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PHARMACY / MEDICAL POLICY – 5.01.540

Miscellaneous Oncology Drugs

Effective Date:	July 1, 2018	RELATED MEDICAL POLICIES:	
Last Revised:	June 22, 2018	5.01.543	General Medical Necessity Criteria for Companion Diagnostics Related to Drug Approval
Replaces:	N/A		

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EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Chemotherapy, often called chemo, is cancer treatment that uses drugs. Radiation and surgery treat one area of cancer. But chemo usually travels through the bloodstream to treat the whole body. Treating the whole body is called a systemic treatment. The goal of chemo is to either treat cancer or ease its symptoms. Treating cancer can be to cure it, decrease the chance it will return, or stop or slow its growth. Easing cancer symptoms without trying to cure the cancer is called palliative therapy. Chemotherapy drugs can be used in many different ways. Chemo can make a tumor smaller before surgery or radiation, destroy cancer cells that surgery or radiation didn't treat, help other treatments work better, or kill cancer cells that have come back or spread. Chemotherapy is given in different ways. This includes by mouth (oral), through a vein (intravenous), by a shot (injection), or with a cream rubbed onto the skin (topical). In some cases chemo is injected between the layers of tissue covering the brain and spinal cord (intrathecal), is given into the belly area (intraperitoneal), or is injected into an artery (intra-arterial). This policy gives information about many different types of chemo drugs and the criteria for when they may be 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 drugs listed below will be 3 months. Continued approval beyond the first 3 months will require documentation of objective response to therapy (depending on the type of malignancy).

Drug	Medical Necessity
Oral Drugs	
Erivedge® (vismodegib)	**Erivedge® (vismodegib) may be considered medically necessary for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.**
Idhifa® (enasidenib)	**Idhifa® (enasidenib) may be considered medically necessary for the treatment of relapsed or refractory acute myeloid leukemia (AML) in patients with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.**
Odomzo® (sonidegib)	**Odomzo® (sonidegib) may be considered medically necessary for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.**
Lynparza® (olaparib)	**Lynparza® (olaparib) may be considered medically necessary as monotherapy in patients who meet the following criteria:** • BRCA positive germ cell line or mutations associated with ovarian cancer (as confirmed by genetic testing, see **Related Policies**) **AND** • When there is recurrent disease after 3+ prior lines of chemotherapy regimens **OR** • Maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who are in a complete or partial response to platinum-based chemotherapy **OR** • Deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-

Drug	Medical Necessity
Oral Drugs	
	negative metastatic breast cancer (as confirmed by genetic testing, see **Related Policies**) who have been previously treated with chemotherapy either in the neoadjuvant, adjuvant or metastatic setting • Patients with hormone receptor (HR)- positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy
Ibrance® (palbociclib)	**Ibrance® (palbociclib) may be considered medically necessary:** • In combination with any aromatase inhibitor for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced Stage IV breast cancer as initial endocrine-based therapy for their metastatic disease • In combination with Faslodex® (fulvestrant) for the treatment of recurrent or metastatic estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer that has progressed on endocrine therapy for postmenopausal women or premenopausal women receiving ovarian suppression with an LHRH agonist • For the treatment of soft tissue sarcoma ○ Well-differentiated/dedifferentiated liposarcoma (WD-DDLS)
Kisqali® (ribociclib)	**Kisqali® (ribociclib) may be considered medically necessary when:** • Used in combination with anaromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer **Use as maintenance therapy following response to chemotherapy regimens is considered not medically necessary.**
Lonsurf® (trifluridine and tipiracil)	**Lonsurf® (trifluridine and tipiracil) may be considered medically necessary for treatment of patients with metastatic colorectal cancer who have been previously treated with**

Drug	Medical Necessity
Oral Drugs	
	fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if the tumor is RAS wild-type, also previously treated with an anti-EGFR therapy.
Ninlaro® (ixazomib)	**Ninlaro® (ixazomib) may be considered medically necessary when used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.**
Rubraca® (rucaparib)	**Rubraca® (rucaparib) may be considered medically necessary for the treatment of adult patients with:** • Deleterious BRCA mutation (germline and/or somatic) associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies • Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy as maintenance treatment **Note:** Patients are to be selected for therapy based on an FDA-approved companion diagnostic for Rubraca.
Zejula® (niraparib)	**Zejula® (niraparib) may be considered medically necessary for the treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.** • Patient must be considered to have platinum sensitive disease, defined as having a complete or partial response and disease progression more than 6 months after completion of the last round of platinum therapy
Rydapt® (midostaurin)	**Rydapt®(midostaurin) may be considered medically necessary for the treatment of adult patients with:** • Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation

Drug	Medical Necessity
Oral Drugs	
	○ Documentation of genetic testing is required for coverage consideration **Note:** Rydapt® is not indicated as a single-agent induction therapy for the treatment of patients with AML Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
Verzenio™ (abemaciclib)	**Verzenio™ (abemaciclib) may be considered clinically necessary for the treatment of adult patients who meet ONE of the following indications:** • In combination with Faslodex® (fulvestrant) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in women with disease progression following endocrine therapy **OR** • As monotherapy for the treatment of HR-positive, HER2 – negative advanced or metastatic breast cancer in patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

Drug	Medical Necessity
Injectable Drugs	
Opdivo® (nivolumab)	**Opdivo® (nivolumab) may be considered medically necessary for treatment of any of the following:** • BRAF V600 wild type unresectable or metastatic melanoma as a single agent; BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent • Unresectable or metastatic melanoma, in combination with Yervoy® (ipilimumab) • Intermediate or poor-risk, previously untreated advanced renal cell carcinoma, in combination with Yervoy® (ipilimumab) • Melanoma with lymph node involvement or metastatic disease

Drug	Medical Necessity
Injectable Drugs	
	who have undergone complete resection, in the adjuvant setting • Metastatic non-small cell lung cancer (NSCLC) and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK/ROS1 genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo® (nivolumab) • Advanced renal cell carcinoma who have received prior anti-angiogenic therapy • Classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin OR three or more lines of systemic therapy that includes autologous HSCT • Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy • Locally advanced or metastatic urothelial carcinoma in patients with: ○ Disease progression during or following platinum-containing chemotherapy ○ Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy • Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan • Hepatocellular carcinoma who have been previously treated with sorafenib
Opdivo® (nivolumab) in combination with Yervoy® (ipilimumab)	**Opdivo® (nivolumab) in combination with Yervoy® (ipilimumab) may be considered medically necessary:** • For treatment of unresectable or metastatic melanoma. • For treatment of patients with intermediate or poor-risk, previously untreated advanced renal cell carcinoma
Keytruda®	**Keytruda® (pembrolizumab) may be considered medically**

Drug	Medical Necessity
Injectable Drugs	

(pembrolizumab)	**necessary:**
	• For unresectable or metastatic melanoma
	• For metastatic non-small cell lung cancer (NSCLC):
	  ○ First-line as a single agent in patients with PD-L1 protein overexpression (ie, greater than 50% of cells positive for PD-L1), with no EGFR or ALK/ROS1 genomic tumor mutations
	  ○ First-line when used in combination with pemetrexed and carboplatin
	  ○ In patients with PD-L1 expression with disease progression on or after platinum-containing chemotherapy treatment
	  ○ In patients with EGFR or ALK/ROS1 genomic mutations who have disease progression on FDA approved therapy for these mutations (ie anti-EGFR or anti-ALK/ROS1 agents)
	• For patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy
	• For patients with refractory Classical Hodgkin Lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy
	• For locally advanced or metastatic urothelial carcinoma:
	  ○ In patients who are not eligible for cisplatin-containing chemotherapy
	  ○ In patients who have disease progression during or following platinum-containing therapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
	• For patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient:
	  ○ Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
	  ○ Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
	• For patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1, with disease progression on or after ≥2

Drug	Medical Necessity
Injectable Drugs	
	prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy **Note:** FDA-approved testing confirming presence of PD-L1, EGFR, or ALK/ROS1 proteins is required before coverage determination for Keytruda can be established.

Yervoy® (ipilimumab)	**Yervoy® (ipilimumab) may be considered medically necessary for:**
	• Treatment of unresectable or metastatic melanoma when used:
	  ○ In combination with Opdivo® (nivolumab) as first-line therapy
	  ○ As a single agent or in combination with Opdivo® (nivolumab) as second-line or subsequent therapy for disease progression for patients with performance status 0-2 if not previously used
	  ○ As a single agent or in combination with Opdivo® (nivolumab)after maximum clinical benefit from BRAF targeted therapy for patients with performance status 0-2
	  ○ As a single agent or in combination with Opdivo® (nivolumab) as re-induction therapy for patients with performance status 0-2 who experience disease control and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation
	• Treatment of patients with intermediate or poor-risk, previously untreated advanced renal cell carcinoma when used in combination with Opdivo® (nivolumab).
	• Adjuvant treatment for cutaneous melanoma as a high-dose single agent for:
	  ○ Stage III sentinel lymph node positive metastasis >1 mm following a complete lymph node dissection
	  ○ Stage III disease with clinically positive node(s) following wide excision of primary tumor and a complete therapeutic lymph node dissection

Drug	Medical Necessity
Injectable Drugs	
	○ Following complete lymph node dissection and/or complete resection of nodal recurrence • As a single agent treatment for brain metastases if active against primary tumor (melanoma) in patients with recurrent disease
Gazyva® (obinutuzumab)	**Gazyva® (obinutuzumab) may be considered medically necessary:** • In combination with chlorambucil, for previously untreated chronic lymphocytic leukemia (CLL) • In combination with bendamustine followed by Gazyva® monotherapy, for relapsed or refractory follicular lymphoma, following a rituximab-containing regimen
Tecentriq® (atezolizumab)	**Tecentriq® (atezolizumab) may be considered medically necessary for:** • The treatment of patients with locally advanced or metastatic urothelial carcinoma who: ○ Have disease progression during or following platinum-containing chemotherapy **OR** ○ Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy **OR** ○ Are not eligible for cisplatin-containing chemotherapy **The treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK/ROS1 genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations (ie, anti-EGFR or anti-ALK/ROS1 agents) prior to receiving Tecentriq®.**
Lartruvo® (olaratumab)	**Lartruvo® (olaratumab) may be considered medically necessary when:** • Used in combination with doxorubicin, for the treatment of

Drug	Medical Necessity
Injectable Drugs	
	adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate, and which is not amenable to curative treatment with radiotherapy or surgery **Please note that Lartruvo® is considered not medically necessary in the setting of:** • Osteosarcoma • Kaposi sarcoma • Gastrointestinal stromal tumor (GIST)

Bavencio® (avelumab)	**Bavencio® (avelumab) may be considered medically necessary for the treatment of:**
	• Adults and pediatric patients 12 years and older with metastatic Merkel Cell Carcinoma (MCC)
	• Patients with locally advanced or metastatic urothelial carcinoma who:
	  ○ Have disease progression during or following platinum-containing chemotherapy
	  ○ Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Imfinzi® (durvalumab)	**Imfinzi® (durvalumab) may be considered medically necessary for the treatment of:**
	• Adult patients with locally advanced or metastatic urothelial carcinoma who:
	  ○ Have disease progression during or following platinum-containing chemotherapy
	  ○ Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
	• Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy

Aliqopa™ (copanlisib)	**Aliqopa™ (copanlisib) may be considered medically necessary for the treatment of:**

Drug	Medical Necessity
Injectable Drugs	
	• Adult patients with relapsed/refractory follicular lymphoma who: ○ Have received at least two prior systemic therapies (ie, bendamustine + rituximab, RCHOP (rituximab, cyclophosphamide, doxorubicin, prednisone), RCVP (rituximab, cyclophosphamide, vincristine, prednisone)) **Note:** Examples of systemic therapies listed above are **not** all inclusive of potential systemic therapies.

Length of Approval	
Approval	**Criteria**
Initial Approval: All oral oncology drugs, unless otherwise specified	**Initial approval for three months, according to the medical necessity criteria specified for each drug.**
Reauthorization	**Continued therapy will be approved for periods of one year as long as the drug-specific conditions are met, and the patient has shown and continues to show clinical benefit.**
Documentation	**Initial**: Chart notes demonstrating that the patient meets the stated criteria for medical necessity. **Reauthorization**: Chart notes demonstrating that the patient continues to show clinical benefit.

Investigational
All other uses of Aliqopa™, Bavencio®, Erivedge®, Gazyva®, Ibrance®, Idhifa®, Imfinzi®, Keytruda®, Kisqali®, Lartruvo®, Lonsurf®, Lynparza®, Ninlaro®, Odomzo®, Opdivo®, Rubraca®, Rydapt®, Tecentriq®, Verzenio™, Yervoy®, and Zejula® not listed in this policy are considered investigational.

Coding

Code	Description
HCPCS	
J3490	Unclassified drugs
J9022	Injection, atezolizumab (Tecentriq®), 10 mg (new code effective 1/1/18)
J9023	Injection, avelumab (Bavencio®), 10 mg (new code effective 1/1/18)
J9228	Injection, ipilimumab (Yervoy®), 1 mg
J9271	Injection, pembrolizumab (Keytruda®), 1 mg
J9285	Injection, olaratumab (Lartruvo®), 10 mg (new code effective 1/1/18)
J9299	Injection, nivolumab (Opdivo®), 1 mg
J9301	Injection, obinutuzumab (Gazyva®), 10 mg

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

Related Information

Description

Opdivo® (nivolumab)

Opdivo® (nivolumab) is a human monoclonal antibody to programmed death receptor-1 (PD-1), which is expressed on antigen-stimulated T cells and induces downstream signaling that inhibits T-cell proliferation, cytokine release, and cytotoxicity. Melanoma and many other tumors express PD-1 ligand (PD-L1) on the cell surface, resulting in suppression of cytotoxic T-cell activity.

Lynparza™ (olaparib)

Ovarian cancer (OC) is the leading cause of death in women with gynecological cancer and is the 5th most common cause of cancer mortality in women. Most patients are diagnosed at advanced stage (stage III or above) with a median age of diagnosis at 63. Epithelial ovarian cancer accounts for the majority (90%) of OC cases. The incidence rate for ovarian cancer between 2006 and 2010 was 12.5 cases per 100,000 women. Women with a family history of

ovarian cancer, such as first-degree family members with ovarian cancer and BRCA1 or BRCA2 mutation, are at increased risk of developing advanced OC. Other risk factors for ovarian cancer include nulliparity, older age at pregnancy and first birth, hormone therapy, pelvic inflammatory disease, etc.

Possible causes of OC include incessant ovulation, increasing age and hormonal exposure. Epithelial OC comprises the majority of primary OC. Histologically, serous tumors account for the majority and are typically associated with a poorer prognosis. Due to deleterious mutations of a tumor suppressor BRCA genes, about 10-15% of epithelial OC and up to 50% of high-grade serous tumors are affected by homologous DNA repair defects. The enzymes poly (ADP-ribose) polymerase (PARP) are required for efficient DNA repair. Inhibition of PARP ensures that DNA breaks cannot be repaired and thus results in cell death. Lynparza™ (olaparib) is an inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and most notably DNA repair. Olaparib disrupts cellular homeostasis and induces cell death by inhibiting PARP enzymatic activity. In the presence of deleterious BRCA mutation, DNA single strand breaks occur which would require PARP enzymes for repair. PARP inhibitors disable this repair pathway rendering cell death.

Current standard treatment for advanced OC include cytoreductive surgery followed by chemotherapy with platinum and taxane based agents. However, there is a high risk for recurrence and developing drug resistance. Patients who relapse within 6 months after initial chemotherapy are termed platinum-resistant. Platinum resistance is associated with lower subsequent response rate to subsequent regimens and lower survival.

Zejula® (niraparib)

Zejula® (niraparib) offers a significant increase in PFS in patients with platinum sensitive recurrent epithelial ovarian cancer. This is also the first PARPi to demonstrate efficacy in this population irrespective of BRCA mutation status. This is useful in that the patient will not be required to undergo expensive genetic testing prior to therapy.

The evidence supporting Zejula's efficacy is sufficient and was demonstrated in the multi-center, randomized, double-blind, placebo-controlled ENGOT-OV16/NOVA trial that included 553 patients. The once-daily dosing and oral dosage form are also aspects which increase ease of use. Zejula has an extremely diverse adverse effect profile including an increased risk in MDS/AML and a warning for fetal toxicity. Post-marketing surveillance and patient reporting will be critical.

Erivedge® (vismodegib)

Erivedge® (vismodegib) is a Hedgehog pathway inhibitor. It binds to and inhibits Smoothened, a trans-membrane protein involved in Hedgehog signal transduction. It is indicated for treatment of advanced or metastatic basal cell carcinoma. While this cancer is most frequently cured by simple resection of the skin lesion, patients occasionally present with tumors that have remained untreated for a long period of time and as a result are either metastatic or have spread locally so as to be unresectable. Vismodegib was approved to provide a nonsurgical alternative for these patients.

Odomzo® (sonidegib)

The safety of ODOMZO was evaluated in Study 1, a randomized, double-blind, multiple cohort trial in which 229 patients received ODOMZO at either 200 mg (n=79) or 800 mg (n=150) daily. The frequency of common adverse reactions including muscle spasms, alopecia, dysgeusia, fatigue, nausea, decreased weight, decreased appetite, myalgia, pain, and vomiting was greater in patients treated with ODOMZO 800 mg as compared to 200 mg. The data described below reflect exposure to ODOMZO 200 mg daily in 79 patients with locally advanced BCC (laBCC; n=66) or metastatic BCC (mBCC; n=13) enrolled in Study 1. Patients were followed for at least 18 months unless discontinued earlier. The median duration of treatment with ODOMZO was 11.0 months (range 1.3 to 33.5 months). The study population characteristics were: median age of 67 years (range 25 to 92; 59% were ≥65 years), 61% male, and 90% white. The majority of patients had prior surgery (75%), radiotherapy (24%), systemic chemotherapy (4%), or topical or photodynamic therapies (18%) for treatment of BCC. No patient had prior exposure to a hedgehog pathway inhibitor. ODOMZO was permanently discontinued in 34% of patients or temporarily interrupted in 20% of patients for adverse reactions. Adverse reactions reported in at least two patients that led to discontinuation of the drug were: muscle spasms and dysgeusia (each 5%), asthenia, increased lipase, and nausea (each 4%), fatigue, decreased appetite, alopecia, and decreased weight (each 3%). Serious adverse reactions occurred in 18% of patients. The most common adverse reactions occurring in ≥10% of patients treated with ODOMZO 200 mg were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

Ibrance® (palbociclib)

Ibrance® (palbociclib) is an orally active selective and reversible inhibitor of CDK 4/6. The agent halts the progression of the cell cycle at G1 via its selective inhibition of CDK 4/6, thereby preventing cellular proliferation. Palbociclib is indicated in combination with letrozole for the treatment of postmenopausal women with ER+/HER2- advanced breast cancer as initial endocrine-based therapy for metastatic disease.

This indication was approved under accelerated approval based on PFS and continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial. The current approval was based on data from an international, randomized, double-blind, placebo-controlled, clinical trial (PALOMA-2) that randomized 666 postmenopausal women (2:1) to palbociclib plus letrozole or placebo plus letrozole. Palbociclib 125 mg or placebo was administered orally once daily for 21 consecutive days, followed by 7 days off. Letrozole 2.5 mg was administered orally once daily. Treatment continued until disease progression or unacceptable toxicity. The median progression-free survival (PFS) was 24.8 months in the palbociclib plus letrozole arm and 14.5 months in the placebo plus letrozole arm (HR=0.576, 95% CI: 0.463, 0.718, p<0.0001). Overall survival data are immature.

Safety data was evaluated in 444 patients who received palbociclib plus letrozole. Neutropenia was the most frequently reported adverse reaction in PALOMA-2 with an incidence of 80%. The most common adverse reactions observed in 10% or more of patients taking palbociclib were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. The most frequently reported grade 3 or greater adverse reactions in patients receiving palbociclib plus letrozole were neutropenia, leukopenia, infections, and anemia

Kisqali® (ribociclib)

Kisqali® (ribociclib) offers a favorable overall response rate of 52.7% versus 37.1% in the ribociclib plus letrozole versus the placebo plus letrozole, respectively, and a median duration of response hazard ratio of 0.59 (95% CI: 0.41,0.85, P=.002). The evidence supporting efficacy are limited to the completed placebo-controlled and ongoing dose expansion-crossover Phase 3 trials, it does however present in favor of ribociclib when used in combination with letrozole. This drug is conveniently dosed in an oral, film-coated tablet has a diverse adverse effect profile with an increased risk of QT prolongation, hepatobiliary toxicity, neutropenia, embryo-fetal toxicity, and a warning for avoidance of the use in pregnancy. Post-marketing surveillance and close-monitoring will be critical.

Rydapt® (midostaurin)

Rydapt® (midostaurin) is approved for the first-line treatment of adults with FMS-like tyrosine kinase 3 mutation-positive (FLT3+) acute myeloid leukemia (AML) as detected by an FDA-approved test, in combination with chemotherapy. It is also approved to treat adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN) or mast cell leukemia (MCL). The recommended dose for AML is 50mg twice daily with food. For ASM, SM-AHN and MCL, the recommended dose is 100mg twice daily with food. It will be available through open distribution.

This is the first significant advance in treatment of a subset of AML patients. AML is difficult to treat, with one year survival rates less than 50%.

The safety and efficacy of Rydapt for patients with AML were studied in a randomized trial of 717 patients who had not been treated previously for AML. In the trial, patients who received Rydapt in combination with chemotherapy lived longer than patients who received chemotherapy alone, although a specific median survival rate could not be reliably estimated. In addition, patients who received Rydapt in combination with chemotherapy in the trial went longer (median 8.2 months) without certain complications (failure to achieve complete remission within 60 days of starting treatment, progression of leukemia or death) than patients who received chemotherapy alone (median three months).

Common side effects of Rydapt in patients with AML include low levels of white blood cells with fever (febrile neutropenia), nausea, inflammation of the mucous membranes (mucositis), vomiting, headache, spots on the skin due to bleeding (petechiae), musculoskeletal pain, nosebleeds (epistaxis), device-related infection, high blood sugar (hyperglycemia) and upper respiratory tract infection. Rydapt should not be used in patients with hypersensitivity to midostaurin or other ingredients in Rydapt. Women who are pregnant or breastfeeding should not take Rydapt because it may cause harm to a developing fetus or a newborn baby. Patients who experience signs or symptoms of lung damage (pulmonary toxicity) should stop using Rydapt.

Rydapt was also approved today for adults with certain types of rare blood disorders (aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm or mast cell leukemia). Common side effects of Rydapt in these patients include nausea, vomiting, diarrhea, swelling (edema), musculoskeletal pain, abdominal pain, fatigue, upper respiratory tract infection, constipation, fever, headache and shortness of breath.

Keytruda® (pembrolizumab)

Keytruda® (pembrolizumab) is a programmed death receptor-1 (PD-1)-blocking antibody which is expressed on antigen-stimulated T-cells and induces downstream signaling that inhibits T-cell proliferation, cytokine release, and cytotoxicity. Melanoma and many other tumors express PD-1 ligand (PD-L1) on the cell surface, resulting in suppression of cytotoxic T-cell activity, allowing the tumor to proliferate unchecked.

Yervoy® (ipilimumab)

Yervoy® (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

Gazyva® (obinutuzumab)

Gazyva® (obinutuzumab) targets the CD20 antigen expressed on the surfaces of pre-B and mature B-lymphocytes. After binding, obinutuzumab mediates B-cell lysis by engaging immune effector cells, directly activating direct cell death pathways, and/or activating the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis.

Tecentriq® (atezolizumab)

Tecentriq® (atezolizumab) is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth. PD-L1 may be expressed on tumor cells and/or tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1

receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Bavencio® (avelumab)

Bavencio® (avelumab) is the first FDA approved pharmacotherapy for Merkel cell carcinoma. avelumab offers a significant increase in ORR and median DOR in patients with histologically confirmed stage IV Merkel cell carcinoma refractory to chemotherapy. Efficacy was demonstrated irrespective of PD-L1 status, eliminating the need for expensive genetic testing prior to therapy administration.

To the evidence supporting avelumab's efficacy was demonstrated in the JAVELIN Merkel 200 trial. The multi-center, open-label, non-randomized trial included 88 patients with stage IV Merkel cell carcinoma. The efficacy results yielded an ORR of 33.0% (95% CI, 23.3-34.8) with a complete response rate of 11.4% (95% CI, 6.6-19.8) and a partial response rate of 21.6% (95% CI, 13.5-31.7). At the time of the data cutoff the median duration of response had not been reached and response duration had ranged from 2.8 months to 23.3+ months.

Imfinzi® (durvalumab)

Infinzi® (durvalumab) received accelerated FDA approval. It is a programmed death ligand 1 (PD-L1) inhibitor approved for use in patients whose locally advanced or metastatic urothelial carcinoma (bladder, ureter and/or urethra cancer) progresses during or following platinum-containing chemotherapy. Durvalumab also is indicated for patients who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. It is administered once every two weeks as a one-hour IV infusion.

Lonsurf® (trifluridine and tipiracil)

Lonsurf® is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor. Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against KRAS wild-type and mutant human colorectal cancer xenografts in mice.

Ninlaro® (ixazomib)

Ninlaro® (ixazomib) is a reversible proteasome inhibitor. It preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. Ixazomib induced apoptosis of multiple myeloma cell lines in vitro. It demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. In vivo, ixazomib demonstrated antitumor activity in a mouse multiple myeloma tumor xenograft model.

Lartruvo® (olaratumab)

Lartruvo® (olaratumab) is a human IgG1 antibody that binds platelet-derived growth factor receptor alpha (PDGFR- α). PDGFR- α is a receptor tyrosine kinase expressed on cells of mesenchymal origin. Signaling through this receptor plays a role in cell growth, chemotaxis, and mesenchymal stem cell differentiation. The receptor has also been detected on some tumor and stromal cells, including sarcomas, where signaling can contribute to cancer cell proliferation, metastasis, and maintenance of the tumor microenvironment. The interaction between olaratumab and PDGFR- α prevents binding of the receptor by the PDGF-AA and –BB ligands as well as PDGF-AA, -BB, and –CC-induced receptor activation and downstream PDGFR- α pathway signaling. Olaratumab exhibits in vitro and in vivo anti-tumor activity against selected sarcoma cell lines and disrupted the PDFGR- α signaling pathway in vivo tumor implant models.

Rubraca® (rucaparib)

Rubraca® (rucaparib) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. In vitro studies have shown that rucaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased rucaparib-induced cytotoxicity was observed in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumor growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.

Verzenio™ (abemaciclib)

Verzenio™ (abemaciclib) selectively inhibits cyclin-dependent kinases (CDK) 4 and 6 (CDK 4/6), It blocks retinoblastoma tumor suppressor protein phosphorylation and prevents progression through the cell cycle, resulting in arrest at the G1 phase.

Aliqopa™ (copanlisib)

Aliqopa™ (copanlisib) inhibits phosphatidylinositol-3-kinase (PI3K), with activity primarily against PI3K-α and PI3K-δ isoforms expressed by malignant B cells. It leads to tumor cell death via apoptosis and inhibition of proliferating malignant B cell lines. Copanlisib inhibits several signaling pathways: b-cell receptor (BCR) signaling, CXCR12 mediated chemotaxis of malignant B cells, and NFκB signaling in lymphoma cell lines.

Evidence Review

Opdivo® (nivolumab)

The advanced melanoma indication for nivolumab received accelerated biologics license application approval based on tumor response rate and durability of response in one open-label, Phase III trial of nivolumab in adults with unresectable or metastatic melanoma following progression on Yervoy® (ipilimumab) and, if BRAF V600 mutation–positive, a BRAF inhibitor (dabrafenib or vemurafenib). An improvement in survival or disease-related symptoms has not yet been established. Phase III trials are to be submitted by end of 2016. CheckMate-372 was a randomized (2:1), open-label trial in which 370 patients with unresectable or metastatic melanoma received nivolumab 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine or carboplatin plus paclitaxel. Primary end points were ORR, by independent radiology review committee, and overall survival (OS). Secondary end points included progression-free survival (PFS); PD-L1 expression; and health-related quality of life (HRQOL).

Efficacy was assessed in a single-arm, noncomparative, preplanned interim analysis in the first 120 patients who received nivolumab in Trial 1 and in whom the minimum duration of follow-up was 6 months. Data are unpublished and taken from the label. ORR in the efficacy subset was 32% (95% confidence interval [CI], 23 to 41), consisting of 4 complete responses and 34 partial

responses in nivolumab-treated patients. Of the 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer. There were objective responses in patients with and without BRAF V600 mutation–positive melanoma.

Warnings and precautions are generally related to the development of moderate-to-severe immune-mediated reactions in a small number of patients. This results in administration of corticosteroids and either withholding the drug (in the majority of cases) or discontinuation of the drug. Such reactions included immune-mediated pneumonitis (2.2%), colitis (2.2%), hepatitis (1.1%), nephritis or renal dysfunction (0.7%), hyperthyroidism (3%) or hypothyroidism (8%), or other immune-mediated events (<1%). Nivolumab was discontinued for adverse reactions in 9% of patients, while 26% of patients receiving nivolumab had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of patients receiving nivolumab. The most frequent grade 3 and 4 adverse reactions reported in 2% to less than 5% of patients receiving nivolumab were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reaction was rash (> 20%).

Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Trial 9 was a randomized (2:1), active-controlled, open-label study enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting.

The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (eg, mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO administered intravenously (IV) at 3 mg/kg every 2 weeks or investigator's choice of cetuxcimab, methotrexate, or docetaxel.

Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR. In Trial 9, a total of 361 patients were randomized; 240 patients to OPDIVO and 121 patients to investigator's choice (45% received docetaxel, 43% received methotrexate, and 12% received

cetuximab). The median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male. Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/ current smokers, and 90% had Stage IV disease. Forty-five percent of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy. Twenty-five percent had HPVp16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status. The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). The survival results are displayed in Table 20 and Figure 11. There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively).

Urothelial Carcinoma

In Trial 10, 270 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with OPDIVO. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received an intravenous infusion of 3 mg/kg of OPDIVO every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR). The median age was 66 years (range 38 to 90), 78% were male, 86% of patients were white. Twenty-seven percent had non-bladder urothelial carcinoma and 84% had visceral metastases. Thirty-four percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy. Twenty-nine percent of patients had received ≥2 prior systemic regimens in the metastatic setting. Thirty-six percent of patients received prior cisplatin only, 23% received prior carboplatin only, and 7% were treated with both cisplatin and carboplatin in the metastatic setting. Forty-six percent of patients had an ECOG performance status of 1. Eighteen percent of patients had a hemoglobin <10 g/dL, and 28% of patients had liver metastases at baseline. Patients were included regardless of their PD-L1 status. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270

patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients, were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 23. Median time to response was 1.9 months (range; 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Lynparza™ (olaparib)

There is limited evidence from a non-randomized open-label study in patients with deleterious or suspected deleterious gBRCAm-associated advanced ovarian cancer. All patients (N=193) were treated with Lynparza™ (olaparib) with an objective response rate of 31% and a median duration of response of 7.4 months.[5] In the subgroup of patients who had 3 or more lines of prior chemotherapy (n=137), ORR was 34%, mostly classified as partial response (CR 2%, PR 32%). Median duration of response was 7.9 months. A separate randomized open-label study showed similar progression free survival (8.8 vs. 7.1 months) and objective response rate (31% vs. 18%, NS) after treatment with olaparib or pegylated liposomal doxorubicin, respectively, in 97 gBRCAm patients. Over half of the patients had received 3 or more prior chemotherapy regimens.[9] The use of olaparib as a maintenance agent following objective response to chemotherapy was not well supported by current evidence and not approved by the FDA. No evidence of real world effectiveness was found at the time of review. An indirect comparison of response rates for olaparib (from the single pivotal trial) to historically reported response rates of other therapeutic agents in heavily pretreated advanced ovarian cancer patients was performed by the FDA. Estimated response rate to 4th- line alternative chemotherapy regimens is 10-20%,[2] but it is expected gBRCAm patients would have a higher response rate. Olaparib appears to provide at least a similar to a more favorable response rate in this heavily pretreated population, with a response rate of 34% from the pivotal trial.

The incidence of myelodysplastic syndrome and/or acute myeloid leukemia (MDS/AML) in olaparib clinical trials is higher than that reported generally in ovarian cancer patients, 0.8% to 3.1% vs. 0.0033% respectively.[2] Seventeen of the 22 cases found in olaparib clinical trials were fatal. Post-marketing surveillance and monthly monitoring of complete blood count is warranted. Other serious concerns include potential development of secondary malignancy and pneumonitis. Common adverse events include mostly gastrointestinal complaints and fatigue. Anemia is the most frequently reported serious adverse event. In the comparative trial against liposomal doxorubicin, olaparib is associated with numerically less serious adverse events than

liposomal doxorubicin. The most reported serious adverse events were anemia for olaparib and palmar-plantar erythrodysesthesia syndrome for liposomal doxorubicin.

Erivedge® (vismodegib)

Erivedge® (vismodegib) is a Hedgehog pathway inhibitor. It binds to and inhibits Smoothened, a trans-membrane protein involved in Hedgehog signal transduction. The evidence of efficacy was established in the pivotal Phase II open label trial of vismodegib 150mg once daily. This study demonstrated a statistically significant single-agent activity for both locally advanced (42.9% response rate; $p<0.0001$) and metastatic (30.3% response rate; $p=0.0011$) basal cell carcinoma (laBCC and mBCC respectively). Overall median duration of treatment for the combined cohorts (n=104) was 9.7 months (range 1.1 to 18.7 months). The median duration of response was 7.6 months and median progression free survival (PFS) was 9.5 months for both groups (independently). This data is pending press in the New England Journal of Medicine and is currently only available from the manufacturer. Published efficacy data is only available from the extension of the open label Phase I study currently ongoing. As of January 2010, there were 2 patients who achieved complete remission and 17 who achieved partial response from the original 33 patients enrolled in the study who had aBCC (overall response of 57%).

Ibrance® (palbociclib)

Ibrance® (palbociclib) was approved under accelerated approval based on PFS and continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial. A single, randomized Phase II trial demonstrated that the addition of palbociclib to letrozole significantly improved PFS compared to letrozole alone for patients with ER+/HER2- advanced breast cancer. The results for PFS were robust and continued to strongly favor palbociclib plus letrozole in a secondary analysis performed by a blinded independent review committee, across multiple sensitivity analyses and in all studied clinical subgroups. The secondary efficacy endpoint results also consistently favored or trended to favor the combination treatment group. The safety profile of palbociclib plus letrozole appeared to be manageable with the majority of AEs mild to moderate and managed by dose delay and modification. There were no cases of febrile neutropenia seen in the registration trial. The rare incidence of PEs that occurred in patients treated with palbociclib was troubling and will need to be further assessed in the larger Phase III trials, There are several ongoing Phase III trials with palbociclib in pre and postmenopausal patients, in advanced and early breast cancer, in

combination with other agents. Palbociclib has also been studied in several early phase trials for various off-label indications including HCC, MCL, MM, NSCLC, and Rb+ germ cell tumors.

Yervoy® (ipilimumab)

Phase III trials suggested a survival benefit in patients with stage III or IV metastatic melanoma compared to gp-100 (10.1 months vs. 6.4 months). However, the investigators' report of 2 to 3.5 months of increased median overall survival is uncertain due to limitations in the trial design. A majority of immune-related adverse events (irAEs) were reduced upon treatment below their respective baselines. With immediate medical attention and treatment, irAEs are manageable and resolvable.

Clinical trials investigated the safety and efficacy of Yervoy® (ipilimumab) in a randomized, double-blind, placebo-controlled trial in patients with resected Stage IIIA (> 1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) histologically confirmed cutaneous melanoma. Patients were randomized to receive ipilimumab 10 mg/kg or placebo every 3 weeks for 4 doses. Enrollment required complete resection of melanoma with full lymphadenectomy within 12 weeks prior to randomization. Forty-nine percent of the ipilimumab arm experienced recurrence-free survival (RFS), whereas it was 62% in the placebo arm. Fourteen deaths occurred with the intervention and 5 in placebo. The AE rate was more severe at this higher dose compared to 3 mg/kg. Common AEs included rash, pruritus, GI disorders, fatigue, pyrexia, and headache. More severe irAEs included enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy. Endocrine AEs eventually require hormone supplementation.

Gazyva® (obinutuzumab)

Clinical trials explored the safety of Gazyva® (obinutuzumab) in previously untreated patients with CLL. Patients were treated with chlorambucil alone, obinutuzumab + chlorambucil, or rituximab + chlorambucil. Adverse reactions included infusion reactions, neutropenia, thrombocytopenia, leukopenia, pyrexia, diarrhea, constipation, nasopharyngitis, and urinary tract infections. These adverse reactions are consistent with those seen comparing obinutuzumab + chlorambucil to chlorambucil alone except back pain (5% vs. 2%), anemia (12% vs. 10%) and cough (10% vs. 7%), which were observed at a higher incidence in the obinutuzumab treated patients. The incidence of Grade 3-4 back pain (<1% vs. 0%), cough (0% vs. <1%) and anemia (5% vs. 4%) was similar in both treatment arms.

Obinutuzumab was approved on the basis of an improvement in progression-free survival (PFS) in a randomized, open-label, multicenter trial in patients with Follicular Lymphoma, which is a type of the Non-Hodgkin Lymphoma, with no response or who have progressed within 6 months of a rituximab-containing regimen. These patients were randomized to bendamustine alone (n = 166) or bendamustine + obinutuzumab (n = 155) for six 28 day cycles. Patients in the combination arm who had a complete response (CR), partial response (PR), or stable disease (SD) at the end continued obinutuzumab monotherapy for two years. The primary endpoints included PFS. The median PFS in the combination arm was not reported, whereas the bendamustine arm was 13.8 months. The best overall response was 78.7% for obinutuzumab combination and 74.7% for bendamustine alone, which was defined as the best CR/PR within 12 months of initiating therapy. The most common adverse reactions (≥ 10%) were infusion reactions, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia, and urinary tract infections. The most common grade 3-4 reactions (≥ 10%) were neutropenia, thrombocytopenia, and infusion reactions. The safety profile was consistent with the overall indolent non-Hodgkin lymphoma population.

Tecentriq® (atezolizumab)

Tecentriq® (atezolizumab) was approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Tecentriq® (atezolizumab) was investigated in Study 1, a multicenter, open-label, two-cohort trial that included patients with locally advanced or metastatic urothelial carcinoma. In Cohort 2 of Study 1, 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with TECENTRIQ. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents or systemic immunosuppressive medications. Patients received an intravenous infusion of 1200 mg of TECENTRIQ every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter.

Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST

v1.1) and duration of response (DoR). In this cohort, the median age was 66 years, 78% were male, 91% patients were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG score of 1 and 35% of patients had a baseline creatinine clearance of < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens. Tumor specimens were evaluated prospectively using the Ventana PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses.

Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [ICs] covering ≥ 5% of the tumor area). The remaining 68% of patients were classified as having PD-L1 expression of <5% (PD-L1 stained tumor infiltrating ICs covering < 5% of the tumor area). The median follow-up time for this cohort was 14.4 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

Tecentriq® (atezolizumab) in Previously Treated Metastatic NSCLC

The efficacy of Tecentriq® (atezolizumab) was investigated in two multi-center, international, randomized, open-label trials in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen. Study 2 was a trial in 1225 patients with the primary analysis population consisting of the first 850 randomized patients and Study 3 was a trial in 287 patients. In both studies, eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients were randomized (1:1) to receive either TECENTRIQ administered intravenously at 1200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical progression, or docetaxel administered intravenously at 75 mg/m2 every 3 weeks until unacceptable toxicity or disease progression.

These studies excluded patients who had: a history of autoimmune disease, had active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. In Study 2, tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells

(TC) and IC using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

In Study 2, among patients in the primary analysis population, the median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen.

In Study 3, the median age was 62 years (range: 36 to 84), and 59% of patients were male. The majority of patients were white (79%). Approximately two-thirds of patients had non-squamous disease (66%), 7% had known EGFR mutation, 1% had ALK rearrangements, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (33%) or 1 (67%). Approximately two-thirds of patients received only one prior platinum-based therapeutic regimen.

The major efficacy outcome measure of Study 2 was overall survival (OS) in the primary analysis population (first 850 randomized patients).

The major efficacy outcome measure of Study 3 was overall survival (OS). Other efficacy outcome measures for Study 3 included investigator-assessed objective response rates and duration of response per RECIST v1.1. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for prespecified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, which is defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression. Results of an updated survival analysis in Study 3 with a median follow-up of 22 months are provided for all randomized patients.

Lonsurf® (trifluridine and tipiracil)

The clinical efficacy and safety of Lonsurf® (trifluridine and tipiracil) were evaluated in an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (CRC).

A total of 800 patients were randomized 2:1 to receive Lonsurf® (N=534) plus best supportive care (BSC) or matching placebo (N=266) plus BSC. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US, Europe and Australia). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients received 35 mg/m2 Lonsurf® or matching placebo orally twice daily after meals on Days 1 - 5 and 8 – 12 of each 28-day cycle until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS). The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG Performance Status (PS) of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab, and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab. A statistically significant improvement in overall survival and progression-free survival were demonstrated in patients in the Lonsurf® plus BSC arm compared to those who received placebo plus BSC.

Ninlaro® (ixazomib)

The efficacy and safety of Ninlaro® in combination with lenalidomide and dexamethasone was evaluated in a randomized, double-blind, placebo-controlled, multicenter study in patients with relapsed and/or refractory multiple myeloma who had received at least one prior line of therapy. Patients who were refractory to lenalidomide or proteasome inhibitors were excluded from the study. A total of 722 patients were randomized in a 1:1 ratio to receive either the combination of Ninlaro®, lenalidomide and dexamethasone (N=360; Ninlaro® regimen) or the combination of placebo, lenalidomide and dexamethasone (N=362; placebo regimen) until disease progression or unacceptable toxicity. Randomization was stratified according to number of prior lines of therapy (1 versus 2 or 3), myeloma International Staging System (ISS) (stage I or II versus III), and previous therapy with a proteasome inhibitor (exposed or naïve). Twenty three percent (N=166) of the patients had light chain disease and 12% (N=87) of patients had free light chain-measurable only disease. Thromboprophylaxis was recommended for all patients in both treatment groups according to the lenalidomide prescribing information. Antiemetics were used in 19% of patients in the Ninlaro® regimen and 12% of patients in the placebo regimen; antivirals in 64% and 60%, respectively, and antihistamines in 27% and 19%, respectively. These medications were given to patients at the physician's discretion as prophylaxis and/or

management of symptoms. Patients received Ninlaro® 4 mg or placebo on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients with renal impairment received a starting dose of lenalidomide according to its prescribing information. Treatment continued until disease progression or unacceptable toxicities. The efficacy of Ninlaro® was evaluated by progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria as assessed by a blinded independent review committee (IRC) based on central lab results. Response was assessed every four weeks until disease progression.

The approval of Ninlaro® was based upon a statistically significant improvement in PFS of the Ninlaro® regimen compared to the placebo regimen. The median time to response was 1.1 months in the NINLARO regimen and 1.9 months in the placebo regimen. The median duration of response was 20.5 months in the Ninlaro® regimen and 15 months in the placebo regimen for responders in the response evaluable population. A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. Hazard ratio of PFS was 0.82 (95% confidence interval [0.67, 1.0]) for Ninlaro® regimen versus placebo regimen, and estimated median PFS was 20 months in the Ninlaro® regimen and 15.9 months in the placebo regimen. At the same time, a planned interim OS analysis was conducted with 35% of the required number of deaths for final OS analysis; there were 81 deaths in the Ninlaro® regimen and 90 deaths in the placebo regimen. An OS benefit was not demonstrated.

Lartruvo® (olaratumab)

The efficacy of Lartruvo® (olaratumab) was demonstrated in Trial 1, an open-label, randomized, active-controlled study. Eligible patients were required to have soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy, a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate but had not been administered, ECOG PS of 0-2, and tumor specimen available for assessment of PDGFR-α expression by an investigational use assay. Patients were randomized (1:1) to receive olaratumab in combination with doxorubicin or doxorubicin as a single agent. PDGFR-α expression (positive versus negative), number of previous lines of treatment (0 versus 1 or more), histological tumor type (leiomyosarcoma versus synovial sarcoma versus all others), and ECOG PS (0 or 1 versus 2) were used to allocate patients in the randomization. olaratumab was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. All patients received doxorubicin 75 mg/m2 as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and were permitted to receive

dexrazoxane prior to doxorubicin in Cycles 5 to 8. Patients randomized to receive doxorubicin as a single agent were offered olaratumab at the time of disease progression. The efficacy outcome measures were overall survival (OS), and progression-free survival (PFS) and objective response rate (ORR) as assessed by investigator and by independent review according to RECIST v1.1. A total of 133 patients were randomized, 66 patients to the LARTRUVO plus doxorubicin arm and 67 patients to the doxorubicin arm. Baseline demographics and disease characteristics were: median age of 58 years (range 22 to 86); 44% men; 86% White, 8% Black, 3% Asian, and 2% Other; 56% ECOG PS 0 and 39% ECOG PS 1; 65% no prior chemotherapy (excluding adjuvant and neoadjuvant therapy); 38% leiomyosarcoma, 1.5% synovial sarcoma, and 61% other histologies [17% liposarcoma (8% dedifferentiated, 4% myxoid, 3% well-differentiated, 1.5% pleomorphic, 1% liposarcoma not otherwise specified (NOS)), 11% undifferentiated pleomorphic sarcoma, 5% angiosarcoma, 5% undifferentiated sarcoma NOS, 3% extraskeletal myxoid chondrosarcoma, 2% malignant peripheral nerve sheath tumor, 2% myxofibrosarcoma, 2% malignant solitary fibrous tumor, 2% endometrial stromal sarcoma, 1.5% chondrosarcoma, 1.5% epithelioid sarcoma, 1.5% fibrosarcoma, 1.5% low-grade fibromyxoid sarcoma, and 5% other histologies with one patient each]. All patients had metastatic disease and were enrolled at U.S. sites. Among patients randomized to doxorubicin, 30 (45%) patients received LARTRUVO as a single agent at the time of disease progression. Trial 1 demonstrated a significant improvement in overall survival.

Rubraca® (rucaparib)

Rubraca® (rucaparib) 600mg twice daily as monotherapy has been studied in 377 patients with ovarian cancer treated in two open label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had BRCA-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197). Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). The median duration of treatment was 5.5 months (range 0.1 to 28.0).

Idhifa® (enasidenib)

The efficacy of Idhifa® (enasidenib) 100 mg was evaluated in an open-label, single-arm, multicenter, two-cohort clinical trial of 199 patients with relapsed or refractory AML and an IDH2

mutation. IDH2 mutations were identified by a local diagnostic test and retrospectively confirmed by the Abbott RealTime IDH2 assay or prospectively identified by the Abbott RealTime IDH2 assay. Efficacy was based off of the rate of complete response (CR)/complete response with partial hematologic recovery (CR/CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. For patients who achieved a CR/CRh, the median time to first response was 1.9 months and the median time to best response was 3.7 months. Of the 157 patients who were dependent on red blood cell and/or platelet transfusions at baseline, 34% became independent of transfusions during any 56-day post baseline period.[65]

Verzenio™ (abemaciclib)

The efficacy of Verzenio™ (abemaciclib) in combination with Faslodex® (fulvestrant) was evaluated in the Monarch 2 trial. Monarch 2 was a randomized, placebo-controlled, multicenter study in 669 women with HR-positive, HER2-negative metastatic breast cancer in patients with disease progression on endocrine therapy. The primary endpoint was progression-free survival. The median extended progression free survival duration for abemaciclib plus fulvestrant vs. fulvestrant alone was 16.4 months vs. 9.3 months. The efficacy of Verzenio ™ as monotherapy was evaluated in the Monarch 1 trial. Monarch 1 was a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during endocrine therapy, had received taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. The primary objective of Monarch 1 was investigator-assessed objective response rate. Other endpoints were clinical benefit rate, progression-free survival, and overall survival. At the 12 month final analysis, the confirmed objective response rate was 19.7%, median progression-free survival was 6 months and median overall survival was 17.7 months.

Keytruda® (pembrolizumab)

Keytruda® (pembrolizumab) is approved for multiple indications based on the following clinical evidence.

Unresectable or Metastatic Melanoma

Study KEYNOTE-006 was a randomized, open-label, active-controlled trial evaluating 834 patients with unresectable or metastatic melanoma and no prior ipilimumab treatment who received either pembrolizumab or ipilumumab. Evaluating pembrolizumab 10 m/kg every 3 weeks or every 2 weeks, pembrolizumab demonstrated significant improvement in the primary endpoints, OS (33%, p=0.004 and 30%, p<0.001) and PFS (57%, p<0.001 and 56%, p<0.001), relative to ipilimumab (OS 40% and PFS 68%). Study KEYNOTE-002 was a randomized, blinded, active-controlled trial evaluating 540 patients with unresectable or metastatic melanoma *with* prior ipilumumab treatment. The study showed statistically significant improvement in PFS for patients randomized to both dosing regimens of pembrolizumab compared to chemotherapy (72% and 70% vs 87%, p<0.001 for all).

Metastatic NSCLC

Study KEYNOTE-024 was a randomized, open-label, active-controlled trial in 305 patients with metastatic NSCLC and had not received prior systemic treament for metastatic NSCLC who received either pembrolizumab or chemotherapy. The study showed statistically significant improvement in PFS for patients randomized to pembrolizumab compared with chemotherapy (47% vs 77%, p<0.001). Study KEYNOTE-021 was a randomized, open-label, multi-cohort study evaluating 123 patients with metastatic NSCLC who received either pembrolizumab in combination with pemetrexed and carboplatin or just pemetrexed and carboplatin. The study showed that there were significant improvements in ORR in the pembrolizumab combination arm (55%) versus the control arm (29%), p=0.0032. Study KEYNOTE-010 evaluated 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy who received either pembrolizumab or docetaxel. The study demonstrated significant improvements in OS in pembrolizumab compared to docetaxel (p<0.001 for all).

Recurrent or metastatic head and neck cancer

Study KEYNOTE-012 was non-randomized, open-label study that evaluated 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy who received pembrolizumab. The ORR was 16% (95% CI 11 to 22), with a complete response rate of 5%. Duration of response had not been reached.

Classical Hodgkin Lymphoma

Study KEYNOTE-087 was a non-randomized, open-label study that evaluated 210 patients with relapsed or refractory cHL who received pembrolizumab. The ORR was 69% (95% CI 62 to 75%) and the duration of response was a median of 11.1 months.

Advanced or metastatic urothelial carcinoma

Study KEYNOTE-052 was an open-label, single-arm trial that evaluated 370 patients with locally advanced or metastatic urothelial carcionoma who were not eligible for cisplatin-containing chemotherapy. The ORR was 29% (95% CI 24 to 34) and the duration of response was not reached. Study KEYNOTE-045 was a randomized, active-controlled trial that evaluated 542 patients with disease progression on or after platinum-containing chemotherapy who received pembrolizumab or chemotherapy. The study demonstrated significant improvements in OS and ORR for pembrolizumab compared to chemotherapy (57% vs 66%, p=0.004 and 21% vs 11%, p=0.002), but there was no statistically significant difference with respect to PFS.

Microsatellite instability-high cancer

The efficacy of pembrolizumab was evaluated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, single-arm trials. A total of 149 patients were evaluated across the five trials. The ORR was 39.6% (95% CI 31.7 to 47.9) across all trials, and the duration of response was not reached.

Gastric cancer

Study KEYNOTE-059 was a non-randomized, open-label trial that evaluated 259 patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. The ORR was 13.3% (95% CI 8.2 to 20.0%), with 1.4% complete response and 11.9% partial response.

Aliqopa™ (copanlisib)

The efficacy of Aliqopa™ (copanlisib) in patients with R/R FL was evaluated in a phase II published trial along with two published study abstracts and provided dossier information. Current evidence is from examining the efficacy of copanlisib in phase II, open-label, uncontrolled trials. In each of these studies, the primary efficacy endpoint was overall response rate (ORR). Copanlisib was not compared to placebo or an active control in any completed trials. Therefore, it is unclear if it is superior to watchful waiting, as measured via placebo, or an active control. Watchful waiting is a common practice with indolent follicular lymphoma.

The pivotal trial was CHRONOS-1 Part A, and included patients with both indolent and aggressive FL. All efficacy endpoints (ORR, median progression free survival (MPFS), median duration of response (MDR)) were larger in the indolent group compared to patients with aggressive FL. This is expected due to the nature of these forms of the disease. For both patient types, survival and response rates ranged from 0 to over 890 days, suggesting some patients simply respond to copanlisib better than others. Median time to response was 52 days (0-109 days) indolent and 51 days (range 0-117) in the aggressive cohort. Providers would most likely be able to assess efficacy and response in less than 2 months, and at most by 4 months of treatment. In CHRONOS-1, patients with aggressive lymphoma were treated for an average of 2 cycles compared to indolent patients with an average of 5.5 cycles.

CHRONOS-1 Part B was an extension in the examination of the efficacy of copanlisib, though only in indolent lymphoma patients. Similar response rates and duration of response were observed to the indolent cohort in Part A. In the study examining copanlisib in DLBCL, an aggressive lymphoma, results were also similar to the aggressive cohort in CHRONOS-1 Part A. DLBCL is considered a curable disease; however, the study failed to report cure rates of any patients.

2013 Update

Policy was updated to reflect new NCCN guidelines which recommend abiraterone as an initial therapy for metastatic castrate-resistant prostate cancer.

2014 Update

A literature search from 7/1/12 to 10/31/14 found no new evidence requiring changes to this policy.

2015 Update

A literature search from 1/1/14 to 3/31/15 found no new evidence requiring changes to the Erivedge® (vismodegib) policy. Added criteria for two recently approved drugs: Opdivo® (nivolumab) and Lynparza™ (olaparib). Added criteria for recently approved drug: Ibrance® (palbociclib).

2016 Update

A literature search and review was conducted focusing on recently FDA-approved indications for use of Opdivo® (nivolumab) and Keytruda® (pembrolizumab) in non-small cell lung cancer, and for nivolumab in renal cell carcinoma. We also reviewed this evidence for combined use of nivolumab and ipilimumab in unresectable or metastatic melanoma. Medical necessity language was updated per new product labels.

Reasonable evidence exists to support the use of ipilimumab, nivolumab, the combination of ipilimumab + nivolumab and Keytruda® (pembrolizumab) in the treatment of advanced and metastatic melanoma. Median survival benefits seem to fall in the range of 3-4 months, with the combination PD-1/CTLA-4 inhibition yielding slightly longer survival. To date the evidence is spotty and lacking in head-to-head comparisons. NCCN guidelines do not rate one option over others. Given the number of different molecular targets now available (PD-1, CTLA-4, BRAF V600, MEK) it is impossible to say at this point which is the best treatment sequence to follow.

Tecentriq's label criteria was added to the policy, along with description and rationale sections for this drug. Keytruda recently got a new recommendation for use in NSCLC as a first-line agent. Added criteria (along with description and rationale) for recently approved drugs: Lonsurf®, Ninlaro, and Lartruvo. Tecentriq's recent approval in the setting of NSCLC was also added to the policy.

Added criteria per label for Rubraca® (rucaparib), along with the drug description and clinical trials rationale.

2017 Update

Added two new indications for Opdivo® (nivolumab). Added four new indications for Keytruda® (pembrolizumab) and included their references.

2018 Update

Added Paloma-2 study for Ibrance® (palbociclib) and Rydapt® (midostaurin) safety and efficacy study in drug description.

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History

Date	Comments
06/12/12	New policy, add to Prescription Drug section. Reviewed by Pharmacy & Therapeutics Committee, June 2012.
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.
10/14/13	Replace policy. Policy updated to reflect new NCCN guidelines which recommend abiraterone as an initial therapy for metastatic castrate-resistant prostate cancer.
11/11/13	Replace policy. Policy section updated with the removal of *Zytiga® (abiraterone)*; Rationale section updated in accordance with this change. (See policy 5.01.544 for coverage on Zytiga®).

Date	Comments
12/08/14	Annual review. Policy updated with literature review; no change in policy statement.
05/27/15	Annual Review. Policy updated with literature review. Title changed to match the scope of the policy which is no longer limited to oral medications. New policy statements added: nivolumab and olaparib may be considered medically necessary; Opdivo for treatment metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy may be considered medically necessary; all other uses of Erivedge, Lynparza or Opdivo are considered investigational. Rationale section updated in accordance with this change and new references added. The word "oral" removed from the title to match the scope of the policy.
07/14/15	Interim Update. Added new policy statements for newly approved drug palbociclib.
01/19/16	Coding update. New HCPCS codes J3380 and J9299 – effective 1/1/16 – added to policy.
01/29/16	Minor update. Removed code J3380.
04/01/16	Annual review, approved March 8, 2016. Policy updated to reflect current labeling indications.
05/26/16	Coding update. J9271 added, effective 1/1/16.
10/01/16	Interim update, approved September 13, 2016: inclusion of a new indication for Opdivo and Keytruda.Addition of length of approval as 3 months. Inclusion of Gazyva criteria, and rationale for Yervoy.
11/01/16	Interim review, approved October 11, 2016. Tecentriq criteria and description added to the policy.
12/01/16	Interim review, approved November 8, 2016. Keytruda's criteria was updated to reflect first-line use in NSCLC. Also, Lonsurf, Ninlaro,and Lartruvo criteria was added to the policy. Tecentriq's newest indication for NSCLC was also added to the policy.
01/01/17	Interim review, approved December 13, 2016. Minor clarifications made to the criteria language. Also, Yervoy's criteria has been expanded based on NCCN guidelines.
02/01/17	Annual review, approved January 10, 2017. Added rupacarib's labeled criteria, as well as drug description and clinical trials rationale. References section has been updated accordingly.
03/01/17	Interim review, approved February 14, 2017. Added two new indications for nivolumab (recurrent or metastatic squamous cell carcinoma of the head and neck; urothelial carcinoma).
04/01/17	Interim review, approved March 14, 2017. Updated criteria for Lartruvo.
06/01/17	Interim review, approved May 16, 2017. Updated an indication for Tecentriq. Updated criteria for Ibrance to include any aromatase inhibitor therapy. Fixed minor grammatical/formatting errors. Added coverage criteria for Odomzo® (sonidegib).
07/01/17	Interim review, approved June 13, 2017. Added coverage criteria for Kisqali®, Zejula®,

Date	Comments
	Bavencio®, Rydapt®, and Imfinzi®.
09/01/17	Minor update; updated title of related policy 5.01.543.
10/01/17	Interim Review, approved September 21, 2017. Added coverage criteria for Idhifa®.
11/01/17	Interim Review, approved October 19, 2017. Added coverage criteria for Verzenio™.
12/01/17	Interim Review, approved November 14, 2017. Added new indications for Keytruda® and its new references. Added new indication for Lynparza™.
01/01/18	Coding update, added HCPCS codes J9022, J9023, and J9285 (new codes effective 1/1/18).
02/01/18	Interim Review, approved January 16, 2018. Added coverage criteria for Aliqopa™ (copanlisib) and added new indication for Opdivo®
03/01/18	Interim Review, approved February 27, 2018. Added new indication for Lynparza - deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been previously treated with chemotherapy either in the neoadjuvant, adjuvant or metastatic setting. Updated Opdivo and Imfinzi criteria to include all FDA approved indications.
06/01/18	Interim Review, approved May 3, 2018. Updated criteria for combination therapy with Opdivo and Yervoy as well as Rubraca to include newly approved FDA labeled indications.
07/01/18	Annual Review, approved June 22, 2018. Added Paloma-2 study for Ibrance and safety and efficacy study for Rydapt. Updated Keytruda criteria for clarity. Added general reauthorization criteria and documentation requirements.

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.

PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
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)
Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በእከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
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. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 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 ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ 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 ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ 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 (کاربران 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 zwrócic 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 dumneavoastre 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 privitoare 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'amatalaga 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. Ang paunawa na ito ay maaaring 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 ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย 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 страхувального 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).