

Oncology Agents, Oral Review

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Oncology Agents, Oral Review

FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indications
capecitabine (Xeloda®) ¹	Roche	<ul style="list-style-type: none"> • Single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred • First-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred • In combination with docetaxel, for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy • For the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated
dasatinib (Sprycel®) ²	Bristol-Meyers Squibb	<ul style="list-style-type: none"> • Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including imatinib • Treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy
erlotinib (Tarceva®) ³	Genentech	<ul style="list-style-type: none"> • Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy • Treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen • First-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine
everolimus (Afinitor®) ⁴	Novartis	<ul style="list-style-type: none"> • Advanced RCC after failure of treatment with sunitinib or sorafenib
*gefitinib (Iressa®) ⁵	AstraZeneca	<ul style="list-style-type: none"> • Monotherapy for the continued treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies

RCC = renal cell carcinoma; Ph+ = Philadelphia chromosome positive; CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer.

*Since September 15, 2005, gefitinib (Iressa) is no longer available for new patients. Existing patients already on drug can continue to get medication through Iressa Access Program. A large, Phase III trial showed no survival benefit for gefitinib versus placebo, in NSCLC.⁶

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
imatinib (Gleevec®) ⁷	Novartis	<ul style="list-style-type: none"> • Newly diagnosed adult patients with Ph+ CML in chronic phase • Patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy • Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy • Adult patients with relapsed or refractory Ph+ ALL • Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene re-arrangements • Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown • Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who are FIP1L1-PDGFRα fusion kinase-negative or unknown • Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans • 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 gastrointestinal stromal tumors
lapatinib (Tykerb®) ⁸	GlaxoSmithKline	<ul style="list-style-type: none"> • In combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab • 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
nilotinib (Tasigna®) ⁹	Novartis	<ul style="list-style-type: none"> • Accelerated phase and chronic phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib
pazopanib (Votrient®) ¹⁰	GlaxoSmithKline	<ul style="list-style-type: none"> • Treatment of advanced RCC

RCC = renal cell carcinoma; Ph+ = Philadelphia chromosome positive; CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
sorafenib (Nexavar®) ¹¹	Bayer	<ul style="list-style-type: none">• Unresectable HCC• Advanced RCC
sunitinib malate (Sutent®) ¹²	Pfizer	<ul style="list-style-type: none">• Gastrointestinal stromal tumors after disease progression on or intolerance to imatinib mesylate• Advanced RCC

RCC = renal cell carcinoma; Ph+ = Philadelphia chromosome positive; CML = chronic myeloid leukemia; ALL = acute lymphoblastic leukemia; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer

Overview^{13,14}

With the increase of treatment options available via oral administration, cancer patients have more diverse treatment options than they did just ten years ago. This can shift some treatment responsibility from the medical infusion facilities and physician offices to the patient. However, many patients have misconceptions regarding oral agents, such as the concepts of increased convenience and improved tolerability. While the convenience of receiving doses at home is appealing, complex monitoring and dosing schedules may remain. Several oral agents are used in combination with IV chemotherapy which means they would have to get these infusions at the physicians' office or clinic anyway. As for tolerability, many of these agents have adverse effects that should be treated in a similar manner to intravenous medications. For these reasons, oral agents can have the detriment of decreased patient adherence compared to the assurance a physician receives from knowing whether a patient received a dose at a clinic or not. The National Comprehensive Cancer Network (NCCN) has reviewed the role of many oral products in the treatment algorithms for indicated diseases; their recommendations for 2010 are as follows:

Breast cancer

Lapatinib (Tykerb) is a preferred agent for patients meeting the description of that indication, according to NCCN guidelines, along with other first-line agents used in combination with trastuzumab (Herceptin).¹⁵ Capecitabine (Xeloda) is also a preferred agent, as indicated, along with several other first-line agents.

CML

CML is a hematologic cancer that affects blood and bone marrow. A majority of patients suffering from CML possess a gene mutation called the Philadelphia chromosome. In the genetic abnormality, a section of chromosome 9 and a section of chromosome 22 switch places and as a result, the breakpoint cluster region (BCR) gene from chromosome 22 is fused with the ABL gene on chromosome 9. As the ABL gene carries a domain that can add phosphate groups to tyrosine residues, transcription of this BCR-ABL fusion gene produces a protein, p210^{BCR-ABL}, which has constitutive abnormal tyrosine kinase activity.

Three phases are used to classify CML based on the number of blast cells in the blood and bone marrow. Chronic phase CML is characterized by the presence of less than ten percent blast cells in blood and bone marrow. If the percentage of blast cells in the blood and bone marrow ranges from ten to 19, the disease is classified as accelerated phase CML. Blast cells representing 20 percent or more of the cells in the blood and bone marrow constitutes blastic phase CML (also known as blast crisis).

For patients newly diagnosed with Philadelphia chromosome-positive CML (Ph+CML) in the chronic phase, the NCCN clinical guidelines recommend imatinib (Gleevec) as the only first-line pharmacologic therapy.¹⁶ Other treatment options including dasatinib (Sprycel) and nilotinib (Tasigna) should be considered if the patient is intolerant to therapy with imatinib or if patients CML progresses despite imatinib therapy.

Colon cancer

Capecitabine (Xeloda) is recommended by NCCN as preferred according to its indication language, along with other first-line chemotherapy regimens.¹⁷

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans is an uncommon tumor that arises in the dermis layer of the skin. Imatinib (Gleevec) is recommended by NCCN as the only first-line pharmacologic therapy.¹⁸

Gastrointestinal stromal tumors

Imatinib (Gleevec) is recommended as first-line therapy for metastatic/recurrent or resected gastrointestinal stromal tumors in the NCCN clinical practice guideline for soft tissue sarcomas.¹⁹ In cases of disease progression despite imatinib therapy, or imatinib failure, sunitinib (Sutent) is recommended as second-line treatment.

Hepatocellular carcinoma

Sorafenib (Nexavar) is recommended as the only first-line pharmacologic therapy by NCCN.²⁰

NSCLC

Erlotinib (Tarceva) is recommended in accordance with its indication language, as are other chemotherapy regimens.²¹ Gefitinib (Iressa) is not included in the NCCN treatment algorithm.

Pancreatic cancer

Erlotinib (Tarceva) is recommended by NCCN as preferred according to its indication language, along with other first-line chemotherapy regimens.²²

Renal cell carcinoma

The NCCN guidelines for kidney cancer recommend sunitinib (Sutent), pazopanib (Votrient), or sorafenib (Nexavar) as first-line therapy alternatives for relapse or Stage IV and medically or surgically unresectable clear cell and non-clear cell RCC; capecitabine (Xeloda) is recommended as a first line alternative for non-clear cell RCC only.²³ Everolimus (Afinitor) is recommended for use according to its indication language.

Other

No NCCN recommendations exist for Ph+ ALL, myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene re-arrangements, aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown, and hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFR α fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who are FIP1L1-PDGFR α fusion kinase-negative or unknown.

Pharmacology^{24,25,26,27,28,29,30,31,32,33,34,35,36,37}

Protein kinase inhibitors function by binding to the adenosine triphosphate (ATP) binding site found on receptor and non-receptor tyrosine kinase proteins. If the ATP binding site is occupied by a protein kinase inhibitor, ATP is unable to bind and hence, donate a phosphate group to the protein residue on the substrate and activate the target protein. Therefore, activation of downstream signaling pathways that could lead to uncontrolled tumor cell growth and differentiation is inhibited.

Capecitabine (Xeloda) is a fluoropyrimidine carbamate which is converted *in vivo* to 5-fluorouracil (5-FU) and causes cell injury by inhibiting DNA synthesis and interfering with RNA processing and protein synthesis.

Pharmacology (continued)

Drug	Tyrosine Kinase Inhibition														
	Non-Receptor					Receptor									
	BCR-ABL	SRC	ABL	mTOR	LCK	VEGF	cKIT	EPHA2	FLT-3	PDGF	RET	CSF-1R	EGFR	HER2	C-FMS
capecitabine (Xeloda)															
dasatinib (Sprycel)	X	X	X				X	X		X					
erlotinib (Tarceva)													X		
everolimus (Afinitor)				X		X	X			X					
gefitinib (Iressa)													X		
imatinib (Gleevec)	X		X				X			X					
lapatinib (Tykerb)													X	X	
nilotinib (Tasigna)	X														
pazopanib (Votrient)					X	X	X			X					X
sorafenib (Nexavar)						X	X		X	X	X				
sunitinib (Sutent)						X	X		X	X	X	X			

BCR = breakpoint cluster region; ABL = Abelson; mTOR = mammalian target of rapamycin; LCT = leukocyte specific; VEGF = vascular endothelial growth factor; cKIT = stem cell factor cKIT; EPHA = ephrin A; PDGF = platelet derived growth factor; RET = glial cell-line derived neurotrophic factor; EGFR = epidermal growth factor; CSF-1R = colony stimulating factor Type 1; HER2 = human epidermal Type 2; C-FMS = transmembrane glycoprotein tyrosine kinase

Pharmacokinetics ^{38,39,40,41,42,43,44,45,46,47,48}

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active metabolites	Elimination (%)	Effect of High Fat Meal (%)
capecitabine (Xeloda)	0.75	< 60	Enzymatic conversion to 5-FU; extensive enzyme metabolism to fluoro-beta-alanine	5-FU	Feces: 2.6 Urine: 95.5	AUC: ▼ 35 Cmax: ▼ 60
dasatinib (Sprycel)	3-5	96	CYP3A4	yes	Feces: 85 Urine: 4	AUC: ▲ 14
erlotinib (Tarceva)	36.2	93	CYP3A4: major CYP1A2, 1A1: minor	none	Feces: 83 Urine: 8	Bioavailability: ▲ 167
everolimus (Afinitor)	30	74	CYP3A4; P-gP	none	Feces: 80 Urine: 5	Cmax: ▼ 42-60 AUC: ▼ 16-32
gefitinib (Iressa)	48	90	CYP3A4	O-desmethyl gefitinib	Feces: 86 Urine: < 4	none
imatinib (Gleevec)	18	95	CYP3A4: major CYP1A2, 2D6, 2C9, 2C19: minor	N-demethyl derivative (half-life 40 hours)	Feces: 68 Urine: 13	none
lapatinib (Tykerb)	24	> 99	CYP3A4, 3A5: major CYP2C19, 2C8: minor	none	Feces: 27 (parent compound) Urine: <2	AUC: ▲ 200-300 Cmax: ▲ 150-200
nilotinib (Tasigna)	17	98	oxidation and hydroxylation	none	Feces: 93	AUC: ▲ 82
pazopanib (Votrient)	30.9	> 99	CYP3A4: major CYP1A2, 2C8: minor	none	Feces: majority Urine: < 4	AUC: ▲ 100 Cmax: ▲ 100
sorafenib (Nexavar)	25-48	99.5	CYP3A4; glucuronidation by UGT1A9	Pyridine N-oxide	Feces: 77 Urine: 19	Bioavailability: ▼ 29
sunitinib (Sutent)	40-60	95	CYP3A4	yes (half-life 80-110 hours)	Feces: 61 Urine: 16	none

Contraindications/Warnings ^{49,50,51,52,53,54,55,56,57,58,59}Contraindications

Capecitabine (Xeloda) is contraindicated in patients with known hypersensitivity to capecitabine or any of the components or 5-fluorouracil (5-FU), known dihydropyrimidine dehydrogenase

(DPD) deficiency, and patients with severe renal impairment (Cockcroft/Gault creatinine clearance [CrCl] less than 30 mL/min).

Nilotinib (Tasigna) should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

Gefitinib (Iressa), lapatinib (Tykerb), and sorafenib (Nexavar) are contraindicated in patients with hypersensitivity to the active drug or any of the components.

Hypersensitivity to everolimus (Afinitor), to other rapamycin derivatives, or to any of the excipients is a contraindication for everolimus. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

There are no contraindications with imatinib (Gleevec), dasatinib (Sprycel), erlotinib (Tarceva), pazopanib (Votrient), or sunitinib (Sutent).

Boxed warnings

Capecitabine labeling has a boxed warning related to a severe interaction with oral coumarin-derivative anticoagulants. Concomitant use may significantly alter coagulation parameters and/or bleeding; deaths have been reported. The events can occur several days up to several months after initiation of capecitabine; one report occurred within one month of discontinuation of capecitabine therapy. Patients should have anticoagulant response (PT and/or INR) monitored frequently in order adjust anticoagulant doses appropriately. Age over 60 years and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Lapatinib labeling has a boxed warning related to hepatotoxicity. Hepatotoxicity has been observed in clinical trials and postmarketing experience and may be severe and even fatal. Causality of the deaths is uncertain. Alanine transaminase (ALT) or aspartate aminotransferase (AST) > three times the upper limit of normal (ULN) and total bilirubin \geq two times ULN have been observed in clinical trials (less than one percent of patients) and postmarketing experience. Hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests, including transaminases, bilirubin, and alkaline phosphatase, should be performed prior to initiation of therapy, every four to six weeks during treatment, and as clinically indicated. If lapatinib is to be administered to patients with severe pre-existing hepatic impairment, a dose reduction should be considered. For those patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued, and patients should not be retreated with lapatinib.

Nilotinib labeling has a boxed warning related to QT prolongation and sudden deaths. Use of nilotinib is associated with prolongation of the QT interval. For this reason, it should not be used in patients with hypokalemia, hypomagnesemia, or in patients experiencing long QT syndrome. Before initiating therapy with nilotinib, hypokalemia and hypomagnesemia must be corrected, and monitoring of these electrolytes is recommended. Concomitant use of medications associated with QT prolongation and strong inhibitors of the CYP3A4 enzyme system should be avoided in patients taking nilotinib. Food should not be consumed two hours before or one hour after the dose is taken due to increased bioavailability when taken with food. An ECG should be obtained at baseline, one week after treatment has started, and periodically thereafter to

monitor the QTc. ECGs should also be obtained after any changes in dosage. A dose reduction of nilotinib is recommended in patients with hepatic impairment.

In an ongoing study of 867 patients, there were five sudden deaths reported in patients receiving treatment with nilotinib. Possible abnormalities in ventricular repolarization are suspected of contributing to these reported deaths given their early occurrence relative to the start of therapy with nilotinib.

Pazopanib carries a boxed warning related to hepatotoxicity manifested as increases in ALT, AST, and bilirubin. Hepatotoxicity can be severe and fatal. Transaminase (ALT, AST) elevations occur early in the course of treatment (92.5 percent of any grade occurred in the first 18 weeks). In all monotherapy studies, ALT > three times ULN was reported in 14 percent and ALT > eight times ULN was reported in four percent of patients receiving pazopanib. Concurrent elevations in ALT > three times ULN and bilirubin > two times ULN regardless of alkaline phosphatase levels were detected in one percent (13 of 977) of patients. Four of the 13 patients had no other explanation for the elevations. Two of the 977 patients died due to disease progression and hepatic failure. Liver function tests should be performed prior to initiation of therapy and at least once every four weeks for at least the first four months of treatment or as clinically indicated. Periodic monitoring should continue after four months. Patients with isolated ALT elevations between three to eight times ULN may continue on pazopanib with weekly monitoring of liver function until ALT returns to Grade 1 or baseline. Patients with isolated ALT elevations of > eight times ULN should temporarily discontinue pazopanib therapy until levels return to Grade 1 or baseline. If the potential benefit of pazopanib therapy outweighs the risk of hepatotoxicity, then reintroduce pazopanib at a reduced dose of no more than 400 mg daily, and measure serum liver function tests weekly for eight weeks. If ALT elevations of > three times ULN recur, then pazopanib therapy should be permanently discontinued. If ALT elevations > three times ULN occur concurrently with bilirubin elevations > two times ULN, pazopanib should be permanently discontinued. Patients should be monitored until resolution.

Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT > three X ULN should be managed as per the recommendations outlined for isolated ALT elevations. The safety of pazopanib in patients with pre-existing severe hepatic impairment, defined as total bilirubin > three X ULN with any level of ALT, is unknown. Treatment with pazopanib is not recommended in patients with severe hepatic impairment.

Selected Warnings and Recommended Monitoring^{60,61,62,63,64,65,66,67,68,69,70}

Drug	Selected Warnings	Recommended Monitoring
capecitabine (Xeloda)	Renal insufficiency (requires dose reduction), coagulopathy with warfarin, severe diarrhea, greater risk of grade 3 or 4 adverse effects for patients >80 years	ECG, bilirubin, CBC with platelet count, fluid status, INR with warfarin therapy
dasatinib (Sprycel)	myelosuppression, bleeding related events, fluid retention, QT prolongation	CBC, ECG
erlotinib (Tarceva)	interstitial lung disease, renal toxicity, hepatotoxicity, gastrointestinal perforation, bullous and exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accident, microangiopathic hemolytic anemia with thrombocytopenia, ocular disorders, INR elevations/bleeding events	pulmonary signs/symptoms, serum creatinine/BUN, chemistry panel, liver function tests (LFTs), ECG, CBC with platelet count, INR
everolimus (Afinitor)	Non-infectious pneumonitis, infections, oral ulcerations	pulmonary signs/symptoms, serum creatinine, BUN, CBC
gefitinib (Iressa)	interstitial pulmonary toxicity including interstitial pneumonia, pneumonitis, and alveolitis	pulmonary signs/symptoms, LFTs
imatinib (Gleevec)	myelosuppression (anemia, neutropenia, thrombocytopenia), hemorrhage, fluid retention and edema, severe CHF and left ventricular dysfunction, hepatotoxicity, hypereosinophilic cardiac toxicity, GI disorders, dermatologic toxicities including erythema multiforme and Stevens-Johnson syndrome, hypothyroidism	CBC, weight, signs/symptoms of fluid retention, signs/symptoms of cardiac failure, LFTs, ECG, serum troponin, thyroid function tests
lapatinib (Tykerb)	hepatotoxicity, decreased left ventricular ejection fraction (LVEF), interstitial lung disease/pneumonitis, QT prolongation, diarrhea	LVEF, LFTs, pulmonary signs/symptoms, ECG, potassium, magnesium, signs/symptoms of CHF, fluid status
nilotinib (Tasigna)	myelosuppression, QT prolongation, sudden deaths, electrolyte abnormalities, hepatotoxicity, elevated serum lipase, drug interactions with strong inhibitors or inducers of CYP3A4, take without food as food greatly increases bioavailability; capsules contain lactose	CBC, ECG, chemistry panel plus phosphate, serum lipase, LFTs

Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
pazopanib (Votrient)	hepatotoxicity, QT prolongation and Torsades de Pointes, hemorrhagic events, gastrointestinal perforation and fistula formation, hemorrhage, hypertension, arterial thrombotic events including myocardial infarction, hypothyroidism, proteinuria	LFTs, bilirubin, ECG, chemistry panel plus phosphate and magnesium, signs/symptoms of bleeding, thyroid function tests, UA, serum lipase/amylase, ECG, LVEF, signs/symptoms of CHF
sorafenib (Nexavar)	cardiac ischemia/infarction, hemorrhage, hypertension, dermatological toxicities including hand-foot skin reaction and rash, gastrointestinal perforation, elevation of INR when given with warfarin, wound healing complications, drug interactions with UGT1A1 substrates (irinotecan), docetaxel, and doxorubicin; caution using in patients with hepatic impairment	signs/symptoms of cardiac ischemia, ECG, signs/symptoms of bleeding, CBC, serum phosphate, blood pressure
sunitinib (Sutent)	left ventricular dysfunction, hemorrhagic events, QT prolongation and Torsades de Pointes, hypertension, thyroid dysfunction, adrenal insufficiency	CBC with platelet count, ECG, chemistry panel plus phosphate and magnesium, LVEF, signs/symptoms of CHF, blood pressure, signs/symptoms of hypothyroidism, thyroid function tests

gefitinib (Iressa)

Gefitinib was initially FDA-approved for treatment of patients with NSCLC under Subpart H accelerated approval regulations that allow products to be approved on the basis of a surrogate endpoint for clinical efficacy. The surrogate end-point for gefitinib was tumor response rate which was approximately 10 percent. The approved indication was for the treatment of patients with NSCLC who were refractory to established cancer treatments (both a platinum drug and docetaxel). Later, erlotinib (Tarceva) was approved for this same group of patients.

The FDA reviewed data from two clinical studies of gefitinib including one of the studies which was part of the drug's accelerated approval. The trial enrolled 1,692 patients with regionally advanced or metastatic NSCLC who had failed one or two prior treatment regimens and were given either gefitinib or placebo. There was no significant survival benefit in the overall study population or in patients who had high levels of a surface marker called "EGFR." In contrast, the presence of EGFR at high levels appears to predict a good response to erlotinib. The second trial enrolled patients with stage III NSCLC after completion of induction and consolidation chemotherapy and radiation therapy. Patients were given either gefitinib or placebo maintenance therapy. No gefitinib survival benefit could be demonstrated.

In 2005, the FDA approved labeling and released a public health advisory for gefitinib limiting therapy to only cancer patients who have already taken gefitinib and in the opinion of the

treating physician, are currently benefiting or have previously benefited from gefitinib treatment.^{71,72} No new patients were to start on gefitinib because a large Phase III study found that gefitinib did not improve survival in NSCLC.⁷³ Gefitinib has a limited distribution program, Iressa Access Program, for patients in 2005 who were currently receiving and benefiting from gefitinib, patients who have previously received and benefited from gefitinib, or patients who were previously enrolled or new patients in non-Investigational New Drug (IND) clinical trials approved by an independent review board prior to June 17, 2005. New patients may also be able to obtain gefitinib if AstraZeneca decides to make it available under IND and the patients meet the criteria for enrollment under the IND.

Drug Interactions^{74,75,76,77,78,79,80,81,82,83,84}

CYP3A4 substrates – enzyme inhibition and induction

All agents in this category except capecitabine (Xeloda) are substrates for the cytochrome P450 3A4 enzyme. When coadministered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, ritonavir, saquinavir, telithromycin), plasma concentrations of all the agents in this category except capecitabine can potentially increase. Concomitant administration of these agents with potent inhibitors of CYP3A4 should be avoided, and selection of an alternate medication with minimal to no enzyme inhibition potential is recommended. However, if the protein tyrosine kinase inhibitor must be coadministered with a CYP3A4 inhibitor, caution should be exercised and/or a dose reduction considered. Patients being treated with everolimus (Afinitor), erlotinib (Tarceva), lapatinib (Tykerb), imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), pazopanib (Votrient), or sunitinib (Sutent) should avoid grapefruit as it can increase the plasma concentrations of these agents.

Administration of all of the agents in the category except capecitabine with potent inducers of CYP3A4 (e.g., dexamethasone, phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin) may result in decreases in plasma concentrations of the protein tyrosine kinase inhibitors. If these agents must be used with a CYP3A4 inducer, a dose increase of dasatinib, gefitinib (Iressa), erlotinib, imatinib, lapatinib, and sunitinib should be considered. Pazopanib should not be used if concomitant use of strong CYP3A4 inducers cannot be avoided. St. John's Wort may unpredictably reduce plasma concentrations of dasatinib, erlotinib, and sunitinib. Use of this herbal product should be avoided. The AUC of imatinib with coadministered St. John's Wort was reduced by 30 percent.

Dasatinib, everolimus, imatinib, pazopanib, nilotinib, and sorafenib (Nexavar) are also inhibitors of CYP3A4, and when coadministered with drugs eliminated by this enzyme, they have the potential to increase the plasma concentrations of the CYP3A4 substrates. Caution is advised when using of dasatinib, imatinib, pazopanib, and nilotinib concurrently with CYP3A4 substrates that have a narrow therapeutic index (e.g., alfentanil, cyclosporine, ergot alkaloids, fentanyl, pimozone, quinidine, sirolimus, and tacrolimus).

Phenytoin levels should be monitored when capecitabine and phenytoin are coadministered as the level of phenytoin may increase and require a dose reduction of phenytoin.

CYP2B6 and CYP2C8 substrates

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro*, and system exposure to substrates of these enzyme pathways is expected to increase when coadministered with sorafenib.

Pazopanib is also a weak inhibitor of CYP2D6 and CYP2C8. Concomitant use of narrow therapeutic drugs metabolized by these pathways should be avoided.

warfarin

Warfarin is metabolized by CYP2C9 and CYP3A4. When coadministered with imatinib and nilotinib, the bioavailability of warfarin could increase. Therefore, warfarin should not be used concomitantly with imatinib or nilotinib. Heparins or low molecular weight heparins are recommended alternatives for patients that require anticoagulation.

Patients receiving warfarin and capecitabine should be monitored closely, as anticoagulation parameters may increase dramatically.

Bleeding events and elevation of INR have occurred in patients receiving gefitinib and warfarin. Monitoring of INR should be performed.

P-glycoprotein (P-gP) Inhibitors

Everolimus is partially metabolized by the multidrug efflux pump P-gP and should not be used with strong or moderate inhibitors of P-gP.

Lapatinib and nilotinib are substrates of P-gP. If either agent is administered with an inhibitor of P-gP, increased concentrations of lapatinib or nilotinib are likely; caution should be exercised.

UGT1A1 and UGT1A9 substrates

Sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways. Systemic exposure to substrates of these pathways such as irinotecan may increase when administered concomitantly with sorafenib.

live vaccines

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

acetaminophen

At therapeutic levels, imatinib inhibits O-glucuronidation of acetaminophen. Systemic exposure of acetaminophen may be increased when coadministered with imatinib, resulting in abnormalities in liver function tests; cautious use of these agents concurrently is advised.

antacids

Concomitant administration of dasatinib with antacids may result in reduced systemic exposure of dasatinib. Therefore, simultaneous administration of the two agents should be avoided. In patients requiring treatment with antacids, the antacid should be given at least two hours prior to or two hours after the dose of dasatinib.

Antacid administration with capecitabine resulted in a small increase in plasma concentrations of capecitabine and one metabolite; other metabolites were not affected.

Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and erlotinib dose should be separated by several hours, if an antacid is necessary.

histamine-2 receptor blockers/proton pump inhibitors

H₂ receptor blockers and proton pump inhibitors are associated with long-term suppression of gastric acid secretion which may result in reduced systemic exposure of dasatinib and erlotinib. Concomitant use of H₂ receptor blockers or proton pump inhibitors with the agents is, therefore, not recommended. Antacids are the recommended therapeutic alternative for patients taking dasatinib. Erlotinib must be taken once a day given ten hours after the H₂-receptor blocker dosing and at least two hours before the next dose of H₂-receptor blocker.

Coadministration of sodium bicarbonate and ranitidine resulting in a gastric pH >5 reduced the mean AUC of gefitinib by 44 percent.

cigarette smoking

Cigarette smoking has been shown to reduce the erlotinib area-under-concentration curve (AUC). Patients should be advised to stop smoking; however, if they continue to smoke, a cautious increase in the dose of erlotinib may be considered, while monitoring the patient's safety. If the erlotinib dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking.

QT interval prolongation

The administration of nilotinib with medications that may prolong the QT interval such as anti-arrhythmics should be avoided.

Other chemotherapeutic agents

Gefitinib and vinorelbine have been used concomitantly and resulted in an increase in an exaggerated neutropenic effect of vinorelbine.

Concomitant use of docetaxel or doxorubicin with sorafenib results in elevated levels of each agent. Caution is recommended when sorafenib is coadministered with docetaxel or doxorubicin. Both increases and decreases in AUC of fluorouracil have been observed with coadministration with sorafenib; use with caution.

Coadministration of capecitabine and leucovorin results in elevated levels of 5-FU and toxicity.

Adverse Effects

Adverse effects reported below are the incidences for all grades of severity.

Drug	Fluid retention /Edema	Diarrhea	Headache	Skin rash	Nausea	Hemorrhage	Muscle pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
capecitabine (Xeloda) ⁸⁵ colon cancer	15	47-55	5-10	7	34-43	epistaxis 2-3	nr	22-25	1-80	nr
capecitabine (Xeloda) ⁸⁶ n=162 breast cancer	9	57	9	nr	53	reported	9	24	72	nr
dasatinib (Sprycel) ⁸⁷ CML	21-35	18-31	15-33	15-21	18-23	11-26	0-19/3-13	1-<10	13-74	1-<10
erlotinib (Tarceva) ⁸⁸ 150 mg; n=433 & 485 NSCLC	nr	20.3-54 (4.5-18)	nr	49.2-75 (5.8-17)	33 (24)	nr	nr	17 (3)	reported	nr
erlotinib (Tarceva) ⁸⁹ 100 mg + IV gemcitabine; n=259 pancreatic cancer	37 (36)	48 (36)	15 (10)	69 (30)	60 (58)	nr	21 (21)	22 (12)	reported	nr
everolimus (Afinitor) ⁹⁰ n=274 RCC	25 (8)	30 (7)	19 (9)	29 (7)	26 (19)	epistaxis 18 (0)	10 (7)	44 (0)	92 (79)	nr
gefitinib (Iressa) ⁹¹ n=216 NSCLC	2	49-76	nr	44-61	13-20	nr	nr	1	nr	nr
imatinib (Gleevec) ⁹² CML	61.7-76	43-57	27-36	36-47	49.5-71	28.9-53	38-49/ 9-27	0.1-1	6-42	0.1-1
imatinib (Gleevec) ⁹³ GIST	76.7-86.1	56.2-58.2	19.7-22	38.1-49.8	58.1-64.5	12.3-13.3	nr	9.2-10	32-34.8	0.1-1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported. HTN = hypertension

The overall safety profile of imatinib (Gleevec) in children is similar to adults with the exception that musculoskeletal pain is less frequent (20.5 percent), and peripheral edema was not reported in a clinical trial of 93 children. Nausea and vomiting were reported most commonly in children receiving imatinib.

Adverse Effects (continued)

Adverse effects reported below are the incidences for all grades of severity.

Drug	Fluid retention /Edema	Diarrhea	Headache	Skin rash	Nausea	Hemorrhage	Muscle pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
lapatinib (Tykerb) ⁹⁴ n=198; breast cancer with capecitabine	nr	65 (50)	nr	28 (14)	44 (43)	nr	nr	14 (11)	56 (53)	nr
nilotinib (Tasigna) ⁹⁵ n=438 CML	11	19-22	21-31	28-33	18-31	reported	14	nr	8-23	1-10
pazopanib (Votrient) ⁹⁶ n=290 RCC	nr	52 (9)	10 (5)	8 (3)	26 (9)	13 (5)	nr	nr	nr	40 (10)
sorafenib (Nexavar) ⁹⁷ n=297 HCC	nr	55 (25)	nr	19 (14)	24 (20)	18 (20)	> 10	1-<10	nr	9 (4)
sorafenib (Nexavar) ⁹⁸ n=451 RCC	nr	43 (13)	10 (6)	40 (16)	23 (19)	15 (8)	> 10	1-<10	44 (49)	17 (2)
sunitinib (Sutent) ⁹⁹ n=202 GIST	nr	40 (27)	nr	14 (9)	≥20	18 (17)	14 (9)	29 (18)	26 (22)	15 (11)
sunitinib (Sutent) ¹⁰⁰ n=375 metastatic RCC	11	58	18	27	49	30	17-19	43	71	30

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported. HTN = hypertension

Special Populations^{101,102,103,104,105,106,107,108,109,110,111}

Pediatrics

Safe and effective use of capecitabine (Xeloda), pazopanib (Votrient), lapatinib (Tykerb), sorafenib (Nexavar), erlotinib (Tarceva), everolimus (Afinitor), gefitinib (Iressa), dasatinib (Sprycel), nilotinib (Tasigna), and sunitinib (Sutent) in patients less than 18 years of age has not been established.

Although there are no data in children less than two years of age, safe and effective use of imatinib (Gleevec) has been established in pediatric patients (> two years of age) with newly diagnosed with Ph+ chronic phase CML or Ph+ chronic phase CML with disease recurrence after stem cell transplantation or resistance to interferon-alpha therapy.

Pregnancy

All agents in the category may cause fetal harm when administered to pregnant women and are classified as Pregnancy Category D. Women should be advised not to become pregnant while on therapy with any agent in the class.

Renal Impairment

No clinical studies were conducted with dasatinib, erlotinib, everolimus, gefitinib, lapatinib, or nilotinib in patients with decreased renal function. Renal impairment is not expected to influence drug exposure, and no dosage adjustment of these products is recommended in patients with renal impairment.

No sorafenib dosage adjustment is necessary in patients with any degree of impaired renal function, however, monitoring of fluid balance and electrolytes in patients at risk for renal dysfunction is recommended.

Doses of capecitabine when used as monotherapy or in combination with docetaxel should be reduced by 75 percent in patients with moderate renal impairment (CrCl 30-50 mL/min); capecitabine is contraindicated in severe renal impairment (CrCl < 30 mL/min).

Patients with RCC and mild/moderate renal impairment were included in clinical trials of pazopanib. Based on pharmacokinetic studies, renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary. Data are not available for patients on dialysis receiving pazopanib.

For imatinib, patients with renal impairment (CrCL=20-39 mL/min) should receive 50 percent decrease in the recommended starting dose. Doses may be increased as tolerated. Doses exceeding 600 mg are not recommended for patient with CrCl=40-59 mL/min; maximum recommended dose is 400 mg daily. Imatinib should be used with caution in patients with severe renal impairment; a dose of 100 mg per day was tolerated by two patients with severe renal impairment.

Hepatic Impairment

Although no dose adjustments are necessary in patients with mild to moderate hepatic impairment taking capecitabine, sunitinib, or sorafenib, the agents have not been studied in patients with severe hepatic impairment.

Patients with moderately and severely elevated biochemical liver abnormalities had gefitinib pharmacokinetics similar to individuals without liver abnormalities.

Pharmacokinetics parameters of dasatinib have been evaluated in patients with hepatic impairment (Child-Pugh class B and C) and were found to be decreased in patients with hepatic impairment. No dosage adjustment of dasatinib is recommended.

Exposure to nilotinib is increased in patients with hepatic impairment. Starting with a lower dose of nilotinib is recommended in patients with hepatic impairment, and QT interval should be monitored closely for these patients.

Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B, and C) should be closely monitored during therapy with erlotinib. Treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN.

In moderate hepatic impairment, the dose of pazopanib should be reduced to 200 mg daily. No data exist in patients with severe hepatic impairment; the use of pazopanib is not recommended in these patients.

For patients with moderate hepatic impairment (Child-Pugh class B), the dose of everolimus should be reduced to 5 mg daily. Everolimus has not been evaluated in severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Patients with severe hepatic dysfunction tend to have higher exposure to imatinib and its metabolites. As such, a 25 percent reduction in imatinib dose is recommended for patients with severe hepatic dysfunction.

A dose reduction of lapatinib should be considered in patients with severe hepatic dysfunction due to a likely increased exposure to the drug. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued, and patients should not be retreated with lapatinib.

Geriatrics

No difference in efficacy or safety between older and younger patients was observed with everolimus, gefitinib, nilotinib, erlotinib, lapatinib, sorafenib, and sunitinib.

Patients receiving pazopanib older than 60 years may be at a greater risk for elevation of ALT (> three X ULN); otherwise, no overall differences in safety or effectiveness of pazopanib have been observed between older and younger subjects.

A higher rate of fluid retention events is associated with dasatinib and imatinib in patients ages 65 years and older. The patient population should be monitored closely for evidence of edema.

Elderly patients receiving capecitabine should be carefully monitored for adverse effects.

Dosages^{112,113,114,115,116,117,118,119,120,121,122}

Drug	Adult Patients						Administration comments	Dosage forms
	CML	RCC	GIST	Metastatic breast cancer	NSCLC	Other diagnoses		
capecitabine (Xeloda)	--	--	--	1,250 mg/m ² twice daily for 14 days then off for seven days; repeat on 21-day cycles	--	Colon cancer: 1,250 mg/m ² twice daily for 14 days then off for seven days; repeat on 21-day cycles	Take with food.	150, 500 mg tablets
dasatinib (Sprycel)	CP CML: 100 to 140 mg daily AP CML: 140 mg daily BP CML: 140 mg daily	--	--	--	--	Ph+ALL: 140 to 180 mg daily	Swallow tablets whole; do not crush or cut. Take with or without food either in the morning or in the evening.	20, 50, 70, 100 mg tablets
erlotinib (Tarceva)	--	--	--	--	150 mg daily	Pancreatic cancer in combination with IV gemcitabine: 100 mg daily	Take on empty stomach one hour before or two hours after a meal.	25, 100, 150 mg tablets
everolimus (Afinitor)	--	10 mg daily	--	--	--	--	May be taken with or without food. Tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.	5, 10 mg tablets

CML = chronic myeloid leukemia; Ph+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia; GIST = gastrointestinal stromal tumor; Ph+CML = Philadelphia chromosome-positive chronic myeloid leukemia; CP = chronic phase; AP = acute phase; BP = blast phase; BC = blast crisis; RCC = renal cell carcinoma, NSCLC = non-small cell lung cancer; HCC = hepatocellular carcinoma

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

Dosages (continued)

Drug	Adult Patients						Administration comments	Dosage forms
	CML	RCC	GIST	Metastatic breast cancer	NSCLC	Other diagnoses		
gefitinib (Iressa)	--	--	--	--	250 mg daily	--	--	250 mg tablets – available under limited distribution program
imatinib (Gleevec)	CP CML: 400 to 600 mg daily AP CML: 600 to 800 mg daily BC CML: 600 to 800 mg daily	--	400 mg to 800 mg daily	--	--	MDS/MPD: 400 mg daily ASM: 100 to 400 mg daily HES/CEL: 100 to 400 mg daily DFSP: 800 mg daily Ph+ ALL: 600 mg daily	Take with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice daily.	100, 400 mg tablets
lapatinib (Tykerb)	--	--	--	Advanced or metastatic breast cancer: 1,250 mg daily on days 1-21 with capecitabine Hormone Receptor Positive, HER2 positive metastatic breast cancer with letrozole: 1,500 mg daily	--	--	Take at least one hour before or one hour after a meal.	250 mg tablets

CML = chronic myeloid leukemia; Ph+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia; GIST = gastrointestinal stromal tumor; Ph+CML = Philadelphia chromosome-positive chronic myeloid leukemia; CP = chronic phase; AP = acute phase; BP = blast phase; BC = blast crisis; RCC = renal cell carcinoma, NSCLC = non-small cell lung cancer; HCC = hepatocellular carcinoma

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

Dosages (continued)

Drug	Adult Patients						Administration comments	Dosage forms
	CML	RCC	GIST	Metastatic breast cancer	NSCLC	Other diagnoses		
nilotinib (Tasigna)	CP CML: 400 mg twice daily AP CML: 400 mg twice daily	--	--	--	--	--	Take with food. Swallow capsules whole with water. No food should be consumed for at least two hours before or one hour after the dose is taken.	200 mg capsules
pazopanib (Votrient)	--	800 mg daily	--	--	--	--	Give at least one hour before or two hours after a meal. Do not crush tablets. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.	200 mg tablets
sorafenib (Nexavar)	--	400 mg daily	--	--	--	HCC: 400 mg daily	Take without food.	200 mg tablets
sunitinib (Sutent)	--	50 mg daily four weeks on therapy, two weeks off therapy	50 mg daily four weeks on therapy, two weeks off therapy	--	--	--	May be taken with or without food.	12.5, 25, 50 mg capsules

CML = chronic myeloid leukemia; Ph+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia; GIST = gastrointestinal stromal tumor; Ph+CML = Philadelphia chromosome-positive chronic myeloid leukemia; CP = chronic phase; AP = acute phase; BP = blast phase; BC = blast crisis; RCC = renal cell carcinoma, NSCLC = non-small cell lung cancer; HCC = hepatocellular carcinoma

imatinib (Gleevec) for Pediatric patients >2 years:

- Ph+ CML new diagnosis: 340 mg/m²/day (not to exceed 600 mg daily)
- Chronic phase recurrent after stem cell transplant or patients resistant to interferon alpha therapy: 260 mg/m²/day

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

Clinical Trials

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled, Phase III trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of data in the literature, clinical trials that are open-label, placebo-controlled, and have drop out rates in excess of 20 percent have been included in this therapeutic class review. Health-related quality of life (HRQOL) studies have been excluded.

Breast Cancer

lapatinib (Tykerb) plus capecitabine (Xeloda) and capecitabine (Xeloda) alone

A multicenter, open-label randomized trial was conducted to assess the relative efficacy and tolerability of lapatinib plus capecitabine versus capecitabine alone in patients with stage IIIb or IV breast cancer with ErbB-2 over expression.¹²³ A total of 399 patients were enrolled and randomized to either lapatinib (1,250 mg once daily on days one to 21) plus capecitabine (1,000 mg/m² every 12 hours on days one to 14) every 21 days or capecitabine alone (1,250 mg/m² every 12 hours on days one to 14) every 21 days. The primary endpoint was time to progression (TPP) defined as time from randomization to tumor progression or death from breast cancer. Median TTP was 27.1 versus 18.6 weeks (hazard ratio, 0.57; p=0.00013) favoring the lapatinib plus capecitabine arm. Response rates were 23.7 percent (lapatinib plus capecitabine) versus 13.9 percent (capecitabine alone). Adverse effects observed in the lapatinib and capecitabine combination arm were generally similar to those in the capecitabine alone arm; a higher incidence of diarrhea and rash was noted with the combination. Grade 3 or 4 adverse reactions that occurred with a frequency of > five percent in patients on the combination arm were diarrhea (13 percent) and palmar-plantar erythrodysesthesia (12 percent). There was a two percent incidence of reversible decreased left ventricular function in the combination arm.

CML

imatinib (Gleevec) and interferon-alfa plus low-dose cytarabine

A randomized, controlled, multicenter, open-label, Phase III study compared the clinical efficacy and safety of imatinib and interferon-alfa combined with low-dose cytarabine in 1,106 newly diagnosed chronic phase CML patients.¹²⁴ Patients were randomized to receive either imatinib 400 mg daily (n=553) or interferon-alfa plus low-dose cytarabine (n=553). Patients were allowed to cross over to the alternate treatment regimen if they had no response, had a loss of response, had an increase in white-cell count, or could not tolerate treatment. The primary

endpoint was disease progression. Secondary endpoints included rate of complete hematologic response (CHR), rate of major cytogenetic response (MCyR), safety, and tolerability. At 12 months, the disease had not progressed in 96.6 percent of patients treated with imatinib and 79.9 percent of patients treated with combination therapy ($p < 0.001$). Estimated rates of freedom from progression to accelerated-phase or blast crisis CML at 12 months were 98.5 percent for the imatinib group and 93.1 percent in the combination therapy group ($p < 0.001$). The estimated survival rates at 18 months for imatinib and the combination group were 97.2 percent and 95.1 percent, respectively ($p = 0.16$). A significantly greater number of patients in the imatinib group achieved CHR (95.3 percent versus 55.5 percent; $p < 0.001$) and MCyR (85.2 percent versus 22.1 percent; $p < 0.001$) compared to the combination therapy group. Imatinib was well tolerated with most adverse effects being mild to moderate in nature. Superficial edema, nausea, muscle cramps, and rashes were the most commonly reported events. Combination therapy had a higher rate of grade 3 or 4 events, including fatigue, depression, myalgias, arthralgias, neutropenia, and thrombocytopenia. After a five-year follow-up, 382 patients in the imatinib group (69 percent) and 16 patients in the combination therapy group (three percent) continued with their initially assigned treatment regimen.¹²⁵ Of the patients given combination therapy, 359 (65 percent) had crossed over to imatinib compared to 14 (three percent) of the patients in the imatinib group had crossed over. Given the relatively small number of patients that remained in the combination therapy group, the results of the five-year follow-up center around those obtained from the imatinib treatment group. At 60 months, the estimated rate of event-free survival was 83 percent and approximately 93 percent of patients had not progressed to accelerated-phase or blast crisis. The rate of CHR and MCyR at 60 months was 98 percent and 92 percent, respectively. Imatinib was well tolerated. The rate of hematologic or hepatic grade 3 or grade 4 adverse events associated with imatinib decreased significantly after two years of treatment.

Gastrointestinal stromal tumor (GIST)

imatinib (Gleevec) and placebo

A randomized, double-blind, placebo-controlled, multicenter, one-year, Phase III trial compared adjuvant imatinib 400 mg ($n = 359$) to placebo ($n = 354$) in patients with fully resected gastrointestinal stromal tumor (GIST) at least 3 cm in size and positive for the KIT protein by immunohistochemistry and after resection.¹²⁶ Patients assigned to placebo were eligible to crossover to imatinib treatment in the event of tumor recurrence. The primary endpoint was recurrence-free survival, and analysis was by intention-to-treat. Accrual was stopped early because the trial results crossed the interim analysis efficacy boundary for recurrence-free survival. At median follow-up of 19.7 months, eight percent of patients in the imatinib group and twenty percent in the placebo group had tumor recurrence or had died. Imatinib significantly improved recurrence-free survival compared with placebo (98 percent [95% CI 96 to 100] versus 83 percent [78 to 88] at one year; HR 0.35 [0.22 to 0.53]; one-sided $p < 0.0001$). Adjuvant imatinib was well tolerated. The most common serious events were dermatitis (three percent versus zero), abdominal pain (three percent versus one percent), and diarrhea (two percent versus one percent) in the imatinib group and hyperglycemia (one percent versus two percent) in the placebo group.

sunitinib (Sutent) and placebo

The efficacy and tolerability of sunitinib and placebo were compared in patients with advanced GIST who were resistant to or intolerant of prior treatment with imatinib.¹²⁷ In the double-blind, placebo-controlled, parallel-group, multicenter, Phase III study, 312 patients were randomized to

receive either sunitinib 50 mg once daily in six week cycles (four weeks on and two weeks off) or placebo. The primary endpoint was time to tumor progression. Secondary endpoints were progression-free survival, overall survival, and confirmed objective response rate. The median time to tumor progression was 27.3 weeks in the sunitinib treatment group and 6.4 weeks in the placebo group ($p < 0.0001$). Patients treated with sunitinib had a significantly longer duration of progression-free survival (24.1 weeks versus 6.0 weeks; $p < 0.0001$) and significantly higher rate of confirmed objective response (seven percent versus zero percent; $p = 0.006$) compared with those treated with placebo. Overall survival achieved with sunitinib prior to execution of the option to cross over was significantly better with sunitinib as compared to placebo (HR=0.49, $p = 0.007$). Overall, sunitinib was well tolerated, with most adverse events being mild to moderate in severity. Fatigue, diarrhea, skin discoloration, and nausea were the more commonly experienced adverse effects in the sunitinib treatment group. Hematologic events appeared to be more prevalent in the sunitinib group.

Hepatocellular carcinoma (HCC)

sorafenib (Nexavar) and placebo

SHARP: A randomized, double-blind, placebo-controlled, multicenter, Phase III study of 602 patients with unresectable hepatocellular carcinoma (HCC) compared sorafenib 400 mg twice daily to placebo.¹²⁸ The trial was stopped early for efficacy since sorafenib significantly prolonged overall survival (OS) (10.7 months compared with 7.9 months for sorafenib versus placebo, respectively; HR, 0.69; 95% CI, 0.55 to 0.87; $p < 0.001$). Improvement in OS was observed across patient subgroups. Based on independent radiologic review from an earlier time point than the survival analysis, time to tumor progression (TTP) was significantly longer compared to placebo in patients with advanced HCC (5.5 months versus 2.8 months for sorafenib and placebo, respectively; HR, 0.58; 95% CI, 0.45 to 0.74; $p < 0.001$). The disease control rate was significantly higher in the sorafenib group than in the placebo group (43 percent versus 32 percent, $p = 0.002$). Treatment-related adverse events were mostly grade 1 or 2, occurred early in treatment, and were medically manageable. Common side effects in the sorafenib group included diarrhea, weight loss, and hand-foot skin reaction.

A randomized, double-blind, placebo-controlled, Phase III trial of 226 patients in the Asia-Pacific region with advanced HCC where the most common cause of HCC is HBV infection, showed the median OS in the sorafenib group was 6.5 months (95% CI, 5.56 to 7.56) compared to 4.2 months (95% CI, 3.75 to 5.46) in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; $p = 0.014$).¹²⁹ The disease control rate was significantly greater in the sorafenib than in the placebo group (35.3 percent versus 15.8 percent, respectively, $p = 0.0019$). Sorafenib significantly increased the median TTP compared to placebo (2.8 months versus 1.4 months, respectively, $p = 0.0005$). The most common drug-related adverse events for sorafenib and placebo, respectively, were hand-foot skin reaction (45 percent versus 2.7 percent), diarrhea (25.5 percent versus 5.3 percent), alopecia (24.8 percent versus 1.3 percent), fatigue (20.1 percent versus 8 percent), rash/desquamation (20.1 percent versus 6.7 percent), hypertension (18.8 percent versus 1.3 percent), anorexia (12.8 percent versus 2.7 percent), and nausea (11.4 percent versus 10.7 percent).

Non-small-cell lung cancer (NSCLC)

erlotinib (Tarceva) and placebo

BR.21: A randomized double-blind, placebo-controlled, multicenter, Phase III study evaluated the safety and efficacy of erlotinib 150 mg/day versus placebo in 731 patients with Stage IIIB/IV, recurrent NSCLC who failed to respond to at least one prior chemotherapy regimen.¹³⁰ The response rate was 8.9 percent in the erlotinib group and less than one percent in placebo ($p < 0.001$); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (HR, 0.61, adjusted for stratification categories; $p < 0.001$). Overall survival was 6.7 months and 4.7 months, respectively (HR, 0.70; $p < 0.001$), favoring erlotinib. Five percent of patients discontinued erlotinib due to toxic effects.

gefitinib (Iressa) and placebo

ISEL: This placebo-controlled Phase III study investigated the effect on survival of gefitinib as second-line or third-line treatment for patients with locally advanced or metastatic NSCLC.¹³¹ A total of 1,692 patients who were refractory to or intolerant of their latest chemotherapy regimen were randomly assigned in a ratio of two to one with either gefitinib (250 mg/day) or placebo, plus best supportive care. The primary endpoint was survival in the overall population of patients and those with adenocarcinoma. The primary analysis of the population for survival was by intention-to-treat. At median follow-up of 7.2 months, median survival did not differ significantly between the groups in the overall population (5.6 months for gefitinib and 5.1 months for placebo; HR 0.89 [95% CI 0.77 to 1.02], $p = 0.087$) or among the 812 patients with adenocarcinoma (6.3 months versus 5.4 months; 0.84 [0.68 to 1.03], $p = 0.089$). Preplanned subgroup analyses showed significantly longer survival in the gefitinib group than the placebo group for never-smokers ($n = 375$; 0.67 [0.49 to 0.92], $p = 0.012$; median survival 8.9 versus 6.1 months) and patients of Asian origin ($n = 342$; 0.66 [0.48 to 0.91], $p = 0.01$; median survival 9.5 versus 5.5 months). Gefitinib was well tolerated.

Renal Cell Carcinoma (RCC)

everolimus (Afinitor) and placebo

RECORD-1: A randomized, double-blind multicenter trial comparing everolimus 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in 416 patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially.¹³² Prior therapy with bevacizumab (Avastin®), interleukin-2, or interferon- α was also permitted. Progression-free survival, documented using RECIST (Response Evaluation Criteria In Solid Tumors) was assessed via blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator; those randomized to placebo were then able to receive open-label everolimus 10 mg daily. Everolimus was superior to placebo for progression-free survival, (4.9 months to 1.9 months respectively, $p < 0.0001$). The treatment effect was similar across prognostic scores and prior sunitinib and/or sorafenib use. The overall survival results were not considered mature as 32 percent of patients had died by the time the study was concluded at 14 months.

pazopanib (Votrient) and placebo

The safety and efficacy of pazopanib in RCC were evaluated in a randomized, double-blind, placebo-controlled, multicenter, Phase III study including 435 patients with locally advanced and/or metastatic RCC who had received either no prior therapy or one prior cytokine-based systemic therapy.¹³³ Patients were randomized to receive pazopanib 800 mg or placebo once daily. There were two subgroups: treatment-naïve subgroup and cytokine-pretreated subgroup. Of the patients in the cytokine-pretreated subgroup, the majority had received interferon-based treatment. The primary outcome was to evaluate and compare the two treatments for progression-free survival. The response rate (complete or partial) for pazopanib recipients was 30 percent (95% CI: 25.1 to 35.6) compared to three percent (95% CI: 0.5 to 6.4) for placebo. The median duration of response for pazopanib recipients was 58.7 weeks (95% CI: 52.1 to 68.1). The treatment-naïve subgroup showed a trend toward a longer median survival compared to the cytokine-pretreated subgroup (11.1 versus 7.4 months).

sorafenib (Nexavar) and placebo

TARGET: This phase III, randomized, double-blind, placebo-controlled trial evaluated the effect of sorafenib 400 mg twice daily on progression-free survival and OS in 903 patients with advanced RCC who had failed previous systemic therapy.¹³⁴ The median progression-free survival for sorafenib patients was 5.5 months versus 2.8 months for placebo patients. Sorafenib was associated with a 56 percent reduction in the risk of progression versus placebo (HR, 0.44; 95% CI, 0.35 to 0.55, $p < 0.001$). Due to the significant improvement in progression-free survival, placebo patients were allowed to cross over to sorafenib. Median OS was 14.7 months in the placebo group but had not been reached in the sorafenib group [HR, 0.72; 95% CI, 0.54 to 0.94; $p = 0.02$]. Treatment-related adverse events were predominantly grade 1 or 2. The most common adverse events were diarrhea, rash, fatigue, hand-foot skin reactions, alopecia, and nausea. A total of 169 sorafenib-treated patients received treatment for more than one year; 27 patients received treatment for over two years. Long-term treatment with sorafenib was not associated with any new or unexpected toxicity.¹³⁵

sunitinib (Sutent) and interferon alpha

A randomized, multicenter, Phase III study of 750 patients with previously untreated, metastatic RCC received either repeated six-week cycles of sunitinib (at a dose of 50 mg given orally once daily for four weeks, followed by two weeks without treatment) or interferon-alfa (at a dose of 9 MU given SC three times weekly).¹³⁶ Interferon alfa was standard of care at the time of this study. The median progression-free survival was significantly longer in the sunitinib group (11 months) than in the interferon-alfa group (five months), corresponding to a HR of 0.42 (95% CI, 0.32 to 0.54; $p < 0.001$). Sunitinib was also associated with a higher objective response rate (secondary end point) than was interferon alfa (31 percent compared with six percent, $p < 0.001$). The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with interferon-alfa. Diarrhea was more common in the sunitinib group ($p < 0.05$). Follow-up showed that sunitinib had longer overall survival compared with interferon alpha. Median overall survival (26.4 versus 21.8 months, respectively; HR=0.821; 95% CI, 0.673 to 1.001; $p = 0.051$) per the primary analysis of unstratified log-rank test ($p = 0.013$ per unstratified Wilcoxon test).¹³⁷ By stratified log-rank test, the HR was 0.818 (95% CI, 0.669 to 0.999; $p = 0.049$). Within the interferon group, 33 percent of patients received sunitinib, and 32 percent received other vascular endothelial growth factor-signaling inhibitors after discontinuation from the trial. Median progression-free survival was 11 months for sunitinib compared with five months for interferon-alfa ($p < 0.001$). Objective response rate was 47 percent

for sunitinib compared with 12 percent for interferon alpha ($p < 0.001$). The most commonly sunitinib-related grade 3 adverse events included hypertension (12 percent), fatigue (11 percent), diarrhea (nine percent), and hand-foot syndrome (nine percent).

Summary

There is a lack of direct comparative data for these oral agents in their indicated malignancies. Most approvals are based on placebo comparator arms. Some approvals have been based on comparison with currently outdated treatments, such as imatinib (Gleevec) for CML versus the old standard of care, interferon. Gefitinib (Iressa) is no longer available to new patients due to its failure to significantly prolong survival in the overall NSCLC population in comparison to placebo. The 2010 update to the National Comprehensive Cancer Network (NCCN) guidelines recommends specific protein tyrosine kinase inhibitors for specific indications. Both intravenous agents and targeted oral agents are being used sequentially in patients during the course of their care, taking into account clinical variables and toxicity concerns. Evolution of future evidence will assist in determining the most appropriate first-line and subsequent therapies.

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