

## Pharmacy Policy Bulletin

**Title:** Oncology Agents

**Policy #:** Rx.01.67

*Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.*

*This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.*

**Members are advised to use participating pharmacies in order to receive the highest level of benefits.**

### **Intent:**

The intent of this policy is to communicate the medical necessity criteria for **acalabrutinib (Calquence®)**, **imatinib mesylate (Gleevec®)**, **Sorafenib (Nexavar®)**, **lenalidomide (Revlimid®)**, **dasatinib (Sprycel®)**, **sunitinib malate (Sutent®)**, **erlotinib (Tarceva®)**, **apalutamide (Erleada™)**, **Thalidomide (Thalomid®)**, **vorinostat (Zolinza®)**, **lapatinib (Tykerb®)**, **nilotinib (Tasigna®)**, **temozolomide (Temojar®)**, **everolimus (Afinitor®)**, **fludarabine phosphate (Oforta®)**, **pazopanib (Votrient®)**, **vandetanib (Caprelsa®)**, **abiraterone (Zytiga®)**, **vemurafenib (Zelboraf®)**, **crizotinib (Xalkori®)**, **ruxolitinib (Jakafi®)**, **axitinib (Inlyta®)**, **vismodegib (Eriedge®)**, **enzalutamide (Xtandi®)**, **bosutinib (Bosulif®)**, **regorafenib (Stivarga®)**, **ponatinib (Iclusig®)**, **cabozantinib (Cometriq®)**, **cabometyx®**, **pomalidomide (Pomalyst®)**, **dabrafenib (Tafinlar®)**, **trametinib (Mekinist®)**, **afatinib (Gilotrif®)**, **ibrutinib (Imbruvica®)**, **ceritinib (Zykadia®)**, **idelalisib (Zydelig®)**, **olaparib (Lynparza®)**, **panobinostat (Farydak®)**, **palbociclib (Ibrance®)**, **lenvatinib (Lenvima®)**, **trifluridine/tipiracil (Lonsurf®)**, **sonidegib (Odomzo®)**, **alectinib (Alecensa®)**, **cobimetinib (Cotellic®)**, **ixazomib (Ninlaro®)**, **venetoclax (Venclexta®)**, **osimertinib (Tagrisso®)**, **rucaparib (Rubraca®)**, **ribociclib (Kisqali®)**, **niraparib (Zejula®)**, **brigatinib (Alunbrig®)**, **neratinib (Nerlynx®)**, **midostaurin (Rydapt®)**, **Peginterferon alfa-2b (Sylatron®)**, **enasidenib (Idhifa®)**, **abemaciclib (Verzenio®)**, **binimetinib (Mektovi®)**, **encorafenib (Braftovi®)**, **ivosidenif (Tibsovo®)**, **duvelisib (Copiktra™)**, **dacomitinib (Vizimpro®)**, **talazoparib (Talzenna®)**, **lorlatinib (Lorbrena®)**, **glasdegib (Daurismo™)**, **larotrectinib (Vitrakvi®)**, **gilteritinib (Xospata®)**, **erdafitinib (Balversa™)**, **bexarotene (Targretin®) oral capsule or topical gel**, **selinexor (Xpovio™)**, **alpelisib (Piqray®)**, **darolutamide (Nubeqa®)**, **pexidartinib (Turalio™)**, **entrectinib (Rozlytrek™)**, **avapritinib (Ayvakit™)**, **zanubrutinib (Brukinsa™)**, **fedratinib (Inrebic®)**, **selumetinib (Koselugo®)**, **tazemetostat (Tazverik™)**, **tucatinib (Tukysa™)**, **pemigatinib (Pemazyre™)**, **ripretinib (Qinlock™)**, **selpercatinib (Retevmo™)**, **capmatinib (Tabrecta™)**, **gefitinib (Iressa®)**, **tretinoin capsules, pralsetinib (Gavreto™)**, **decitabine and cedazuridine (Inqovi®)**, **relugolix (Orgovyx™)**, **azacitidine (Onureg®)**, **tepotinib (Tepmetko®)**, **umbralisib (Ukoniq™)**, **Fotivda® (tivozanib)**, **Truseltiq™ (infigratinib)**, **Lumakras™ (sotorasib)**, **mechlorethamine (Valchlor®)**, **mobocertinib (Exkivity™)**, and **belzutifan (Welireg™)** as provided under the member's prescription drug benefit.

### **Description:**

#### **Alpelisib (PIQRAY®)**

Alpelisib was approved by the FDA via priority review on May 24, 2019 in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, Phosphatidylinositol 3- Kinase (PIK3CA)-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen

Alpelisib is an orally bioavailable, small-molecule,  $\alpha$ -specific PI3K inhibitor that selectively inhibits p110 $\alpha$  approximately 50 times as strongly as other isoforms. PI3K inhibition by alpelisib has been shown to induce an increase in ER transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased antitumor

activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA-mutated breast cancer cell lines

### **Bexarotene (Targretin®), bexarotene**

**Bexarotene (Targretin®)** is a selective retinoid X receptor (RXR) ligand. Binding of the drug to retinoic acid receptors (RAR) is minimal, and it may be devoid of significant transactivation of RAR-responsive genes. Activation of the RXR pathway leads to the induction of programmed cell death (apoptosis) and other cellular activities.

**Bexarotene (Targretin®)** is indicated for the treatment of cutaneous manifestations of T-cell lymphoma in patients refractory to at least one prior systemic therapy.

### **BINIMETINIB (MEKTOVI®)**

**Binimetinib (Mektovi®)** is indicated to be used in combination with encorafenib for the treatment of unresectable metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test.

### **ENCORAFENIB (BRAFTOVI®)**

**Encorafenib (Braftovi®)** is a kinase inhibitor indicated to be used in combination with kinase inhibitor, binimetinib for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. BRAFTOVI is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy. BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC.

### **ERDAFITINIB (BALVERSA™)**

Erdafitinib is indicated for the treatment of adults with locally advanced or metastatic urothelial carcinoma, that has susceptible fibroblast growth factor receptor, FGFR3 or FGFR2 genetic alterations, and progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for the treatment with erdafitinib based on the presence of susceptible FGFR genetic alterations in tumor specimens

### **IVOSIDENIB (TIBSOVO®)**

**Ivosidenib (Tibsovo®)** is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.

### **IMATINIB MESYLATE (GLEEVEC®)**

**Imatinib mesylate (Gleevec®)** is indicated for the treatment of all of the following:

Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase, Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy, Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy, Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements, Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown, Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR $\alpha$  fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR $\alpha$  fusion kinase negative or unknown, Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP), Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST), Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.

**Imatinib mesylate (Gleevec®)** is the first signal transduction inhibitor to be approved by the US Food and Drug Administration (FDA). These drugs are designed to prevent and stop the growth of cancer cells. Imatinib mesylate (Gleevec®) directly blocks BCR-ABL, the protein necessary for leukemia cells to survive. Imatinib mesylate (Gleevec®)

also targets the activity of certain enzymes called tyrosine kinases, which play an important role within certain cancer cells. The activity of one of these tyrosine kinases, known as a stem cell factor receptor (c-Kit), is thought to drive the growth and division of most gastrointestinal stromal tumors (GISTs).

### **SORAFENIB (NEXAVAR®)**

**Sorafenib (Nexavar®)** is indicated for the treatment of advanced renal cell carcinoma differentiated thyroid cancer and advanced unresectable hepatocellular carcinoma.

**Sorafenib (Nexavar®)** is a multikinase inhibitor that decreases tumor cell proliferation. The mechanism of action of sorafenib (Nexavar®) is not well understood, but it is believed to inhibit tumor growth in murine renal cell carcinoma and several other human tumor xenograft models. Sorafenib (Nexavar®) has also been shown to interact with multiple intracellular (CRF, BRAF, and mutant BRAF) and cell surface kinases (KIT, FMS-like tyrosine kinase-3 [FLT-3], vascular endothelial growth factor receptors [VEGFR-3], and platelet-derived growth factor receptors [PDGFR $\beta$ ]), several of which are thought to be involved in angiogenesis.

### **LENALIDOMIDE (REVLIMID®)**

Lenalidomide (Revlimid®) is indicated for the treatment of individuals who have transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes that are associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities. Lenalidomide (Revlimid®) in combination with dexamethasone is indicated for the treatment of multiple myeloma in individuals who have received at least one prior therapy. Lenalidomide (Revlimid®) is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

**Lenalidomide (Revlimid®)** is a thalidomide analogue. The mechanism of action of lenalidomide (Revlimid®) is not well understood. It possesses immunomodulatory and antiangiogenic properties, inhibits the secretion of proinflammatory cytokines, and increases the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide (Revlimid®) inhibits cell proliferation with varying effectiveness in some, but not all, cell lines. Of the cell lines tested, lenalidomide (Revlimid®) was effective in inhibiting the growth of Namalwa cells (a line of human B-lymphocytes with a deletion of one chromosome 5) but was much less effective in the inhibition of KG-1 cells (human myeloblastic cell lines with a deletion of one chromosome 5) and other cell lines without a chromosome 5 deletion. Lenalidomide (Revlimid®) is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one one of which included bortezomib.

Hematologic toxicity: Lenalidomide can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with deletion 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for deletion 5q myelodysplastic syndromes should have their complete blood cell count (CBC) monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

### **DASATINIB (SPRYCEL®)**

Dasatinib (Sprycel®) is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. Dasatinib (Sprycel®) is also indicated for the treatment of adult patients with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. Dasatinib (Sprycel®) is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) who have demonstrated resistance or intolerance to prior therapy. Dasatinib (Sprycel®) is also indicated for the treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. Dasatinib (Sprycel®) is indicated for the treatment of pediatric patients 1 year of age and older with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) in combination with chemotherapy.

**Dasatinib (Sprycel®)** is a multityrosine kinase inhibitor that limits the activity of BCR-ABL, SRC family, c-Kit, EPHA2, and PDGFR $\beta$  tyrosine kinases. This results in an inhibition of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines that overexpress BCR-ABL. Dasatinib (Sprycel®) has also been shown to be effective for individuals who have demonstrated resistance or intolerance to imatinib mesylate (Gleevec®).

### **SUNITINIB MALATE (SUTENT®)**

Sunitinib malate (Sutent®) is indicated for the treatment of the following conditions:

1. GIST after trial and failure of or intolerance to imatinib mesylate (Gleevec®)
2. Advanced renal cell carcinoma (RCC)
3. Progressive, well differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease
4. Adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.

**Sunitinib malate (Sutent®)** is a multikinase inhibitor that targets several receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and/or a metastatic progression of cancer. The mechanism of action of sunitinib malate (Sutent®) is not well understood. It is believed that sunitinib malate (Sutent®) inhibits platelet-derived growth factor receptors (PGFR $\alpha$  and PDGFR $\beta$ ), vascular endothelial growth factor receptors (VEGR1, VEGFR2, and VEGFR3), c-Kit, FLT3, colony-stimulating factor 1 receptor (CSF-1R), and the glial cell line-derived neurotrophic factor receptor (RET). Several of these kinases are thought to be involved in angiogenesis.

### **ERLOTINIB (TARCEVA®)**

Erlotinib (Tarceva®) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. Also indicated for pancreatic cancer as first line treatment.

**Erlotinib (Tarceva®)** is described as a human epidermal growth factor receptor type 1 (HER1)/EGFR tyrosine kinase inhibitor. Its mechanism of antitumor action is not fully understood. It inhibits the phosphorylation of tyrosine kinase associated with EGFR. The specificity of tyrosine kinase receptor inhibition has not been defined. EGFR is expressed on the cell surfaces of normal cells and cancer cells. Two multicenter, placebo-controlled, randomized Phase III trials were conducted in first-line individuals who had locally advanced or metastatic non-small cell lung cancer (NSCLC), and the results showed no clinical benefit with the concurrent administration of erlotinib (Tarceva®). Erlotinib (Tarceva®) with platinum-based chemotherapy (carboplatin and paclitaxel or gemcitabine and cisplatin) is not recommended for use in this setting.

### **APALUTAMIDE (ERLEADA™)**

**Apalutamide (Erleada™)** is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-sensitive prostate cancer and non-metastatic castration-resistant prostate cancer.

### **THALIDOMIDE (Thalomid®)**

**Thalidomide (Thalomid®)** is indicated:

1. In combination with dexamethasone, for the treatment of patients with newly diagnosed multiple myeloma (MM)
2. For the acute treatment of cutaneous manifestations of severe erythema nodosum leprosum (ENL); not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis
3. As maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL relapse

The mechanism of action of **thalidomide (Thalomid®)** is not fully understood. Thalidomide possesses immunomodulatory, antiinflammatory and antiangiogenic properties. Available data from in vitro studies and clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF- $\alpha$ ) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration. For example, administration of thalidomide has been reported to decrease circulating levels of TNF- $\alpha$  in patients with erythema nodosum leprosum (ENL); however, it has also been shown to increase plasma TNF- $\alpha$  levels in HIV-seropositive patients. Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of multiple myeloma patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis in a human umbilical artery explant model in vitro. The cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells.

**VORINOSTAT (ZOLINZA®)**

**Vorinostat (Zolinza®)** is a histone deacetylase (HDAC) inhibitor indicated for the treatment of individuals with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following two systemic therapies.

**Vorinostat (Zolinza®)** inhibits the enzymatic activity of histone deacetylases (HDACs) Class I (i.e., HDAC1, HDAC2, and HDAC3) and Class II (ie, HDAC6) at nanomolar concentrations (inhibitory concentration [IC50] less than 86 nM). In some cancer cells, there is an overexpression of HDACs or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues, resulting in an open chromatin structure and transcription activation. In vitro, vorinostat (Zolinza®) causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells. The mechanism of the antineoplastic effect of vorinostat (Zolinza®) is not fully understood.

**LAPATINIB (TYKERB®)**

Lapatinib (Tykerb®) is indicated for use in combination with capecitabine (Xeloda®) for the treatment of individuals with advanced or metastatic breast cancer whose tumors overexpress the HER2 protein and who have received prior therapy with an anthracycline, a taxane, and trastuzumab (Herceptin®). It is also indicated for use in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB® in combination with capecitabine.

**Lapatinib (Tykerb®)** is an inhibitor of the EGFR (Epidermal growth factor receptor; also called HER1 or ErbB1) and HER2 receptor tyrosine kinases, thereby inhibiting ErbB-driven tumor cell growth.

**NILOTINIB (TASIGNA®)**

Nilotinib (Tasigna®) is indicated for the following:

1. Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
2. Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib. Treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib. Clinical benefit, such as improvement in disease-related symptoms or increased survival, has not been demonstrated.
3. Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

**Nilotinib (Tasigna®)** is a selective tyrosine kinase inhibitor which binds to and stabilizes the inactive conformation of the kinase domain of the Abl protein. Bcr-Abl is the oncogenic tyrosine kinase expressed by Philadelphia chromosome-positive (Ph+) stem cells, directly involved in the pathogenesis of CML. Nilotinib inhibits the autophosphorylation of Bcr-Abl, PDGFR, and c-Kit, thereby reducing the tumor size.

**TOPOTECAN CAPSULES (HYCAMTIN®)**

Topotecan capsule (Hycamtin®) is indicated for the treatment of relapsed small cell lung cancer in patients with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy.

**Topotecan capsule (Hycamtin®)** is a semi-synthetic derivative of camptothecin and is an anti-tumor drug. The anti-tumor activity of topotecan involves the inhibition of topoisomerase-I, an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilizing the covalent complex of enzyme and strand-cleaved DNA, which is an intermediate of the catalytic mechanism. The cellular sequel of inhibition of topoisomerase-I by topotecan is the induction of protein-associated DNA single-strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

**TEMOZOLOMIDE (TEMODAR®)**

Temozolomide (Temodar®) is indicated for the treatment of adult patients with refractory anaplastic astrocytoma (ie, patients who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine) and for the treatment of adults with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

**Temozolomide (Temodar®)**, an imidazotetrazine derivative, is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be caused primarily by alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

**EVEROLIMUS (AFINITOR®)**

Everolimus (Afinitor®) is indicated for the treatment of advanced renal cell carcinoma (RCC), in patients who failed treatment with sunitinib (Sutent®) or sorafenib (Nexavar®). Everolimus (Afinitor®) is also indicated for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Afinitor® is also indicated for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. Afinitor® is also indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.

**Everolimus (Afinitor®)** is a kinase inhibitor, a derivative of the natural macrocyclic lactone sirolimus with immunosuppressant and anti-angiogenic properties. In cells, everolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production.

**FLUDARABINE PHOSPHATE (Oforta™)**

Fludarabine Phosphate (Oforta™) is indicated for a diagnosis of B-cell chronic lymphocytic leukemia (CLL) whose disease has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen.

**Fludarabine Phosphate (Oforta™)** is a synthetic purine nucleotide antimetabolite agent. Upon administration, fludarabine phosphate is rapidly dephosphorylated in the plasma to 2F-ara-A, which then enters into the cell. Intracellularly, 2F-ara-A is converted to the 5'-triphosphate, 2-fluoro-ara-ATP (2F-ara-ATP). 2F-ara-ATP competes with deoxyadenosine triphosphate for incorporation into DNA. Once incorporated into DNA, 2F-ara-ATP functions as a DNA chain terminator, inhibits DNA polymerase alpha, gamma, and delta, and inhibits ribonucleoside diphosphate reductase. 2F-ara-A also inhibits DNA primase and DNA ligase I. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

**PAZOPANIB (Votrient™)**

**Pazopanib (Votrient™)** is indicated for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy.

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

**VANDETANIB (Caprelsa®)**

Vandetanib (Caprelsa®) is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

**Vandetanib (Caprelsa®)** is a kinase inhibitor. Studies have shown that vandetanib inhibits the activity of tyrosine kinases including members of the epidermal growth factor receptor (EGFR) family. Vandetanib inhibits endothelial cell migration, proliferation, survival and new blood vessel formation in in vitro models of angiogenesis. Vandetanib inhibits EGFR-dependent cell survival in vitro. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated receptor tyrosine kinase phosphorylation in tumor cells and endothelial cells and VEGF-stimulated tyrosine kinase

phosphorylation in endothelial cells.

### **ABIRATERONE (Zytiga®)**

**Abiraterone (Zytiga®)** in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

**Abiraterone acetate (Zytiga®)** is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17  $\alpha$ -hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Zytiga® decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial.

### **VEMURAFENIB (ZELBORAF®)**

**Vemurafenib (Zelboraf®)** is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test and for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation.

**Vemurafenib (Zelboraf®)** is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAFV600E. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated BRAFV600E

### **CRIZOTINIB (XALKORI®)**

**Crizotinib (Xalkori®)** is a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test. Crizotinib is indicated for pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.

Limitations of Use: The safety and efficacy of XALKORI have not been established in older adults with relapsed or refractory, systemic ALK-positive ALCL.

**Crizotinib (Xalkori®)** is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

### **RUXOLITINIB (JAKAFI®)**

**Ruxolitinib (Jakafi®)** is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. Ruxolitinib is also indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

**Ruxolitinib (Jakafi®)**, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

### **AXITINIB (Inlyta®)**

**Axitinib (Inlyta®)** is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

**Axitinib (Inlyta®)** has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated

in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib in vitro and in mouse models. Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models.

#### **VISMODEGIB (Erivedge®)**

**Vismodegib (Erivedge®)** is indicated 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.

**Vismodegib (Erivedge®)** is an inhibitor of the Hedgehog pathway. Vismodegib binds to and inhibits smoothed, a transmembrane protein involved in Hedgehog signal transduction.

#### **ENZALUTAMIDE (Xtandi®)**

**Enzalutamide (Xtandi®)** is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. Xtandi® is also indicated for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

**Enzalutamide (Xtandi®)** is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro, and decreased tumor volume in a mouse prostate cancer xenograft model.

#### **BOSUTINIB (Bosulif®)**

**Bosutinib (Bosulif®)** is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy. Bosutinib is also indicated for the treatment of adult patients with newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML).

**Bosutinib (Bosulif®)** is a tyrosine kinase inhibitor. Bosutinib inhibits the Bcr-Abl kinase that promotes CML; it is also an inhibitor of Src-family kinases including Src, Lyn, and Hck. Bosutinib inhibited 16 of 18 imatinib-resistant forms of Bcr-Abl expressed in murine myeloid cell lines. Bosutinib did not inhibit the T315I and V299L mutant cells. In mice, treatment with bosutinib reduced the size of CML tumors relative to controls and inhibited growth of murine myeloid tumors expressing several imatinib-resistant forms of Bcr-Abl.

#### **REGORAFENIB (Stivarga®)**

**Regorafenib (Stivarga®)** is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. Regorafenib is also indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. Regorafenib is also indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

**Regorafenib (Stivarga®)** is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.

#### **PONATINIB (Iclusig®)**

**Ponatinib (Iclusig®)** is indicated for the treatment of adult patients with accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated, and chronic phase CML with resistance or intolerance to at least two prior kinase inhibitors. Ponatinib is also indicated for the treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

**Ponatinib (Iclusig®)** inhibits the in vitro tyrosine kinase activity of Abelson murine leukemia (ABL) and T315I mutant ABL with half maximal inhibitory concentrations (IC50) of 0.4 and 2 nM, respectively. Ponatinib also inhibits the in vitro activity of additional kinases with IC50 concentrations between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib inhibits the in vitro viability of cells expressing native or mutant breakpoint cluster region-ABL, including T315I.



## **CABOZANTINIB MALATE (Cometriq®, Cabometyx®)**

**Cabozantinib malate (Cometriq®)** is indicated for the treatment of medullary thyroid cancer.

**Cabozantinib malate (Cabometyx®)** is indicated for treatment of patients with advanced renal cell carcinoma and as the first-line treatment of patients with advanced renal cell carcinoma RCC in combination with nivolumab. It is also indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with Nexavar® (sorafenib).

**Cabozantinib malate (Cometriq®, Cabometyx®)** inhibits the tyrosine kinase activity of RET; MET; VEGFR-1, -2, and -3; KIT; TRKB; FLT-3; AXL; and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

## **POMALIDOMIDE (Pomalyst®)**

**Pomalidomide (Pomalyst®)** is indicated for the treatment of adult patients:

- A. In combination with dexamethasone for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.
- B. With AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIVnegative. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)

**Pomalidomide (Pomalyst®)**, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In *in vitro* cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis.

## **DABRAFENIB (Tafinlar®)**

**Dabrafenib (Tafinlar®)** For the treatment of unresectable or metastatic melanoma in patients with a BRAF V600E mutation. Indicated in combination with trametinib, for the treatment of metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation.

**Dabrafenib (Tafinlar®)**, a kinase inhibitor, inhibits some mutated forms of BRAF kinases with *in vitro* concentration that inhibits 50% (IC<sub>50</sub>) values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC<sub>50</sub> values of 3.2 and 5 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Dabrafenib inhibits BRAF V600 mutation–positive melanoma cell growth *in vitro* and *in vivo*.

## **TRAMETINIB (Mekinist®)**

**Trametinib (Mekinist®)** is indicated as a single agent, for the treatment of unresectable or metastatic melanoma in patients with a BRAFV600E or BRAFV600K mutation as detected by a Food and Drug Administration (FDA)–approved test. Trametinib is indicated, in combination with dabrafenib, for the treatment of patient with unresectable or metastatic melanoma with BRAF V600E or V600K mutations and metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation. **Trametinib (Mekinist®)** is not indicated in patients who have received prior BRAF-inhibitor therapy.

**Trametinib (Mekinist®)**, a kinase inhibitor, is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAFV600E mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2. Trametinib inhibits BRAFV600 mutation-positive melanoma cell growth *in vitro* and *in vivo*.

## **AFATINIB (Gilotrif®)**

**Afatinib (Gilotrif®)** is indicated as a first-line treatment of metastatic non–small cell lung cancer in patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by a Food and Drug Administration–approved test. Afatinib is also indicated for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy.

**Afatinib (Gilotrif®)** a tyrosine kinase inhibitor, covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4), and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling.

### **IBRUTINIB (Imbruvica®)**

**Ibrutinib (Imbruvica®)** is indicated for the treatment of chronic lymphocytic leukemia (CLL) who have received at least 1 prior therapy; the treatment of mantle cell lymphoma (MCL) in patients who have received at least 1 prior therapy; the treatment of Waldenström's macroglobulinemia (WM), the treatment of marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy; and the treatment of adult patients with previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in combination with Gazyva® (obinutuzumab).

**Ibrutinib (Imbruvica®)** is a potent and irreversible inhibitor of Bruton tyrosine kinase (BTK), an integral component of the B-cell receptor (BCR) and cytokine receptor pathways. Constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells; BTK inhibition results in decreased malignant B-cell proliferation and survival.

### **CERTINIB (Zykadia®)**

**Ceritinib (Zykadia®)** is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)–positive metastatic nonsmall cell lung cancer (NSCLC) who has progressed on or are intolerant to crizotinib

**Ceritinib (Zykadia®)** is a potent inhibitor of anaplastic lymphoma kinase (ALK), a tyrosine kinase involved in the pathogenesis of nonsmall cell lung cancer. ALK gene abnormalities due to mutations or translocations may result in expression of oncogenic fusion proteins (e.g., ALK fusion protein) which alter signaling and expression and result in increased cellular proliferation and survival in tumors which express these fusion proteins. ALK inhibition reduces proliferation of cells expressing the genetic alteration. Ceritinib also inhibits insulinlike growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. Ceritinib has demonstrated activity in crizotinib-resistant tumors in NSCLC xenograft models.

### **IDELALISIB (Zydelig®)**

**Idelalisib (Zydelig®)** is indicated:

1. in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate due to other co-morbidities
2. for the treatment of patients with relapsed follicular B-cell non Hodgkin lymphoma (FL) who have received at least two prior systemic therapies
3. for the treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies

**Idelalisib (Zydelig®)** is an inhibitor of PI3K $\delta$  kinase, which is expressed in normal and malignant B-cells. Idelalisib induced apoptosis and inhibited proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib inhibits several cell signaling pathways, including B-cell receptor (BCR) signaling and the CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow. Treatment of lymphoma cells with idelalisib resulted in inhibition of chemotaxis and adhesion, and reduced cell viability. It is indicated for chronic lymphocytic leukemia, follicular B-cell non-hodgkin lymphoma, and small lymphocytic lymphoma.

### **OLAPARIB (Lynparza®)**

Ovarian Cancer

**Olaparib (Lynparza®)** is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to

1<sup>st</sup> line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Patients will be selected for therapy based on an FDA approved companion diagnostic for Lynparza®

#### Breast Cancer

Olaparib (Lynparza®) is indicated for the treatment of metastatic breast cancer in patients with deleterious or suspected deleterious germline BRCA mutated, human epidermal growth factor receptor 2 (HER2)-negative who have been treated with chemotherapy in neoadjuvant, adjuvant or metastatic setting.

#### Pancreatic Cancer

Olaparib (Lynparza®) is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regime.

#### Prostate Cancer

Olaparib (Lynparza®) is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza®.

#### **PANOBINOSTAT (Farydak®)**

**Panobinostat (Farydak®)** is approved, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

**Panobinostat (Farydak®)** is a histone deacetylase inhibitor (HDAC). Inhibition of HDAC activity results in increased acetylation of histone proteins, leading to transcriptional activation. In vitro, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells.

#### **PALBOCICLIB (Ibrance®)**

**Palbociclib (Ibrance®)** is indicated for the treatment of hormone receptor (HR)-positive, human epithelial growth factor receptor (HER2)-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or in combination with fulvestrant I women with disease progression following endocrine therapy.

**Palbociclib (Ibrance®)** inhibits cyclin-dependent kinase (CDK) 4 and 6. In vitro, palbociclib reduced cellular proliferation of ER-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle.

#### **LENVATINIB (Lenvima®)**

**Lenvatinib (Lenvima®)** is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer and advanced renal cell carcinoma.

**Lenvatinib (Lenvima®)** is a receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFR $\alpha$ ), KIT, and RET.

#### **TRIFLURIDINE/TIPIRACIL (Lonsurf®)**

**Trifluridine/tipiracil (Lonsurf®)** is indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth

factor (VEGF) biological therapy, and if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

**Trifluridine/tipiracil (Lonsurf®)** is a new orally administered antineoplastic combination of trifluridine, a thymidine-based nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor.

### **SONIDEGIB (Odomzo®)**

**Sonidegib (Odomzo®)** the second drug in the class of Hh pathway inhibitors, was approved for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

### **ALECTINIB (Alecensa®)**

**Alectinib (Alecensa®)** is a kinase inhibitor indicated for the treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response.

### **COBIMETINIB (Cotellic™)**

**Cobimetinib (Cotellic™)** is a MEK inhibitor approved to be used in combination with vemurafenib (Zelboraf) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.

### **IXAZOMIB (Ninlaro®)**

**Ixazomib (Ninlaro®)** is the first oral proteasome inhibitor approved by the FDA. Ixazomib is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior line of therapy.

### **OSIMERTINIB (Tagrisso™)**

**Osimertinib (Tagrisso™)** is an irreversible third-generation TKI, indicated for:

1. Adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test
2. First-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
3. Treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

### **VENTOCLAX (Venclexta™)**

**Ventoclax (Venclexta™)** is a BCL-2 inhibitor indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma. It is also indicated for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy when used in combination with azacitidine, or decitabine, or low-dose cytarabine (LDAC)

**RUCABARIB (Rubraca™)** is a PARP inhibitor indicated:

- A. For the maintenance 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.
- B. As monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.
- C. For the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for rucabarib

**RIBOCICLIB (Kisqali®)** is a kinase inhibitor indicated in combination with an aromatase 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.

**NIRAPARIB (Zejula™)** is a PARP inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

### **BRIGATINIB (Alunbrig™)**

**Brigatinib (Alunbrig™)** is a kinase inhibitor indicated for the treatment of ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed or are intolerant to crizotinib. The indication is 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 a confirmatory trial. This drug works by inhibiting autophosphorylation of ALK and ALK-mediated phosphorylation of downstream signaling proteins. This helps to inhibit the in vitro viability of cells expressing certain ALK and mutant ALK forms.

### **NERATINIB (Nerlynx™)**

Neratinib (Nerlynx™) is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. This drug works by reducing EGFR and HER2 autophosphorylation and downstream signaling pathways. It is also indicated in combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

### **MIDOSTAURIN (Rydapt™)**

Midostaurin (Rydapt™) is a kinase inhibitor indicated for the treatment of adult patients with the following conditions:  
(1): 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  
(2) aggressive systemic mastocytosis (ASM) or systemic mastocytosis with associated hematological neoplasm (SM-AHN)  
(3) mast cell leukemia

### **PEGINTERFERON ALFA-2B (Sylatron®)**

**Peginterferon alfa-2b (Sylatron®)** is indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.

**Alfa interferons induce various cellular activities related to binding with specific cell-surface membrane receptors, including suppression of cell proliferation, antiviral activity, and immunomodulatory effects.** The exact mechanism of **peginterferon alfa-2b** in treating melanoma is unknown.

### **ENASIDENIB (Idhifa®)**

Enasidenib (Idhifa®) is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

Enasidenib is a small molecule inhibitor of the isocitrate dehydrogenase 2 (IDH2) enzyme. Enasidenib targets the mutant IDH2 variants R140Q, R172S, and R172K at approximately 40-fold lower concentrations than the wild-type enzyme in vitro. Inhibition of the mutant IDH2 enzyme by enasidenib led to decreased 2-hydroxyglutarate (2-HG) levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH2 mutated AML. In blood samples from patients with AML with mutated IDH2, enasidenib decreased 2-HG levels, reduced blast counts and increased percentages of mature myeloid cells.

## **ABEMACICLIB (Verzenio®)**

Abemaciclib (Verzenio®) is a kinase inhibitor indicated:

- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

## **Acalabrutinib (Calquence®)**

**Acalabrutinib (Calquence®)** is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Acalabrutinib works by forming a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a small molecule which in B cells activates the pathway necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.

**Acalabrutinib (Calquence®)** is also indicated for the treatment of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

## **Duvelisib (Copiktra™)**

Duvelisib (Copiktra™) is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after two prior therapies. Copiktra™ is also indicated for relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. Duvelisib is an inhibitor of PI3K with inhibitory activity predominantly against PI3K- $\delta$  and PI3K- $\gamma$  isoforms expressed in normal and malignant B-cells. Duvelisib induced growth inhibition and reduced viability in cell lines derived from malignant B-cells and in primary CLL tumor cells. Duvelisib inhibits several key cell-signaling pathways, including B-cell receptor signaling and CXCR12-mediated chemotaxis of malignant B-cells. Additionally, duvelisib inhibits CXCL12-induced T cell migration and M-CSF and IL-4 driven M2 polarization of macrophages.

## **Dacomitinib (Vizimpro®)**

Dacomitinib (Vizimpro®) is a kinase inhibitor indicated for the first line treatment of individuals with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA approved test. Dacomitinib is an irreversible inhibitor of the kinase activity of the human EGFR family (EGFR/HER1, HER2, and HER4) and certain EGFR activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation). In vitro dacomitinib also inhibited the activity of DDR1, EPHA6, LCK, DDR2, and MNK1 at clinically relevant concentrations.

## **Talazoparib (Talzenna®)**

Talazoparib (Talzenna®) is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer. In vitro studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA 1 and 2, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis.

### **Lorlatinib (Lobrena®)**

Lorlatinib (Lobrena®) is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. Lorlatinib demonstrated in vitro activity against multiple mutant forms of ALK enzyme, including some mutations detected in tumors at the times of disease progression on crizotinib and other ALK inhibitors. Lorlatinib (Lobrena®) is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC).

### **Glasdegib (Daurismo™)**

Glasdegib (Daurismo™) is an inhibitor of the Hedgehog pathway. Glasdegib binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction. Glasdegib (Daurismo™) is indicated, in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy.

### **Larotrectinib (Vitrakvi®)**

Larotrectinib (Vitrakvi®) is an inhibitor of the tropomyosin receptor kinases (TRK), TRKA, TRKB, and TRKC. In in vitro and in vivo tumor models, larotrectinib demonstrated anti-tumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression. Larotrectinib (Vitrakvi®) is indicated for the treatment of adult and pediatric patients with solid tumors that have neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment.

### **Gilteritinib (Xospata®)**

Gilteritinib (Xospata®) is a small molecule that inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3). Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD. Gilteritinib (Xospata®) is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

### **Selinexor (Xpovio™)**

Selinexor is a nuclear export inhibitor. Selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and messenger ribonucleic acids (mRNAs) of oncogenic proteins by blocking exportin 1 (XPO1). This inhibition leads to accumulation of TSPs in the nucleus, reductions in several oncoproteins, cell cycle arrest, and apoptosis of cancer cells.

Selinexor is indicated:

1. In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
2. In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
3. For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

### **DAROLUTAMIDE (NUBEQA®)**

**Darolutamide (Nubeqa®)** is an androgen receptor (AR) inhibitor and competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. In vitro, darolutamide decreased prostate cancer cell proliferation

and functioned as a progesterone receptor (PR) antagonist. Darolutamide is indicated for the treatment of adults with non-metastatic, castration-resistant prostate cancer (nmCRPC)

### **PEXIDARTINIB (TURALIO™)**

**Pexidartinib (Turalio™)** is a small molecule tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD). Overexpression of CSF1R ligand promotes cell proliferation and accumulation in the synovium; pexidartinib inhibits proliferation of CSF1R-dependent cell lines. In vitro, pexidartinib also inhibits ligand-induced autophosphorylation of CSF1R. Pexidartinib is indicated for the treatment of adults with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery

### **ENTRECTINIB (ROZLYTREK™)**

**Entrectinib (Rozlytrek™)** is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2, and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK). Entrectinib also inhibits JAK2 and TNK2. Entrectinib inhibits cancer cell lines derived from multiple tumor types harboring NTRK, ROS1, and ALK fusion genes thus inhibiting tumorigenic potential through hyperactivation of downstream signaling pathways and uncontrolled cell proliferation caused by fusion proteins. Entrectinib is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumors are ROS1-positive. Select patients for the treatment of metastatic NSCLC based on the presence of ROS1 rearrangement(s) in tumor specimens. An FDA-approved test for detection of ROS1 rearrangement(s) in NSCLC for selecting patients for treatment with entrectinib is not available. Entrectinib is also indicated for the treatment of adults and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have progressed following treatment or have no satisfactory alternative therapy.

### **FEDRATINIB (INREBIC®)**

**Fedratinib (Inrebic®)** is a kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). Fedratinib is a JAK2-selective inhibitor with higher inhibitory activity for JAK2 over JAK1, JAK3 and TYK2. In cell models expressing mutationally active JAK2V617F or FLT3ITD, fedratinib reduced phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibited cell proliferation, and induced apoptotic cell death. Fedratinib is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)

### **AVAPRITINIB (AVYAKIT™)**

Avapritinib is a tyrosine kinase inhibitor that targets PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC50s) less than 25 nM. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumor cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1. AVYAKIT is indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. AVYAKIT is also indicated for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

### **ZANUBRUTINIB (BRUKINSA™)**

Zanubrutinib is a small-molecule inhibitor of BTK. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth. BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

### **SELUMETINIB (KOSELUGO™)**



Selumetinib is an inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Both MEK and ERK are critical components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. In genetically modified mouse models of NF1 that generate neurofibromas that recapitulate the genotype and phenotype of human NF1, oral dosing of selumetinib inhibited ERK phosphorylation, and reduced neurofibroma numbers, volume, and proliferation. KOSELUGO indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

### **TAZEMETOSTAT (TAZVERIK™)**

Tazemetostat is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations including Y646X, A682G, and A692V. Tazemetostat also inhibited EZH1 with a half-maximal inhibitory concentration (IC50) of 392 nM, approximately 36 times higher than the IC50 for inhibition of EZH2. The most well-characterized function of EZH2 is as the catalytic subunit of the polycomb repressive complex 2 (PRC2), catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3. Trimethylation of histone H3 leads to transcriptional repression. SWI/SNF/Sucrose Non-Fermentable (SWI/SNF) complexes can antagonize PRC2 function in the regulation of the expression of certain genes of patients with epithelioid sarcoma. Preclinical in vitro and in vivo models with the loss or dysfunction of certain SWI/SNF complex members (e.g., integrase interactor 1 [INI1/SNF5/SMARCB1/BAF47], SMARCA4, and SMARCA2) can lead to aberrant EZH2 activity or expression and a resulting oncogenic dependence on EZH2. Tazemetostat suppressed proliferation of B-cell lymphoma cell lines in vitro and demonstrated antitumor activity in a mouse xenograft model of B-cell lymphoma with or without EZH2 gain-of-function mutations. Tazemetostat demonstrated greater effects on the inhibition of proliferation of lymphoma cell lines with mutant EZH2.

TAZVERIK is indicated for the treatment of:

1. Adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.
2. Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
3. Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

### **TUCATINIB (TUKYSA™)**

Tucatinib is a tyrosine kinase inhibitor of HER2. In vitro, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream MAPK and AKT signaling and cell proliferation, and showed anti-tumor activity in HER2 expressing tumor cells. In vivo, tucatinib inhibited the growth of HER2 expressing tumors. The combination of tucatinib and trastuzumab showed increased anti-tumor activity in vitro and in vivo compared to either drug alone. TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

### **PEMIGATINIB (PEMAZYRE™)**

Pemigatinib is a small molecule kinase inhibitor that targets FGFR1, 2 and 3 with IC50 values of less than 2 nM. Pemigatinib also inhibited FGFR4 in vitro at a concentration approximately 100 times higher than those that inhibit FGFR1, 2, and 3. Pemigatinib inhibited FGFR1-3 phosphorylation and signaling and decreased cell viability in cancer cell lines with activating FGFR amplifications and fusions that resulted in constitutive activation of FGFR signaling. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Pemigatinib exhibited anti-tumor activity in mouse xenograft models of human tumors with FGFR1, FGFR2, or FGFR3 alterations resulting in constitutive FGFR activation including a patient-derived xenograft model of cholangiocarcinoma that expressed an oncogenic FGFR2Transformer-2 beta homolog (TRA2b) fusion protein. PEMAZYRE is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test

### **GEFITINIB (IRESSA®)**

Gefitinib reversibly inhibits the kinase activity of wild-type and certain activating mutations of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signaling and blocking EGFR-dependent proliferation. Gefitinib binding affinity for EGFR exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild-type EGFR. Gefitinib also inhibits IGF and PDGF-mediated signaling at clinically relevant concentrations; inhibition of other tyrosine kinase receptors has not been fully characterized.

Gefitinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

### **RIPRETINIB (QINLOCK™)**

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

Ripretinib is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

### **SELPERCATINIB (RETEVMO™)**

Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. In cellular assays, selpercatinib inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3.

Selpercatinib is indicated for the treatment of:

1. Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)<sup>1</sup>
2. Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy<sup>1</sup>
3. Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)<sup>1</sup>

<sup>1</sup>This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

### **CAPMATINIB (TABRECTA™)**

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

Capmatinib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA approved test.

### **TRETINOIN CAPSULES**

Tretinoin is a retinoid that induces maturation of acute promyelocytic leukemia (APL) cells in culture. Tretinoin is not a cytolytic agent but instead induces cytodifferentiation and decreased proliferation of Acute Promyelocytic Leukemia APL cells in culture and in vivo. In APL patients, tretinoin treatment produces an initial maturation of the primitive promyelocytes derived from the leukemic clone, followed by a repopulation of the bone marrow and peripheral blood by normal, polyclonal hematopoietic cells in patients achieving complete remission (CR). The exact mechanism of action of tretinoin in APL is unknown.

### **PRALSETINIB (GAVRETO™)**

Pralsetinib is a kinase inhibitor of wild-type RET and oncogenic RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M and RET M918T) with half maximal inhibitory concentrations (IC50s) less than 0.5 nM. In purified enzyme assays, pralsetinib inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRB, and FGFR1 at higher concentrations that were still clinically achievable at Cmax. In cellular assays, pralsetinib inhibited RET at approximately 14-, 40-, and 12-fold lower concentrations than VEGFR2, FGFR2, and JAK2, respectively.

Pralsetinib is indicated for the treatment of:

1. Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer as detected by an FDA approved test (NSCLC).<sup>1</sup>
2. Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.<sup>1</sup>
3. Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).<sup>1</sup>

<sup>1</sup>This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s)

### **AZACITIDINE (ONUREG®)**

Azacitidine is a pyrimidine nucleoside analog of cytidine that inhibits DNA/RNA methyltransferases. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates.

Azacitidine is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

### **DECITABINE AND CEDAZURIDINE (INQOVI®)**

Decitabine is a nucleoside metabolic inhibitor that is believed to exert its effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine is a CDA inhibitor. Administration of cedazuridine with decitabine increases systemic exposure of decitabine.

Decitabine and cedazuridine is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

### **RELUGOLIX (ORGOVYX™)**

Relugolix is an oral GnRH receptor antagonist that competitively binds to the GnRH receptor, resulting in reduced release of LH, FHS, and consequently testosterone. Clinical trials have shown its effect in testosterone suppression to castrate levels (50ng/dl) which was sustained through 48 weeks in 96.7% in advanced prostate cancer patients along with a confirmed PSA response by day 15 observed in 79.4% of the study group.

Relugolix is indicated for the treatment of advanced metastatic prostate cancer.

### **TEPOTINIB (TEPMETKO®)**

Tepotinib is an oral kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF) dependent and independent MET phosphorylation and MET-dependent downstream signaling pathways. In vitro, tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells. In mice implanted with tumor cell lines with oncogenic activation of MET, including METex14 skipping alterations, tepotinib inhibited tumor growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases.

TEPMETKO is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

### **UMBRALISIB (UKONIQ™)**

Umbralisib inhibits multiple kinases. In biochemical and cell-based assays, umbralisib inhibited PI3Kδ and casein kinase CK1ε. PI3Kδ is expressed in normal and malignant B-cells; CK1ε has been implicated in the pathogenesis of

cancer cells, including lymphoid malignancies. Umbralisib also inhibited a mutated form of ABL1 in biochemical assays. Umbralisib inhibited cell proliferation, CXCL12-mediated cell adhesion, and CCL19-mediated cell migration in lymphoma cell lines in studies conducted in vitro. Umbralisib is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen.

#### **FOTIVDA® (TIVOZANIB)**

FOTIVDA is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

#### **LUMAKRAS™ (SOTORASIB)**

LUMAKRAS is an inhibitor of the RAS GTPase family indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

#### **TRUSELTIQ™ (INFIGRATINIB)**

TRUSELTIQ is a kinase inhibitor indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

#### **VALCHLOR® (MECHLORETHAMINE)**

VALCHLOR is an alkylating drug indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy

#### **TARGRETIN® (BEXAROTENE)**

TARGRETIN (bexarotene) is a retinoid indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy

#### **EXKIVITY™ (mobocertinib)**

EXKIVITY is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Mobocertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR) that irreversibly binds to and inhibits EGFR exon 20 insertion mutations at lower concentrations than wild type (WT) EGFR. Two pharmacologically-active metabolites (AP32960 and AP32914) with similar inhibitory profiles to mobocertinib have been identified in the plasma after oral administration of mobocertinib. In vitro, mobocertinib also inhibited the activity of other EGFR family members (HER2 and HER4) and one additional kinase (BLK) at clinically relevant concentrations (IC50 values <2 nM).

#### **WELIREG™ (belzutifan)**

WELIREG is a hypoxia-inducible factor inhibitor indicated for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2 $\alpha$ ). HIF-2 $\alpha$  is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2 $\alpha$  is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional

VHL protein results in stabilization and accumulation of HIF-2 $\alpha$ . Upon stabilization, HIF-2 $\alpha$  translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1 $\beta$ ) to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2 $\alpha$ , and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2 $\alpha$ -HIF-1 $\beta$  interaction, leading to reduced transcription and expression of HIF-2 $\alpha$  target genes. In vivo, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

**Policy:**

Oncology agents are approved when ONE of the following inclusion criteria is met:

1. Drug is FDA approved for indication and regimen requested, including confirmation by genetic and/or biomarker testing when appropriate; or
2. The indication and regimen are classified as Category 1 or 2A by National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium™; or
3. The narrative text in American Hospital Formulary Service--Drug Information (AHFS-DI®) is supportive of the use; or
4. The indication is classified as Class I or Class IIa in Micromedex®

Yonsa®, Erleada®, and Zytiga® are approved when BOTH of the following inclusion criteria are met:

1. One of the following:
  - a. Drug is FDA approved for indication and regimen requested, including confirmation by genetic and/or biomarker testing when appropriate; OR
  - b. The indication and regimen are classified as Category 1 or 2A by National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium™; OR
  - c. The narrative text in American Hospital Formulary Service—Drug Information (AHFS-DI®) is supportive of the use; OR
  - d. The indication is classified as Class I or Class IIa in Micromedex®; and
2. ONE of the following:
  - a. Cancer stages I, II, III only, ONE of the following applies:
    - i. For Erleada®: inadequate response or inability to tolerate Xtandi® or Nubeqa®; or
    - ii. For Yonsa®, Zytiga®: inadequate response or inability to tolerate Xtandi®; or
  - b. Cancer stage IV only, the medication is requested for the treatment of stage IV, advanced metastatic cancer or a severe adverse health condition experienced as a result of stage IV, advanced metastatic cancer

Authorization duration: 2 years

**Black Box Warning as shown in the drug Prescribing Information:**

**Tibsovo®**

**Differentiation Syndrome:** Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

**Revlimid®**

**Fetal risk:** Do not use lenalidomide during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe, life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing fetus. In women of childbearing potential, obtain 2 negative pregnancy tests before starting lenalidomide treatment. Women of childbearing potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after lenalidomide treatment. To avoid fetal exposure to lenalidomide, it is only available under a restricted distribution program called RevAssist.

Information about the RevAssist program is available at <http://www.revlimid.com> or by calling the manufacturer's toll-free number 1-888-423-5436.

**Hematologic toxicity:** Lenalidomide can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with deletion 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for deletion 5q myelodysplastic syndromes should have their complete blood cell count (CBC) monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors

**Venous and arterial thromboembolism:** lenalidomide has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with lenalidomide and dexamethasone therapy. Monitor for and advise patients about the signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risk factors.

#### **Sutent®**

Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe, and deaths have been reported. Causality of the deaths is uncertain.

#### **Tykerb®**

Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe, and deaths have been reported. Causality of the deaths is uncertain.

#### **Tasigna®**

QT prolongation and sudden deaths: Nilotinib prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. Do not use nilotinib in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to nilotinib administration and should be monitored periodically. Avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Patients should avoid food 2 hours before and 1 hour after taking a nilotinib dose. A dose reduction is recommended in patients with hepatic impairment. Obtain electrocardiograms (ECGs) to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, as well as following any dose adjustments.

#### **Thalomid®**

##### EMBRYO -FETAL TOXICITY

If thalidomide is taken during pregnancy, it can cause severe birth defects or embryo-fetal death. Thalidomide should never be used by females who are pregnant or who could be pregnant while taking the drug. Even a single dose [1 capsule (regardless of strength)] taken by a pregnant woman during her pregnancy can cause severe birth defects.

Pregnancy must be excluded before start of treatment. Prevent pregnancy thereafter by the use of two reliable methods of contraception.

THALOMID® (thalidomide) is only available through a restricted distribution program, the THALOMID REMSTM program (formerly known as the System for Thalomid Education and Prescribing Safety (S.T.E.P.S.®) program).

##### VENOUS THROMBOEMBOLISM

Significant increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving THALOMID® (thalidomide) with dexamethasone.

#### **Hycamtin®**

Bone marrow suppression: Administer topotecan only to patients with baseline neutrophil counts of 1,500 cells/mm<sup>3</sup> or more and a platelet count of 100,000 cells/mm<sup>3</sup> or more. In order to assess the occurrence of bone marrow suppression, monitor blood cell counts.

#### **Oforta®**

Some patients who received high doses of this medicine to treat acute leukemia developed severe nervous system side effects, including blindness, coma, and death. Similar nervous system side effects, including coma, seizures, agitation, and confusion, have occurred in patients at doses recommended for the treatment of chronic lymphocytic leukemia. Discuss any questions or concerns with your doctor. Contact your doctor right away if any of these effects occur.

This medicine may severely decrease bone marrow function. This can lower your body's ability to fight infection and reduce the ability of your blood to clot properly. Some patients have developed severe and sometimes fatal blood problems (e.g., hemolytic anemia, autoimmune thrombocytopenia, hemophilia) while using this medicine. Your doctor will need to monitor you closely for these conditions. Tell your doctor right away if you develop signs or symptoms of an infection (e.g., swollen glands, sore throat, fever, chills), bleeding problems (e.g., easy bruising; black, tarry stools; bleeding from the gums), or hemolytic anemia (e.g., yellowing of eyes or skin, dark urine, severe tiredness or weakness). Be sure to keep all doctor and laboratory appointments.

Fatal lung problems have been reported in patients receiving this medicine along with pentostatin. This medicine is not recommended for use with pentostatin.

#### **Votrient®**

Hepatotoxicity: Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue regorafenib for hepatotoxicity as manifested by elevated liver function tests (LFTs) or hepatocellular necrosis, depending upon severity and persistence.

#### **Caprelsa®**

QT prolongation, torsades de pointes, and sudden death: Vandetanib can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving vandetanib. Do not use vandetanib in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia, and/or hypomagnesemia must be corrected prior to vandetanib administration and should be periodically monitored. Avoid drugs known to prolong the QT interval. If a drug known to prolong the QT interval must be administered, more frequent electrocardiogram (ECG) monitoring is recommended. Given the half-life of 19 days, obtain ECGs to monitor the QT interval at baseline, at 2 to 4 and 8 to 12 weeks after starting treatment with vandetanib, and every 3 months thereafter. Following any dose reduction for QT prolongation or any dose interruptions more than 2 weeks, conduct QT assessment as previously described. Because of the 19-day half-life, adverse reactions, including a prolonged QT interval, may not resolve quickly. Monitor appropriately. Only health care providers and pharmacies certified with the restricted distribution program are able to prescribe and dispense vandetanib.

#### **Erivedge®**

ERIVEDGE can result in embryo-fetal death or severe birth defects. Verify pregnancy status prior to initiation of ERIVEDGE. Advise male and female patients of these risks. Advise females of the need for contraception and advise males of the potential risk of ERIVEDGE exposure through semen.

#### **Stivarga®**

Hepatotoxicity: Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue regorafenib for hepatotoxicity as manifested by elevated liver function tests (LFTs) or hepatocellular necrosis, depending upon severity and persistence.

#### **Iclusig®**

Arterial occlusive events (AOEs), including fatalities, have occurred in Iclusig-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue Iclusig based on severity. Consider benefit-risk to guide a decision to restart Iclusig. Venous thromboembolic events (VTEs)

have occurred in Iclusig-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue Iclusig based on severity.

Heart failure, including fatalities, occurred in Iclusig treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue Iclusig for new or worsening heart failure.

Hepatotoxicity: Hepatotoxicity, liver failure, and death have occurred in ponatinib-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue ponatinib for hepatotoxicity.

### **Cometriq®**

Perforations and fistulas: GI perforations occurred in 3% and fistula formation in 1% of cabozantinib-treated patients. Discontinue cabozantinib for perforation or for fistula formation.

Hemorrhage: Severe and sometimes fatal hemorrhage, including hemoptysis and GI hemorrhage, occurred in 3% of cabozantinib-treated patients. Monitor patients for signs and symptoms of bleeding. Do not administer cabozantinib to patients with severe hemorrhage.

### **Pomalyst®**

**Embryo-fetal toxicity:** Pomalidomide, a thalidomide analogue, is contraindicated in pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In women of reproductive potential, obtain 2 negative pregnancy tests before starting pomalidomide. Women of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sexual intercourse during and for 4 weeks after stopping treatment. Pomalidomide is only available through a restricted distribution program called **Pomalyst** Risk Evaluation and Mitigation Strategy (REMS).

**Venous and arterial thromboembolism:** Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Antithrombotic prophylaxis is recommended. Consider prophylactic measures after assessing an individual patient's underlying risk factors.

### **Zydelig®**

Fatal and/or serious hepatotoxicity occurred in 16%-18% of Zydelig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Zydelig.

Fatal and/or serious and severe diarrhea or colitis occurred in 14%-20% of Zydelig-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue Zydelig.

Fatal and serious pneumonitis can occur in 4% of Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig.

Fatal and/or serious infections occurred in 21% to 48% of Zydelig-treated patients. Monitor for signs and symptoms of infection. Interrupt Zydelig if infection is suspected.

Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig if intestinal perforation is suspected.

### **Farydak®**

Severe diarrhea occurred in 25% of FARYDAK treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt FARYDAK and then reduce dose or discontinue FARYDAK.



Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving FARYDAK. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.

### **Odomzo®**

#### **EMBRYO-FETAL TOXICITY**

Odomzo can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is embryotoxic, fetotoxic, and teratogenic in animals. Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose. Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose.

### **Sylatron®**

**Depression and other neuropsychiatric disorders:** The risk of serious depression with suicidal ideation, completed suicides, and other serious neuropsychiatric disorders are increased with alpha interferons, including Sylatron. Permanently discontinue Sylatron in patients with persistently severe or worsening signs or symptoms of depression, psychosis, or encephalopathy. These disorders may not resolve after stopping Sylatron.

### **Idhifa®**

**Differentiation syndrome:** Patients treated with Idhifa have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom reduction.

### **Copiktra™**

**Fatal and serious toxicities: infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.** Fatal and/or serious infections occurred in 31% of COPIKTRA treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected. Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA. Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA. Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA.

### **Daurismo™**

**Embryo-Fetal Toxicity:** Daurismo™ can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. DAURISMO is embryotoxic, fetotoxic, and teratogenic in animals. Conduct pregnancy testing in females of reproductive potential prior to initiation of Daurismo™ treatment. Advise females of reproductive potential to use effective contraception during treatment with Daurismo™ and for at least 30 days after the last dose. Advise males of potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with Daurismo™ and for at least 30 days after the last dose to avoid potential drug exposure.

### **Targretin®, bexarotene**

**Birth Defects:** TARGRETIN is a member of the retinoid class of drugs that is associated with birth defects in humans. Bexarotene also caused birth defects when administered orally to pregnant rats. Bexarotene (Targretin®) must not be administered to a pregnant woman.

### **Pexidartinib (Turalio™)**

Pexidartinib can cause serious and potentially fatal liver injury. Monitor liver tests prior to initiation of pexidartinib and at specified intervals during treatment. Withhold dose and reduce or permanently discontinue pexidartinib based on

severity of hepatotoxicity. Pexidartinib is available only through a restricted program call the Turalio Risk Evaluation and Mitigation Strategy (REMS) Program.

### **Fedratinib (Inrebic®)**

Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with fedratinib. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. Do not start fedratinib in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue fedratinib and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize

### **Tretinoin capsule**

#### **EXPERIENCED PHYSICIAN AND INSTITUTION**

Patients with acute promyelocytic leukemia (APL) are at high risk in general and can have severe adverse reactions to tretinoin capsules. Tretinoin capsules should therefore be administered only to patients with APL under the strict supervision of a physician who is experienced in the management of patients with acute leukemia and in a facility with laboratory and supportive services sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity, including respiratory compromise. Use of tretinoin capsules requires that the physician concludes that the possible benefit to the patient outweighs the following known adverse effects of the therapy.

#### **RETINOIC ACID-APL SYNDROME**

About 25% of patients with APL treated with tretinoin capsules have experienced a syndrome called the retinoic acid-APL (RA-APL) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. It has been observed with or without concomitant leukocytosis. Endotracheal intubation and mechanical ventilation have been required in some cases due to progressive hypoxemia, and several patients have expired with multi-organ failure. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of tretinoin capsules.

The management of the syndrome has not been defined rigorously, but high-dose steroids given at the first suspicion of the RA-APL syndrome appear to reduce morbidity and mortality. At the first signs suggestive of the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously administered every 12 hours for 3 days or until the resolution of symptoms) should be immediately initiated, irrespective of the leukocyte count. The majority of patients do not require termination of tretinoin capsules therapy during treatment of the RA-APL syndrome. However, in cases of moderate and severe RA-APL syndrome, temporary interruption of tretinoin capsules therapy should be considered.

#### **LEUKOCYTOSIS AT PRESENTATION AND RAPIDLY EVOLVING LEUKOCYTOSIS DURING TRETINOIN CAPSULES TREATMENT**

During tretinoin capsules treatment about 40% of patients will develop rapidly evolving leukocytosis. Patients who present with high WBC at diagnosis ( $>5 \times 10^9 / L$ ) have an increased risk of a further rapid increase in WBC counts. Rapidly evolving leukocytosis is associated with a higher risk of life-threatening complications.

If signs and symptoms of the RA-APL syndrome are present together with leukocytosis, treatment with high-dose steroids should be initiated immediately. Some investigators routinely add chemotherapy to tretinoin capsules treatment in the case of patients presenting with a WBC count of  $>5 \times 10^9 / L$  or in the case of a rapid increase in WBC count for patients leukopenic at start of treatment, and have reported a lower incidence of the RA-APL syndrome. Consideration could be given to adding full-dose chemotherapy (including an anthracycline if not contraindicated) to the tretinoin capsules therapy on day 1 or 2 for patients presenting with a WBC count of  $>5 \times 10^9 / L$ , or immediately, for patients presenting with a WBC count of  $<5 \times 10^9 / L$ , if the WBC count reaches  $\geq 6 \times 10^9 / L$  by day 5, or  $\geq 10 \times 10^9 / L$  by day 10, or  $\geq 15 \times 10^9 / L$  by day 28.

#### **TERATOGENIC EFFECTS**

There is a high risk that a severely deformed infant will result if tretinoin capsules are administered during pregnancy. If, nonetheless, it is determined that tretinoin capsules represent the best available treatment for a pregnant woman or a woman of childbearing potential, it must be assured that the patient has received full information and warnings of the risk to the fetus if she were to be pregnant and of the risk of possible contraception failure and has been instructed in the need to use two reliable forms of contraception simultaneously during therapy and for 1 month following discontinuation of therapy, and has acknowledged her understanding of the need for using dual contraception, unless abstinence is the chosen method.

Within 1 week prior to the institution of tretinoin capsules therapy, the patient should have blood or urine collected for a serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL. When possible, tretinoin capsules therapy should be delayed until a negative result from this test is obtained. When a delay is not possible, the patient should be placed on two reliable forms of contraception. Pregnancy testing and contraception counseling should be repeated monthly throughout the period of tretinoin capsules treatment.

**Xospata®:**

Differentiation Syndrome: Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution

**Targretin®:**

Birth defects: TARGRETIN is a member of the retinoid class of drugs that is associated with birth defects in humans. Bexarotene also caused birth defects when administered orally to pregnant rats. TARGRETIN must not be administered to a pregnant woman.

**Exkivity™:**

**QTc PROLONGATION AND TORSADES DE POINTES**

EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation.

Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc.

Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation.

**Welireg™:**

**EMBRYO-FETAL TOXICITY**

Exposure to WELIREG during pregnancy can cause embryo-fetal harm. Verify pregnancy status prior to the initiation of WELIREG. Advise patients of these risks and the need for effective non-hormonal contraception. WELIREG can render some hormonal contraceptives ineffective.

**Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

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**Applicable Drugs:**

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Gleevec®	imatinib mesylate
Nexavar®	sorafenib
Revlimid®	lenalidomide
Sprycel®	dasatinib
Sutent®	sunitinib malate
Tarceva®	erlotinib
Thalomid®	thalidomide
Zolinza®	vorinostat
Tykerb®	lapatinib
Tasigna®	nilotinib
Hycamtin®	topotecan
Temodar®	temozolimide
Afinitor®	everolimus
Oforta®	fludarabine Phosphate
Votrient®	pazopanib
Caprelsa®	vandetanib
Zytiga®	abiraterone
Zelboraf®	vemurafenib
Xalkori®	crizotinib
Jakafi®	ruxolitinib
Inlyta®	axitinib
Erivedge®	vismodegib
Xtandi®	enzalutamide
Bosulif®	bosutinib
Stivarga®	regorafenib
Iclusig®	ponatinib
Cometriq®, Cabometyx®	cabozantinib
Pomalyst®	pomalidomide

Tafinlar®	dabrafenib
Mekinist®	trametinib
Gilotrif®	afatinib
Imbruvica®	ibrutinib
Zykadia®	ceritinib
Zydelig®	idelalisib
Lynparza®	olaparib
Farydak®	panobinostat
Ibrance®	palbociclib
Lenvima®	lenvatinib
Lonsurf®	trifluridine/tipiracil
Odomzo®	sonidegib
Alecensa®	alectinib
Cotellic®	cobimetinib
Ninlaro®	ixazomib
Tagrisso®	osimertinib
Venclexta®	venetoclax
Rubraca®	rucaparib
Kisqali®	ribociclib
Zejula®	niraparib
Alunbrig®	brigatinib
Nerlyx®	neratinib
Rydapt®	midostaurin
Idhifa®	enasidenib
Verzenio®	abemaciclib
Sylatron®	peginterferon alfa-2b
Calquence®	acalabrutinib
Tibsovo®	ivosidenib
Mektovi®	binimetinib
brafтови®	encorafenib
Erleada™	apalutamide
Copiktra™	duvelisib
Vizimpro®	dacomitinib
Talzenna®	talazoparib
Lorbrena®	lorlatinib
Daurismo™	glasdegib
Vitrakvi®	larotrectinib
Xospata®	gilteritinib
Balversa®	erdafitinib
Piqray®	alpelisib
Xpovio™	selinexor
Targretin® oral capsule and topical gel	bexarotene
Nubeqa®	darolutamide
Turalio™	pexidartinib
Rozlytrek™	entrectinib
Inrebic®	fedratinib
Ayvakit™	avapritinib
Brukinsa®	Zanubrutinib
Koselugo™	selumetinib

Tazverik™	tazemetostat
Tukysa™	tucatinib
Pemazyre™	pemigatinib
Qinlock®	ripretinib
Retevmo™	selpercatinib
Tabrecta™	capmatinib
Iressa®	Gefitinib
	tretinoin capsules
Gavreto™	Pralsetinib
Inqovi®	Deciabine and cedazuridine
Onureg®	azacitidine
Orgovyx™	relugolix
Tepmetko®	tepotinib
Ukoniq™	umbralisib
Fotivda®	tivozanib
Truseltiq™	infigratinib
Lumakras™	sotorasib
Valchlor®	mechlorethamine
Exkivity™	mobocertinib
Welireg™	belzutifan

**Cross References:**

Rx.01.33 Off-Label Use

Rx.01.76 Quantity Level Limits for Pharmaceuticals Covered Under the Prescription Drug Benefit

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<b>Policy Version Number:</b>	37.00
<b>P&amp;T Approval Date:</b>	December 09, 2021
<b>Policy Effective Date:</b>	April 01, 2022
<b>Next Required Review Date:</b>	September 23, 2022

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