa (P <.000001). Also, 31% of patients on sunitinib achieved an objective clinical response compared with 6% of patients on the interferon regimen (103 patients versus 20 patients). Another 160 patients on sunitinib and 160 on interferon achieved disease stabilization.

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

## Soft Tissue Sarcoma

The safety of Votrient® has been evaluated in 382 patients 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 patients 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 patients who participated in a randomized, double-blind, placebo-controlled trial. The median duration of treatment was 4.5 months (range: 0 to 24) for patients who received Votrient® and 1.9 months (range: 0 to 24) for the placebo arm. Fifty-eight percent of patients on Votrient® required a dose interruption. Thirty-eight percent of patients on Votrient® had their dose reduced. Seventeen percent of patients who received Votrient® discontinued therapy due to adverse reactions.

## Hepatocellular Carcinoma

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

One Phase II study, N=137 patients, looked at the safety and efficacy of four week cycles of soratenib 400 mg given twice daily to patients with inoperable HCC, no prior systemic treatment and Child-Pugh A or B scores. After independent assessment, three patients (2.2%) had a partial response, eight patients (5.8%) had minor response and 46 patients (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 patients with advanced HCC. These patients had no prior systemic treatment, ECOG 0-2 and were Child-Pugh Class A. Primary endpoints were median overall survival (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.

The NCCN Practice Guidelines for hepatocellular carcinoma reflect the results of the Phase III study and recommend sorafenib as first line treatment for patients with Child-Pugh Class A or B status and who have unresectable or inoperable HCC. Sorafenib is also recommended for HCC metastatic disease.





## Melanoma

Melanoma accounts for a small (<5%) proportion of all skin cancers but, because it is more likely to metastasize than squamous cell or basal cell cancers, it causes a disproportionately high amount of skin cancer mortality. If recognized and treated early, it is almost always curable. Approximately 84% of melanomas are diagnosed at a localized stage with 5-year survival of 98%. However, the 5-year survival for the 4% of patients with metastatic disease at diagnosis is 15%.

Incidence rates for melanoma have been rising for at least 30 years. The age-adjusted incidence rate of melanoma was 20.8 per 100,000 men and women per year for the years 2004 to 2008. The American Cancer Society estimates that approximately 70,000 new melanomas will be diagnosed (approximately 40,000 in men and 30,000 in women), and that approximately 9,000 people will die of melanoma in 2011 the U.S.

The lifetime risk of melanoma is about 2% for Caucasians, 0.5% for Hispanics, and 0.1% for African Americans. Major risk factors for melanoma include atypical nevi (moles), more than 50 benign or atypical nevi, giant congenital nevus, and a personal or family history of melanoma. Other risk factors for all skin cancer types include: sun sensitivity (defined as easily being sun burned), freckling, tanning with difficulty, or having naturally blond or red hair. Other risk factors include having a history of excessive sun exposure (including sunburns), use of tanning booths and immune-deficiency states (eg, immunosuppressive chemotherapy, post-transplant immunosuppression, HIV/AIDS).

## Tafinlar® (dabrafenib)

Efficacy of Tafinlar® (dabrafenib) in treating metastatic melanoma is supported by one Phase III (n = 250), open-label RCT, two Phase II open-label studies, and a trial of dabrafenib plus trametinib combination therapy vs. dabrafenib monotherapy. PFS on dabrafenib was 5.1 months vs. 1.5 months on dacarbazine (p<0.0001). Six-month OS was 87% with dabrafenib vs. 79% with dacarbazine (95% CI: 0.25-1.48). In the phase II trial of patients with brain metastases, the overall intracranial response (OIR) was 39.2% (95% CI: 15.7, 21.9) in patients who had not received localized brain treatment (cohort A) vs. 30.8% (25.6, NR) in those who had (cohort B). Cohort A patients had a PFS of 16.1 weeks and an OS of 33.1 weeks. In the small phase II trial, the ORR was 59% (48.2, 70.3) for V600E (+) patients and 13% (0, 28.7) for V600K (+) patients. The PFS was 27.4 (19.9, 33.4) weeks, and after 6.5 months of treatment, 70% patients were still alive. At present, dabrafenib is approved only for monotherapy and NCCN recommendations agree with the label.



## **Mekinist™ (trametinib)**

Mekinist™ (trametinib) is the first mitogen-activated extracellular signal regulated kinase (MEK) inhibitor to receive FDA approval. Efficacy of trametinib in treating metastatic melanoma is supported by one Phase III, 22 patient published open-label RCT, a small Phase II study comparing trametinib in patients with or without prior exposure to BRAF inhibitor therapy (dabrafenib or vemurafenib), and a trial of trametinib + dabrafenib combination therapy vs dabrafenib monotherapy. Compared to standard chemotherapy (either dacarbazine or paclitaxel), PFS on trametinib was 4.8 months vs. 1.5 months on chemotherapy ( $p < 0.001$ ). Overall survival rate at 6 months was 81% with trametinib vs. 67% with chemotherapy ( $p = 0.01$ ). The smaller study had no statistically significant outcomes but did find a trend toward much earlier disease progression in patients that had previously seen a BRAF inhibitor. The BRAFI-experienced arm was stopped prematurely for futility.

Combination therapy with dabrafenib is supported by one Phase II RCT comparing dabrafenib/trametinib with dabrafenib monotherapy. PFS was about 9.3 months with combination therapy vs. 5.8 months with dabrafenib alone. After a median follow up of 14.1 months, 23 patients were still surviving and receiving treatment in each of the combination groups vs. only 3 patients in the dabrafenib monotherapy group. At present, dabrafenib is approved only for monotherapy. NCCN guidelines recommend that trametinib be used as monotherapy in patients that have not tolerated dabrafenib or vemurafenib.

## **Zelboraf® (vemurafenib)**

In BRIM-3, 675 patients, 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. Patients ranged in age from 17 to 86 years and had Eastern Cooperative Oncology Group (ECOG) performance scores 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). Patients were randomized to receive Zelboraf® (vemurafenib) 960 mg orally twice daily or dacarbazine 1000 mg/m<sup>2</sup> 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 patients) 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 patients to the vemurafenib group due to the magnitude of effect.

## ***BRAF<sup>V600E</sup> Mutation and Response to Dabrafenib, Trametinib and Vemurafenib***

BRAF (B member of the Rapidly Accelerated Fibrosarcoma family of serine/threonine tyrosine kinases) is a protein that in normal melanocytes is part of the mitogen-activated protein kinase (MAPK) – extracellular signal-regulated kinase (ERK) signal transduction pathway. This signaling pathway controls cell growth, survival, differentiation and senescence. More than 40 mutations of BRAF are known in human cancer, 90% to 95% of which are V600E, in which glutamic acid is substituted for valine at amino acid position 600. Mutated BRAF leads to constitutive activation of the MAPK-ERK signaling pathway, resulting in tumor maintenance and progression. BRAF mutation may be a negative prognostic indicator in metastatic melanoma.

## **K-Ras Mutations and Their Impact on the Clinical Effectiveness EGFR 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, patient 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 patients taking combination therapy of cetuximab with irinotecan, while no difference in overall survival was seen in the same patients 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 patients, 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 progression-free-survival (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 patients, a statistically significant difference in PFS was seen (HR 0.45, 95% CI: -.34-0.59). One study with patients 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 patients. 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 patients. Five hundred seventy-two patients were enrolled in the original clinical trial, of which tissue samples were examined for 394 patients (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 patients with wild type K-Ras. There was no difference in survival between cetuximab and supportive care groups for patients with K-Ras mutations.

## NCCN Drug Compendium

This policy is in agreement with the March 2010 National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium indications and uses of drugs listed in the Categories of Evidence and consensus of 1 and 2A as proven and Categories of Evidence and Consensus of 2B and 3 as unproven. However, Category 2B uses may be considered for coverage if they are substantiated by provider submission of significant peer-reviewed phase II or phase III studies demonstrating treatment effectiveness.

In 2009, Schneider et al. studied the effect of various polymorphisms involving the EGFR signaling pathway in 311 patients receiving erlotinib in NSCLC. None of 17 patients with a KRAS mutation had a tumor response, but the impact of KRAS mutation status on survival outcomes was of borderline statistical significance. Similarly, Miller et al. studied a series of 101 patients with bronchioalveolar carcinoma, of which no patient (zero of 18; 95% CI: 0% to 19%) whose tumor harbored a KRAS mutation responded to erlotinib.

This policy also includes pazopanib labeled indications and off-label use in agreement with March 2010 NCCN Drugs and Biologics Compendium recommendations of 1 and 2A. A single good quality trial has been published with pazopanib. The double blind, placebo controlled, phase III trial in 435 patients with advanced or metastatic clear cell RCC found pazopanib significantly improved the progression free survival (PFS) by five months ( $p < 0.0001$ ) as well as



the overall response rate (30% with pazopanib vs. 3% with placebo,  $p < 0.001$ ). Overall survival data are not yet available.

Based on the RCT data above, the NCCN designated pazopanib among first line agents for metastatic RCC. This recommendation is based on Category 1 RCT evidence.

Results from several Phase II trials are also available. An open label, non-randomized trial in metastatic RCC found response rates similar to those seen in the Phase III RCC trial. Additional Phase II trials in non-FDA approved indications found positive responses warranting further study with soft tissue sarcoma and HER2+ breast cancer. The breast cancer trial found decreased progressive disease rates in patients randomized to pazopanib + lapatinib compared to lapatinib alone. Positive results were not seen in a Phase II non-small cell lung cancer trial.

No meta-analysis or head to head trials are available with pazopanib. Unfortunately, no trials are available comparing pazopanib and interferon- $\alpha$ , the comparator in the majority of trials with other tyrosine kinase inhibitors for RCC (sunitinib, sorafenib, temsirolimus and bevacizumab/IFN). A Phase III trial comparing pazopanib and sunitinib is currently recruiting patients.

Common adverse events with pazopanib include increased LFTs (53%), diarrhea (52%), hypertension (40%), changes in hair color (38%) and nausea (26%). Due to adverse events, dose interruptions were required in 42% of patients on pazopanib during clinical trials and a dose reduction was needed in 36% of patients.

Pazopanib carries a black box warning for hepatotoxicity as deaths have occurred during clinical trials (0.2%). LFTs should be monitored monthly for four months, then periodically. The package insert contains detailed instructions for monitoring and dose reductions with elevated LFTs. Hypertension reported in clinical trials was defined as SBP  $> 150$  and/or DBP  $> 100$ . Treatment with antihypertensives is recommended. Additional recommended monitoring includes TSH, UA as well as ECG and electrolytes due to a risk of QT prolongation ( $< 2\%$ ). Pazopanib increases the risk of both hemorrhage and arterial thrombotic events and is not recommended in patients with hemoptysis, hemorrhage, MI or stroke in the last six months. Finally, use is not recommended within 7 days of surgery due to impaired wound healing.

In comparison with other tyrosine kinase inhibitors for RCC, pazopanib is associated with more hypertension than other agents. However, less rash, fatigue, creatinine increases and anemia are seen with pazopanib than other agents. LFT increases with pazopanib are similar to those seen with sunitinib.

Initial research indicates that biomarkers such as VHL mutation status and sVEGF-2 levels may predict which patients will have an improved response to tyrosine kinase therapy for RCC.



However, additional research is needed linking biomarkers with progression free survival or overall survival. The NCCN does not recommend the assessment of biomarkers prior to the initiation of treatment for RCC.

## 2014 Update

A literature search was conducted from January 2013 to June 4, 2014. A Phase III trial (N=330) compared cabozantinib (140mg) with placebo in patients 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 patients receiving cabozantinib than placebo (8% vs 16%). A Phase II trial in patients 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).

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 patients with the V600E mutation (N=76), 59% of patients had a confirmed response and 7% had a complete response. In patients 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). Patients with the BRAF-V600K mutation may still benefit from treatment with dabrafenib, indicated by comparable median overall survival to patients 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. Patients treated with sunitinib had a higher incidence of fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%), while patients 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 patients with metastatic gastroenteropancreatic neuroendocrine tumors (pancreatic or colorectal, N=37), with a primary endpoint of objective response rate according to the Response Evaluation Criteria in Solid Tumors (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  $\geq$  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  $\geq$  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 patients 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 patients 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 patients 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%) patients 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 patients receiving axitinib, and 24 (25%) of 96 patients 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 patients with a diastolic blood pressure  $\geq 90$  mm Hg compared with  $\leq 90$  mm 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,<sup>7</sup> 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 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.

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## 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 <i>Vandetanib (Caprelsa®)</i> ; 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 patients 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 patients with unresectable or metastatic melanoma with BRAFV600 mutations. (Testing will be covered whenever use of trametinib is contemplated.) Policy statements added for nlyta (axitinib) to policy for RCC;and, Imbruvica (ibrutinib) to policy for MCL and 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.



Date	Comments
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.

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



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**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.



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Civil Rights Coordinator - Complaints and Appeals  
PO Box 91102, Seattle, WA 98111  
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357  
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services  
200 Independence Avenue SW, Room 509F, HHH Building  
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)  
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この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

**한국어 (Korean):**

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

**ລາວ (Lao):**

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວົ້ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

**ភាសាខ្មែរ (Khmer):**

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងដូចជា ធានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអនាគតរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

**ਪੰਜਾਬੀ (Punjabi):**

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

**فارسی (Farsi):**

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

**Polskie (Polish):**

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

**Português (Portuguese):**

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

**Română (Romanian):**

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

**Русский (Russian):**

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

**Fa'asamoa (Samoan):**

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

**Español (Spanish):**

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

**Tagalog (Tagalog):**

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

**ไทย (Thai):**

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

**Український (Ukrainian):**

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

**Tiếng Việt (Vietnamese):**

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).