Published in final edited form as:
Curr Probl Cancer. 2013 ; 37(3): 110–144. doi:10.1016/j.currproblcancer.2013.06.001.

US FDA Approved Oral Kinase Inhibitors for the Treatment of Malignancies

Woondong Jeong[1], **James H. Doroshow**[1,2], and **Shivaani Kummar**[1,2]

[1]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD

[2]Center for Cancer Research, National Cancer Institute, Bethesda, MD

Keywords

small molecule inhibitors; tyrosine kinase inhibitors; molecularly targeted agents

1 Introduction

The United States Food and Drug Administration (FDA) has approved 19 oral kinase inhibitors (KIs) for the treatment of malignancies in hematology/oncology as of May 2013, see Table 1. We review the general principles and guidelines for using KIs for cancer treatment. This article is not designed for cross trial comparison or to make recommendations for treatment of certain patients, but as a general practice guide. To facilitate individual KI usage in daily practice, “must-know” practical aspects were grouped and highlighted rather than discussing individual KIs in depth.

A kinase is an enzyme that transfers phosphate groups from high-energy donor molecules, such as adenosine-5′-triphosphate (ATP), to specific substrates in a process known as phosphorylation. More than five hundred different kinases have been identified in humans.[1] Some KIs inhibit tyrosine sites on receptors, known as tyrosine kinase inhibitors (TKIs), by occupying the ATP-binding site, while others inhibit tyrosine or serine/threonine sites of nonreceptor kinases. KIs targeting a given receptor/pathway may show a similar adverse reaction profile; for instance, administration of any of the anti-angiogenic inhibitors causes hypertension, bleeding, and delayed wound healing.[2] Similarly, most KIs are metabolized principally by the liver and eliminated via the hepatic route. CYP3A4 inducers reduce plasma the concentration of most KIs, requiring either an increase in the KI dose to maintain adequate exposures or discontinuation of the CYP inducer. CYP3A4 inhibitors, on the other hand, increase the plasma concentrations of most KIs.

2 Drug Targets

At least 40 kinases are known to be inhibited by FDA-approved KIs. KIs can target multiple kinases–regorafenib is known to target at least 14 kinases–or have a more limited spectrum of kinase inhibition such as lapatinib, vismodegib, axitinib, and ruxolitinib. Platelet-derived

Corresponding Author: Dr. Shivaani Kummar, Head, Early Clinical Trials Development, Office of the Director, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Building 31, Room 3A44, 31 Center Drive, Bethesda, MD 20892-2440, Tel: +1 301 435 0517, Fax: +1 301 496 0826, kummars@mail.nih.gov.

growth factor receptor (PDGFR), c-KIT, and VEGFR are the most commonly inhibited kinases (Table 2).

3 Concurrent Medications Affecting Drug Exposure

Oral medications, while offering convenience and prolonged target inhibition, cannot be as closely monitored as intravenous (IV) therapies administered in the practitioner's office. Issues such as non-compliance, miscommunication, and errors in how patients take their medications, as well as interaction with food or other medications, pose challenges to delivering safe and efficacious oral therapy. Such considerations can cause significant differences in the pharmacokinetics (PK) and drug exposures of KIs. For example, per the package insert, administration of a crushed rather than whole pazopanib tablet increased the area under the curve (AUC) by 46% and C_{max} by approximately 2-fold. Co-administration of antacids or proton pump inhibitors along with oral kinase inhibitors can also reduce the absorption of KIs, affecting bioavailability.

3.1 Cytochrome P450 (CYP)

Most KIs are principally metabolized by the liver and eliminated via the hepatic route except for ruxolitinib, which is excreted via the renal route. The medication lists of patients should be reviewed thoroughly before prescribing KIs and caution should be taken if new drugs are added (Table 3, 4, 5). During drug metabolism, polar groups are added to lipophilic molecules by oxidation, reduction, or hydrolysis to facilitate water-solubility (phase I metabolism); these reactions are catalyzed predominantly by the cytochrome P450 superfamily. Clinically the most important enzyme responsible for phase I metabolism is CYP3A4, which comprises approximately 60% of all hepatic cytochromes and catalyses the biotransformation of over 50% of commonly used drugs.[3]

When a KI is co-administered with a compound classified as a “CYP inhibitor,” KI plasma concentrations may increase.[3] For example, grapefruit and grapefruit-containing containing foods should be avoided as these can inhibit CYP3A4 and increase plasma concentrations of KIs, causing inadvertent toxicity. On the other hand, the co-administration of a “CYP inducer” would potentially lower plasma KI concentrations. When a drug classified as a CYP substrate is coadministered with a KI, higher substrate plasma concentrations may result (Table 5).

CYP3A4 inducers reduce plasma concentration of most KIs with the exceptions of vismodegib and ruxolitinib (Table 6), while CYP3A4 inhibitors increase the plasma concentrations of most KIs with the exceptions of sorafenib, vandetanib, and vismodegib (Table 6). KIs can also modulate the activity of CYP enzymes, thereby affecting the levels of CYP substrates. For example, imatinib increases the plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, warfarin).[4] Detailed CYP interactions are beyond the scope of this review, so only the most clinically relevant CYP enzyme, CYP3A4, will be discussed. A complete list of medications that can interact with CYP 450 enzymes can be found online in the Cytochrome P450 Drug Interaction Table at http://medicine.iupui.edu/flockhart/.

3.2 Food Effect

The presence of food in the stomach can change drug absorption and exposure. Generally, food with a high fat content increases the drug AUC, although there are some exceptions based on drug type. Ten of 19 KIs have no specific food and time requirements (see Table 6). Six KIs are required to be taken on an empty stomach, defined in most early clinical trials as at least one hour before or two hours after food consumption unless gastrointestinal (GI) motility is changed (i.e., delayed gastric emptying or gastrectomy; see Table 6). Only

regorafenib, bosutinib, and imatinib, are required to be taken with food.[4-6] Imatinib is associated with GI irritation when taken on an empty stomach. To minimize the effect of food on drug absorption, phase 1 clinical evaluation of KIs is usually conducted in fasting subjects.

The food-labeling recommendations for recently approved oral oncology drugs are inconsistent with fundamental principles of oral drug delivery. The marked increase in bioavailability with food has generally led to recommendations to administer non-oncology drugs in a fed state.[7] However, despite a marked increase in bioavailability with food, the recommendations for some oncology drugs are for administration in the fasting state. As noted above, because early-phase oncology trials generally administer drugs to fasting subjects, some approved KIs lack adequate food effect studies with supportive PK data. Kang et al. (2010) reported a study supporting the conduct of oral oncology drug trials in the fed condition for several reasons. Co-administration with food reduces the risk of several adverse events, especially GI side effects. In most cases, food increases drug bioavailability, which results in decreased inter-individual variability of AUC. Increased drug absorption reduces wasted drug and improves pharmacoeconomic efficiency. Unwarranted food restrictions compromise the practicality of drug administration for patients and can result in decreased adherence. [7]

3.3 Antacids

Proton pump inhibitors (PPI), H2 blockers, and antacids decrease the solubility of KIs, excluding axitinib and lapatinib. However, the solubility of 11 KIs are not known (see Table 6). Because PPI affects the pH of the upper GI tract for an extended period, separation of PPI intake from KI administration may not eliminate the pH issue. If a patient needs antacid treatment, administration of aluminum or magnesium hydroxide is recommended 2 hours prior to or after drug. Recommendations for histamine 2 (H2) blockers differ for each KI. For example, the administration of H2 blockers or PPIs (above you used PPI to designate plural tense, but not there is an “s” after. Please use consistent nomenclature for abbreviations) are not recommended with dasatinib due to reduced absorption.[8] H2 blockers can be used 2 hours after nilotinib, bosutinib, and erlotinib are taken.[5, 9, 10] Increasing the dose of the KI when co-administered with an antacid drug is not likely to compensate for the loss of KI absorption. However, clinical studies to evaluate the effects of PPIs (same as above) on KI PK are more frequently conducted than for H2 blockers or antacids, and side effects are less well known.

4 Other Factors Affecting Drug Exposure

Patients with gastrectomy can have decreased KI absorption either due to lack of gastric acid or rapid transit time.[11] Median steady-state trough concentrations of nilotinib decreased by 53% in patients with total gastrectomy compared to patients who had not undergone gastrectomy.[10] Patient history should therefore include history of GI tract surgery including gastrectomy, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption, such as malabsorption syndrome.

4.1 P-glycoprotein

P-glycoprotein (P-gp) is encoded by the multidrug resistance 1 gene and enhances the energydependent cellular efflux of many substrates, such as bilirubin and several medications, and can affect intracellular KI and other drug concentrations. Most KIs, other than axitinib and ruxolitinib, are P-gp substrates. KIs can increase the concentration of P-gp substrates because of competitive binding to P-gp, or vice versa. For example, vemurafenib

is both a substrate and an inhibitor of P-gp. Systemic exposure of vismodegib may be increased when co-administered with drugs that inhibit P-gp (e.g., clarithromycin, erythromycin, azithromycin, rifampin, quinidine, ketoconazole, verapamil, or amiodarone). Digoxin, fexofenadine, vincristine, and colchicine are examples of other P-gp substrates. [12-14]

4.2 HMG CoA Reductase Inhibitors

Some statins are substrates for the CYP3A4 enzyme and susceptible to drug interactions with KIs.[15] Co-administration of imatinib or dasatinib increases the mean AUC of simvastatin, a CYP3A4 substrate, 3.5-fold and 1.2-fold, respectively; suggesting CYP3A4 inhibition by these drugs.[4, 8] Concomitant use of pazopanib and simvastatin increases the incidence of alanine aminotransferase (ALT) elevations.[16] In pazopanib studies, ALT > 3X the upper limit of normal (ULN) was reported in 14% of patients who did not use statins compared with 27% of patients who concomitantly used simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.[16] The effect of concurrent use of statins with other KIs is not reported in the package insert of the KIs. Because statins are associated with a risk of transaminitis, care should be taken when administering these drugs with KIs known to cause drug-induced liver injury, such as pazopanib.

4.3 Warfarin

Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive either low-molecular weight or standard heparin, or INR should be closely monitored to prevent significant drug interactions. INR was increased in patients receiving warfarin and erlotinib or vemurafenib, but there were no significant changes in patients receiving nilotinib or pazopanib.[9, 13]

5 Adverse Reactions

5.1 Black Box Warning

Based on clinical data, the FDA may require the pharmaceutical company to insert a black box warning in the package insert. Black box warnings are the strongest warning required by the FDA, and although uncommon, this designation signifies that a drug carries a specific risk of serious or life-threatening adverse effects. Lapatinib, pazopanib, regorafenib, sunitinib and ponatinib each have a black box warning for risk of fatal hepatic failure, with incidences of less than 1% (see Table 7); ponatinib also has a black box warning for arterial thrombosis. Risk of Torsade de pointes is a black box warning for nilotinib and vandetanib, while risk for perforation, fistula, and hemorrhage are black box warnings for cabozantinib.

It is important to know the plasma half-life of a KI when side effects need to be monitored or when the drug is combined with other CYP interacting agents. { Vandetanib has a 19-day half-life; therefore, adverse reactions, including a prolonged QT interval, may not resolve quickly and ECGs should be obtained to monitor the QT interval for greater than 2 weeks following any dose reduction for QT prolongation, or any dose interruptions.} awkward and prolix sentence, please edit. Half-life data were obtained primarily from single-dose studies, and thus may differ following chronic dosing. For example, the estimated elimination half-life of vismodegib is 12 days after a single dose, but shortens to 4 days with continuous, once-daily dosing.[14] The median half-life of most KIs is about 24 hours and ranges from 2.5 hours to 19 days (Table 9).

5.2 Hepatotoxicity

In general, the incidences of grade 3/4 ALT or bilirubin elevation were < 10% this use of except is confusingfollowing administration of erlotinib, pazopanib or regorafenib (Table 7). [6, 16] Co-administration of erlotinib with gemcitabine in a trial of patients with pancreatic cancer resulted in a 13% incidence of grade 3/4 ALT elevation, and a 10% incidence of grade 3/4 bilirubin elevation.(ref) In contrast, in a NSCLC trial, the incidence of both was ≤ 1%.(ref) Administration of pazopanib was associated with a 12% incidence of grade 3/4 ALT elevation in trials of renal cell carcinoma (RCC), and a 10% incidence in a trial in soft tissue sarcoma. [16] Regorafenib administration (in what setting) resulted in grade 3/4 bilirubin (13%) and ALT (6%) elevation.[14] If a patient develops a grade 3 AST/ALT or bilirubin elevation, most KIs should be held until these return to ≤ grade 1, and the dose reduced according to the guidelines in the package insert. [5, 17] If a patient taking pazopanib develops an isolated ALT elevation between 3 to 8 × ULN, the drug may be continued with weekly liver function tests (LFT) until ALT returns to ≤ grade 1(≤ 3× ULN). For patients with isolated ALT elevation >8 × ULN, pazopanib should be held until the ALT returns to ≤ grade 1. If the potential benefit outweighs the risk of hepatotoxicity, pazopanib can be reintroduced at a dose of no more than 400 mg once daily and LFTs measured weekly for 8 weeks. Patients with Gilbert's syndrome can have a mild indirect hyperbilirubinemia with pazopanib. In general, KIs should be discontinued permanently if a patient develops grade 2 elevation of AST/ALT and bilirubin concurrently.

5.3 Hypothyroidism

Hypothyroidism is reported as a side effect of KIs that target angiogenesis—axitinib, sunitinib, pazopanib, and regorafenib— with an incidence ranging from 4.2 to 19% (Table 11).[6, 12, 16, 18] Symptoms of hypothyroidism include dry skin, cold sensitivity, fatigue, muscle cramps, voice changes, and constipation.[19] The incidence of hypothyroidism was less frequent in clinical trials of sorafenib.[20]

An expert panel was convened to formulate guidelines for treating patients with sunitinib-induced hypothyroidism.[21] The panel recommendations included measurement of thyroid stimulating hormone (TSH) at baseline, on day 1 of each cycle for 4 cycles, and every 3 months thereafter. If TSH is elevated, free rather than total T4 should be measured to determine the degree of hypothyroidism. Total T4 can be erroneously low because T4 is primarily bound to serum thyroxine-binding globulin (TBG), which can be low in cancer patients. Free T4 should be collected before thyroxine intake because the level will be transiently increased by up to 20% after thyroxine administration.[19, 22, 23] Recommendations formulated to manage sunitinib-induced hypothyroidism can be applied to hypothyroidism induced by other KIs. The level of TSH elevation that warrants treatment has not been established. Several expert groups (American Thyroid Association, The Endocrine Society) recommend thyroid hormone be initiated when TSH rises to 10 mcU/mL;[24] however, those guidelines do not address TKI-induced hypothyroidism. Overtreatment of hypothyroidism should be avoided because potential benefit of hypothyroidism on cancer growth inhibition has been noted both in preclinical and clinical studies.[24] The American Thyroid Association recommendation as follows,

- **a.** If TSH is > 10 mcU/mL with no symptoms; observe (some recommend to treat if TSH > 10 regardless of symptoms)
- **b.** If TSH is > 10 mcU/mL with symptoms, treat with L-thyroxine at a starting dose of 25 to 75 μg daily, depending on the degree of TSH elevation. L-thyroxine should be taken with water consistently 30 to 60 minutes before breakfast or at bedtime 4 hours after the last meal and should not be taken with substances or medications

that interfere with absorption, such as antacids, calcium supplements, and multivitamins.[19]

5.4 Hypertension

Hypertension is a common adverse effect of KIs that inhibit angiogenesis (see also, *Common Adverse Reactions Associated with Kinase Inhibitors with Anti-angiogenic Properties*). {The Investigational Drug Steering Committee of the National Cancer Institute (NCI) formed a Cardiovascular Toxicities Panel, joining members from its Angiogenesis Task Force with experts in the management of hypertension and cardiovascular toxic effects in cancer patients, with the objective of generating consensus recommendations for risk assessment, monitoring, and safe administration of these agents.[25] }break up this long sentence please. The Panel's recommendations are to manage blood pressure during therapy, with a goal of less than 140/90 mmHg for most patients; but this should be lower in patients with specific preexisting cardiovascular risk factors such as diabetes or chronic kidney disease. Also, patients who develop a 20-mmHg increase in diastolic blood pressure over baseline should be treated. Several considerations may influence the choice of antihypertensive therapy. Antihypertensives that have significant CYP3A4 interactions (Table 4) should be avoided.[26] Agents that are optimal choices for avoiding or minimizing potential drug-interactions with CYP450 include telmisartan, valsartan, lisinopril, atenolol, nifedipine, amlodipine, and hydrochlorothiazide.[25, 26]

5.5 QT Interval

QT interval is a measure of cardiac muscle cell membrane repolarization. The QT interval is measured from the beginning of the QRS complex to the end of the T wave. The QT interval on the electrocardiogram is used to identify individuals at risk for ventricular arrhythmias and sudden death, which the FDA has used in the evaluation of new drug applications. QT interval is dependent upon heart rate; it is shorter at faster heart rates and longer at slower heart rates. Thus, the QT interval needs to be corrected for heart rate (QTc). It is often calculated based on Bazett's formula as follows, $QTc = \frac{QT}{\sqrt{RR}}$. In order to correct the measurement for varying heart rates, different formulas are available for determining the QTc, but the Bazett correction is uniformly accepted, including by the FDA. Recently, the FDA has focused attention on the use of the Fridericia correction because it corrects for the effects of tachycardia on the QT interval.[27] The Fridericia correction can give a more accurate QTc interval than the Bazett correction.[28] However, in the development of KIs, ECG reports corrected by the Bazett formula have been used more widely than the Fridericia formula.

A prolonged QT interval is present when the corrected QT interval is > 450 milliseconds (ms) in males and >470 ms in females. QT prolongation can occur either due to drugs such as antiarrhythmic agents, phenothiazines, tricyclic antidepressants, and cumulative high-dose anthracycline therapy, conditions such as hypothermia, cerebrovascular disease, ischemic heart disease, or due to a congenital channelopathy (prolonged QT syndrome). A long QT syndrome (either acquired or congenital) is associated with a potentially life-threatening arrhythmia known as torsade des pointes. QT prolongation may also be a result of delayed repolarization from a metabolic abnormality, such as hypocalcemia or hypomagnesemia.[28]

Overall incidence of QT prolongation after treatment with KIs are uncommon and cases of torsade de pointes are rare (<1%)(Table 7). Vandetanib has the highest incidence of grade 3 QT prolongation (QTc ≥ 501 milliseconds) at 8% and has a black box warning for this A

comprehensive list of agents with the potential to cause QTc prolongation can be found at http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm.

5.6 Dose for Patients with Organ Dysfunction

Patients with compromised organ function are rarely enrolled in early-phase clinical trials of KIs unless in separate organ dysfunction studies. Childs-Pugh criteria (CPC) or NCI Organ Dysfunction Working Group (ODWG) criteria are used for assigning patients to mild, moderate, and severe dysfunction groups, with study drugs dosed accordingly. Usual eligibility criteria for early phase trials are listed in Table 8 and can be used for screening patients for KIs. When a patient does not meet eligibility criteria, the KI package insert should be consulted (see also Table 9).

5.6.1 Hepatic Adjustment—Patients with hepatic dysfunction may need KI dose modification based on the degree of hepatic dysfunction. Hepatic dysfunction is assessed using the CPC, the use of which is advocated by the FDA.[29] The CPC is used for patients with end-stage liver disease and is calculated from five components: total bilirubin (TB), albumin, prothrombin time, ascites, and encephalopathy. NCI's ODWG-sponsored trials have used a different classification that uses two laboratory parameters, TB and aspartate aminotransferase (AST).[30] Patients were stratified into four groups by NCI ODWG criteria based on TB and AST (Table 10). The NCI ODWG normal-to-mild hepatic dysfunction group correlates with CPC A, and the moderate-to-severe hepatic dysfunction group correlates with CPC groups B and C. TB is the most important factor in both classifications.[30] The majority of KI organ dysfunction studies and dose modifications in package inserts are based on the CPC. For CPC A liver dysfunction, most KIs can be used without dose reduction, excluding nilotinib, bosutinib, and ruxolitinib, all of which require dose reductions (Table 9). Dose adjustment data for vandetanib, vismodegib, cabozantinib, and crizotinib are unknown or limited in CPC A. For CPC B liver dysfunction, only about half of the KIs can be used without dose reductions. For CPC C liver dysfunction, only dasatinib can be used without dose reduction; in these patients, most KIs either require dose reduction, or are prohibited for use.[29]

5.6.2 Renal Adjustment—FDA renal dysfunction is classified as normal, CrCl > 80 mL/minute; mild, 60 to 80 mL/minute; moderate, 30 to 60 mL/minute; severe, < 30 mL/minute; and end stage, on dialysis. Most KIs do not need dose adjustments for mild renal dysfunction, but there is no available for dasatinib, vismodegib, lapatinib, and erlotinib (see Table 9). Imatinib should not be administered at more than 600 mg to patients with mild renal dysfunction. Three KIs are approved for patients with RCC and severe renal dysfunction, sorafenib, sunitinib, axitinib, and these can be administered without dose adjustments.[31]

6 Common Adverse Reactions Associated with Kinase Inhibitors with Anti-angiogenic Properties

Seven KIs inhibit angiogenesis through inhibition of VEGFR: axitinib, cabozantinib, pazopanib, regorafenib, sunitinib, sorafenib, and vandetanib. The specificity of these KIs varies, with axitinib being the most specific. Each of these KIs causes hypertension in about 30 to 40% of patients and grade 3/4 hypertension occurs in about 10% of patients (Table 11). Hypertension occurs mostly within the first or second month. Hypothyroidism is uncommon after sorafenib treatment, in contrast to other VEGFR inhibitors like axitinib and sunitinib that cause hypothyroidism in up to 19% of patients. Proteinuria (all grades) occurs in about 10% of patients, except in patients treated with regorafenib where the prevalence was 60% reflecting poor risk group of patients in regorafenib trials. Recommendation to

stop VEGFR KI treatment in anticipation of surgery is variable, and ranged from 1 day for axitinib (half-life 2.5-6 hours) to 28 days for cabozantinib. Arterial thromboembolism is uncommon, pazopanib-treated patients had the most occurrences (3%).[16] Venous thromboembolism and grade 3/4 hemorrhage was less than 5% in general. Hand foot syndrome (all grades) was mostly seen after treatment with regorafenib (45%) and cabozantinib (50%), see Table 11.[6, 12, 16, 18, 32, 33]

7 Kinase Inhibitors

7.1 Axitinib (Inlyta; Pfizer)

Axitinib is approved for use in advanced RCC after failure of one prior systemic therapy. Axitinib inhibits the receptor tyrosine kinases VEGFR 1, 2, and 3. The starting dose is 5 mg orally twice daily with water, with or without food. It is available as 1 and 5 mg tablets. In a randomized, open-label, multicenter phase 3 study, 723 patients with advanced RCC whose disease had progressed during or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine- containing regimens were randomized (1:1) to receive axitinib (n = 361) or sorafenib (n = 362).[34] For patients without hypertension or adverse reactions above grade 2, the dose was allowed to increase to 7 and 10 mg. The median progression free survival (PFS) was significantly increased after axitinib treatment (6.7 months) compared to 4.7 months with sorafenib treatment (hazard ratio (HR) 0.665; one-sided $p < 0.0001$).

Adverse Reactions—Adverse events occurred in more than 20% of patients and included diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight loss, vomiting, asthenia, and constipation. Grade 3/4 adverse events (>5%) were HTN (16%), diarrhea (11%), fatigue (11%).[12]

7.2 Pazopanib (Votrient; GlaxoSmithKline)

Pazopanib is approved for patients with advanced RCC and advanced soft tissue sarcoma (STS) who have received prior chemotherapy.[16] Pazopanib is a multi-tyrosine kinase inhibitor of VEGFR 1, 2, 3; PDGFR-α, -β, fibroblast growth factor receptor (FGFR)-1 and -3; c-Kit; interleukin-2 receptor inducible T-cell kinase; leukocyte-specific protein tyrosine kinase; and transmembrane glycoprotein receptor tyrosine kinase. The starting dose is 800 mg (200 mg × 4 tablets) orally once daily without food. Pazopanib is available as a 200 mg tablet.

Renal Cell Carcinoma—A randomized, double-blind, placebo-controlled, phase 3 trial was conducted for patients with clear cell histology (90%) or predominantly clear cell histology (10%).[35] Similar proportions of patients in each arm had prior nephrectomy (89% and 88% for pazopanib and placebo, respectively). Of 435 patients enrolled, 233 (54%) were treatment-naive and 202 (46%) had been pretreated with cytokines. PFS was significantly prolonged with pazopanib compared to placebo in the overall study population (median, PFS 9.2 versus 4.2 months; HR, 0.46; $p < 0.0001$), the treatment-naive subpopulation (median PFS 11.1 versus 2.8 months; HR, 0.40; $p < 0.0001$), and the cytokine-pretreated subpopulation (median PFS, 7.4 versus 4.2 months; HR, 0.54; $p < 0.001$). The objective response rate was 30% with pazopanib compared to 3% with placebo ($p < 0.001$). The median duration of response was longer than 1 year. There was no evidence of clinically important differences in quality of life for pazopanib compared to placebo. At the protocol-specified final analysis of overall survival (OS), the median OS was 22.9 months for the pazopanib arm and 20.5 months for the placebo arm (HR = 0.91; 95% CI: 0.71, 1.16). The median OS for the placebo arm includes 79 patients (54%) who

discontinued placebo treatment because of disease progression and crossed over to pazopanib.[16]

Soft Tissue Sarcoma—A randomized, double-blind, placebo-controlled trial was conducted for 369 patients with metastatic STS who had received prior chemotherapy or were unsuited for chemotherapy, not including adipocytic sarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumor, primitive neuroectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma, and mixed mesodermal tumor of the uterus.[36] Patients were randomized (2:1) to receive pazopanib 800 mg once daily or placebo. Forty-three percent of patients had leiomyosarcoma, 10% had synovial sarcoma, and 47% had other soft tissue sarcomas. Median PFS was 4.6 months (95% CI: 3.7, 4.8) for the pazopanib arm compared with 1.6 months (95% CI: 0.9, 1.8) for the placebo arm (HR 0.31; $p < 0.0001$). Overall survival was 12.5 months (95% CI: 10.6, 14.8) with pazopanib versus 10.7 months (95% CI: 8.7, 12.8) with placebo (HR 0.86, 95% CI: 0.67, 1.11; $p = 0.25$).

Adverse Reactions—The most common adverse reactions (≥20%) in patients with advanced RCC were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. Grade 3/4 adverse events (>5%) in RCC included elevated ALT/AST (12/7%). The most common adverse reactions in patients with advanced STS (≥20%) were fatigue, diarrhea, nausea, vomiting, decreased appetite and weight, hypertension, tumor and musculoskeletal pain, headache, dysgeusia, dyspnea, and hair and skin hypopigmentation.[16]. Grade 3/4 adverse events (>5%) in STS were fatigue (14%), vomiting (8%), HTN (7%), loss of appetite (6%), and elevated ALT/AST (10/8%).[16]

7.3 Sorafenib (Nexavar; Bayer/Onyx)

Sorafenib is approved for the treatment of unresectable hepatocellular carcinoma (HCC) and advanced RCC. Sorafenib inhibits multiple intracellular (C-RAF, b-RAF and mutant b-RAF) and cell surface kinases (c-Kit, Fms-like tyrosine kinase-3 (FLT3), rearranged during transfection (RET), VEGFR 1, 2, 3, and PDGFR-β). The starting dose is 400 mg (200 mg × 2 tablets) orally daily without food. The dose may be reduced to 400 mg once daily or to 400 mg every other day. Sorafenib is available as a 200 mg tablet.

Hepatocellular Carcinoma—A phase 3, randomized, double blind, placebo-controlled trial was conducted.[37] The median OS was 11 versus 8 months (sorafenib versus placebo, $p = 0.00058$). The time to progression (TTP) was 6 months in the sorafenib arm versus 3 months in the placebo arm ($p < 0.0001$). There were no complete responses (CRs), but there were 7 patients in the sorafenib group with partial responses (PRs, 2%) versus two patients in the placebo group (1%; $p = 0.05$). [20]

Renal Cell Carcinoma—A phase 3, international, multicenter, randomized, double blind, placebo-controlled trial was conducted in patients with advanced RCC who had received one prior systemic therapy.[38, 39] Nine hundred three patients of an intermediate-risk or low-risk status, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (calculated using 5 variables; performance status, serum lactate dehydrogenase, hemoglobin, calcium and prior nephrectomy), were randomly assigned to receive sorafenib or placebo. The OS of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 versus 15.2 months, respectively; HR 0.88; $p = 0.146$). Patients in the placebo group were offered sorafenib. When the post-crossover placebo survival data were excluded, the difference became significant (17.8 versus 14.3 months, respectively; HR 0.78; $p = 0.029$). The median PFS was significantly longer in

those receiving sorafenib compared with placebo (5.5 versus 2.8 months; HR 0.44, 95% CI: 0.35, 0.55). The overall response rate (ORR) was 10 versus 2% in the sorafenib and placebo groups, respectively.

Adverse Reactions—The most common adverse reactions (≥20%) in trials of HCC and RCC were fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea, and abdominal pain.[20] Grade 3/4 adverse events (>5%) in HCC patients were fatigue (10%), HFS (8%), diarrhea (10%), and abdominal pain (9%). In RCC patients, grade 3/4 adverse events (>5%) were HFS (6%).[20]

7.4 Sunitinib (Sutent; Pfizer)

Sunitinib is approved for advanced RCC, gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib, and well-differentiated pancreatic neuroendocrine tumors (pNET) at an advanced stage.[40] It inhibits PDGFR-α, -β, VEGFR 1, 2, 3, c-Kit, FLT3, colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (GDNF). The starting dose for GIST and RCC is 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off. The starting dose for pNET is 37.5 mg orally once daily, with or without food, continuously. It is available as 12.5, 25, and 50 mg capsules.

Second line GIST—A randomized, double blind, placebo-controlled trial was conducted for patients with advanced GIST who were resistant to or intolerant of previous treatment with imatinib.[41, 42] Sunitinib or placebo was given orally once daily at a 50 mg starting dose in 6-week cycles with 4 weeks on and 2 weeks off treatment. There were 243 patients randomized to receive sunitinib and 118 to receive placebo, 103 patients that received placebo crossed over to sunitinib at disease progression. Median TTP was 5.5 months in the sunitinib arm and 1.4 months in placebo (HR 0.33; $p < 0.0001$). The ORR was 6.8% in sunitinib arm and 0% in the placebo group ($p = 0.006$). There were no significant difference in median OS between the two groups; the sunitinib group had an OS of 16.7 months versus 15 months in the placebo arm (HR, 0.876; $p = 0.306$).

Renal Cell Carcinoma—In a randomized, phase 3 trial of 750 treatment-naïve patients with metastatic clear cell RCC, patients were assigned to sunitinib 50 mg orally once daily on a 4 weeks on, 2 weeks off dosing schedule or to interferon (IFN)-α 9 million units (MU) subcutaneously 3 times per week.[43] Median OS was greater in the sunitinib group compared to the IFN-α group (26.4 versus 21.8 months, respectively $p = 0.051$). Within the IFN-α group, 33% of patients received sunitinib, and 32% received other VEGF-signaling inhibitors after discontinuation from the trial. Median PFS was 11 months for sunitinib compared to 5 months for IFN-α ($p < 0.001$). The ORR was 47% for sunitinib compared to 12% for IFN-α ($p < 0.001$).

The 50 mg 4/2 week schedule of sunitinib was compared to continuous daily 37.5 mg in a randomized trial that included 292 patients with advanced RCC. Preliminary results showed that the 37.5 mg continuous dosing resulted in a lower TTP compared to 50 mg 4/2 week dosing (median 7.1 versus 9.9 months, HR 0.77, 95% CI: 0.57, 1.04).[44] OS and adverse events profiles were similar with the two regimens.

pNET—A randomized, double blind, placebo-controlled phase 3 trial was conducted for 171 patients with advanced, well-differentiated pancreatic neuroendocrine tumors. Patients were randomly assigned to receive sunitinib at a dose of 37.5 mg per day or placebo. Median PFS was 11.4 months in the sunitinib group compared to 5.5 months in the placebo

group ($p < 0.001$). The ORR was 9.3% in the sunitinib group versus 0% in the placebo group.[45]

Adverse Reactions—The most common adverse reactions (≥20%) in clinical trials of RCC, GIST, and pNET were fatigue/asthenia, fever, diarrhea, nausea, vomiting, altered taste, anorexia, mucositis/stomatitis, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, hair and skin discoloration, dry skin, headache, arthralgia, back and extremity pain, cough, dyspnea, and bleeding.[43-45] Grade 3/4 non-laboratory adverse events (>5%) in 2nd line GIST were fatigue (10%) and HTN (8%).[42] Grade 3/4 non-laboratory adverse events (>5%) in RCC were fatigue (15%), HTN (13%), diarrhea (10%), hand-foot syndrome (8%), mucositis (6%) and dyspnea (6%).[40] Grade 3/4 non-laboratory adverse events (>5%) in pNET were HTN (10%), hand-foot syndrome (6%), and stomatitis (6%).[40]

7.5 Regorafenib (Stivarga; Bayer)

Regorafenib is approved for refractory metastatic colorectal cancer patients and for locally advanced, unresectable or metastatic GIST patients who have been treated previously with imatinib and sunitinib. Regorafenib is a small-molecule inhibitor of multiple membrane-bound and intracellular kinases RET, VEGFR 1, 2, 3, c-Kit, PDGFR-α, β, FGFR1, 2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl. The recommended dose is 160 mg (40 mg × 4 tablets) orally, once daily for the first 21 days of each 28-day cycle with food (low-fat breakfast).[6] It is available as a 40-mg tablet.

Colorectal carcinoma—A randomized, double blind, placebo-controlled trial in 760 patients with previously- treated metastatic colorectal cancer was conducted.[46] Patients were randomized to receive either 160 mg regorafenib orally once daily (n=505) or placebo (n=255). All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab, or cetuximab/panitumumab. Patients assigned to regorafenib had a modest, though statistically significant, improvement in median OS (6.4 versus 5 months, HR 0.77, $p = 0.01$). The difference in PFS was statistically significant with a HR of 0.49 (median 2 versus 1.7 months, $p < 0.0001$), and 5 patients in the regorafenib arm (1%) experienced a PR, versus one patient (0.4%) receiving placebo.

GIST—A randomized, double-blind, placebo-controlled trial was conducted in 199 patients with histologically confirmed metastatic or unresectable GIST who experienced disease progression on imatinib and on sunitinib. Patients were randomly assigned (2:1) to receive either oral regorafenib 160 mg daily (n=133) or placebo (n=66) for the first 3 weeks of each 4-week cycle. All patients also received best supportive care.

Median PFS was 4.8 months (95% CI: 3.9-5.7) for patients on the regorafenib arm and 0.9 months (95% CI: 0.9-1.1) for patients who received placebo (hazard ratio of progression 0.27 (95% CI: 0.19- 0.39; $p<0.0001$). Following disease progression, 56 patients on the placebo arm (85 %) crossed over to receive regorafenib.

Adverse Reactions—The most common adverse reactions (≥20%) in trials in patients with colorectal cancer or GIST were asthenia/fatigue, decreased appetite, HFS, diarrhea, mucositis, infection, hypertension, and dysphonia.[6] Grade 3/4 adverse drug reactions (>5%) in the colorectal cancer trial were HFS (17%), fatigue (15%), infection (9%), HTN (8%), and diarrhea (8%).[6] Grade 3/4 adverse drug reactions (>5%) in the GIST trial were HTN (28%), HFS (22%), diarrhea (8%) and rash (7%).

7.6 Cabozantinib (Cometriq; Exelixis)

Cabozantinib is approved for patients with progressive, metastatic medullary thyroid cancer.[33] It inhibits the tyrosine kinase activity of RET, MET, VEGFR 1, 2 3, c-Kit, TRKB, FLT3, AXL, and TIE2. The recommended dose of cabozantinib is 140 mg orally once daily on an empty stomach, and it is available as 20 mg and 80 mg capsules.

A double-blind trial was conducted in 330 patients with evidence of actively progressive, metastatic medullary thyroid cancer within 14 months prior to study entry.[47] Patients were randomized (2:1) to receive cabozantinib 140 mg (n = 219) or placebo (n = 111) orally once daily, without food. No crossover was allowed at the time of progression. Forty-eight percent of patients were reported to have a RET-positive mutation. A statistically significant prolongation in PFS was reported in cabozantinib-treated patients compared to placebo (HR 0.28; $p < 0.0001$), with median PFS 11.2 months versus 4.0 months, respectively. Patients receiving cabozantinib had significantly greater PRs (27%) than the placebo group (0%; $p < 0.0001$). The median duration of response was 14.7 months (95% CI: 11.1, 19.3) in the cabozantinib arm. There was no statistically significant difference in OS between the treatment arms at the planned interim analysis.

Adverse Reactions—The most common adverse drug reactions for cabozantinib (>30%) were diarrhea, nausea, stomatitis, oral pain, hypertension, fatigue, decreased appetite and weight, dysguesia, hair depigmentation, hand foot reaction, AST/ALT elevation, hypocalcemia, neutropenia, and thrombocytopenia.[33] Grade 3/4 adverse events (>5%) were diarrhea (16%), hand foot reaction (13%), hypocalcemia (12%), fatigue (9%), HTN (8%), elevated ALT (6%) and asthenia (6%).[33]

7.7 Vandetanib (Caprelsa; AstraZeneca)

Vandetanib inhibits receptors of EGFR family, VEGFRs, RET, protein tyrosine kinase 6 (BRK), TIE2, EPH, and the Src family; there is no evidence of a relationship between RET mutations and vandetanib efficacy. Vandetanib is approved for patients with symptomatic or progressive medullary thyroid cancer.[32] Use of vandetanib in patients with indolent, asymptomatic, or slowly progressing disease should be carefully considered because of treatment-related side effects. The starting dose is 300 mg once daily taken with or without food, and the drug is available as 100 or 300 mg tablets. Because of vandetanib's 19-day half-life, adverse reactions including prolonged QT interval may not resolve quickly. Because of the risks of QT prolongation, vandetanib is available only through a restricted distribution program called the Caprelsa Risk Evaluation Mitigation Strategy Program (http://www.caprelsarems.com). The 300 mg daily dose can be reduced to 200 mg, and to 100 mg for grade 3 or greater toxicities. A double-blind, placebo-controlled study randomized patients with unresectable locally advanced or metastatic medullary thyroid cancer to vandetanib 300 mg (n=231) or placebo (n=100).[48] Fifty-eight percent of the patients receiving placebo crossed over to vandetanib at disease progression. The analysis showed a statistically significant improvement in PFS for patients randomized to vandetanib (22.6 versus 16.4 months, HR 0.35; 95% CI: 0.24, 0.53; $p < 0.0001$). Analyses in the subgroups of patients who were symptomatic or had progressed within 6 months prior to enrollment showed similar PFS results (HR 0.31; 95% CI: 0.19, 0.53 for symptomatic patients; HR 0.41; 95% CI: 0.25, 0.66 for patients who had progressed within 6 months prior to enrollment). At the time of the primary analysis of PFS, 15% of the patients had died and there was no significant difference in OS between the two treatment groups. The ORR for patients randomized to vandetanib was 44% compared to 1% for patients randomized to placebo.

Adverse Reactions—The most common adverse drug reactions reported in the above study (>20%) were diarrhea, rash, acne, nausea, hypertension, headache, fatigue, decreased appetite, and abdominal pain.[48] Grade 3/4 adverse events (>5%) were diarrhea/colitis (11%), HTN (9%), QT prolongation (8%), and fatigue (6%).[32]

7.8 Crizotinib (Xalkori; Pfizer)

Crizotinib inhibits the ALK tyrosine kinase receptor, mesenchymal epithelial transition growth factor (c-MET), and ROS1 receptor tyrosine kinase. The echinoderm microtubule protein-like 4 (EML4)-ALK fusion oncogene arises from an inversion on the short arm of chromosome 2 that joins the EML4 and ALK exons. The resulting chimeric protein, EML4-ALK, mediates ligand-independent, constitutive kinase activity. Crizotinib is approved for the treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC).[17] The starting dose of crizotinib is 250 mg orally BID, with or without food, and the dose may be reduced to 200 mg BID or 250 mg once daily depending on tolerability. Crizotinib is available as 200 or 250 mg capsules.

In a phase 1 study in ALK-positive patients, 143 were evaluable; 87 patients achieved a response (60.8%, 95% CI 52.3-68.9), including 3 CRs and 84 PRs.[49] Median time to response was 7.9 weeks (range: 2.1-39.6), median duration of response was 49.1 weeks (95% CI: 39.3, 75.4), and median PFS was 9.7 months (95% CI: 7.7, 12.8). Median OS data were not mature, but OS estimated at 6 and 12 months was 87.9% (95% CI: 81·3, 92·3) and 74.8% (66·4-81·5), respectively.[49]

A randomized phase 3 study comparing crizotinib with chemotherapy (pemetrexed or docetaxel) as second-line therapy was performed in patients with stage IIIB/IV ALK-positive NSCLC (PROFILE 1007).[50] The trial randomized 347 patients who had received previous treatment with a platinum-based regimen to receive crizotinib 250 mg orally BID or pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 IV every 21 days. Crossover was allowed at disease progression. The study met its primary objective by demonstrating the superiority of crizotinib over chemotherapy in prolonging PFS (median 7.7 versus 3 months; HR 0.49; $p < 0.0001$). ORR was significantly higher in patients treated with crizotinib (65% versus 20%; $p < 0.0001$). Interim analysis of OS (28% events) showed no statistically significant difference between crizotinib and chemotherapy (preliminary median estimate 20.3 compared to 22.8 months; HR 1.02; $p = 0.5394$), but this was not adjusted for crossover.

Adverse Reactions—The most common adverse reactions (≥20%) reported in the above study were vision disturbance, nausea, diarrhea, vomiting, edema, and constipation.[50] Grade 3/4 adverse events >5% were not reported.[17]

7.9 Erlotinib (Tarceva; Osi Pharmaceuticals)

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with EGFR; its specificity with regard to other tyrosine kinase receptors has not been fully characterized. Erlotinib is approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions detected by an FDA-approved test (Cobas®); for the maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy; for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen; and as first-line treatment in combination with gemcitabine of patients with locally advanced, unresectable, or metastatic pancreatic cancer. [9] The doss for patients with NSCLC and pancreatic cancer are 150 mg and 100 mg/day, respectively, taken on an empty stomach. Doses should be reduced in 50-mg decrements when necessary. Erlotinib is available as 25, 100, and 150 mg tablets.

First line Therapy for EGFR-mutated Non-small Cell Lung Cancer—A randomized, multicenter, open label trial was conducted comparing erlotinib (n=86) to platinum-based doublet chemotherapy (n=88) in patients with metastatic NSCLC whose tumors had EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as determined by the Sanger sequencing method. Tumor samples from 134 patients were tested retrospectively using the Cobas EGFR mutation test. The majority of the patients were female (72%), Caucasian (99%), never-smokers (69%), and had adenocarcinoma (93%). The ORR and median PFS was 65% and 10.4 months for the erlotinib arm and 16% and 5.2 months for the chemotherapy arm [PFS HR 0.34 (95% CI: 0.23, 0.49), p <0.001]. Median OS was 22.9 months and 19.5 months, respectively, for the erlotinib and chemotherapy arms [HR 0.93 (95% CI: 0.64, 1.35), p=0.6482]. The majority of the patients in the platinum-based chemotherapy arm (82%) subsequently crossed over to receive erlotinib following disease progression. [51]

Non-small Cell Lung Cancer Maintenance—In a double-blind, placebo-controlled trial conducted in 26 countries, 889 patients with locally advanced or metastatic NSCLC whose disease did not progress during 4 cycles of first-line platinum-based doublet chemotherapy, were randomly assigned to treatment with erlotinib or placebo.[44] Of the patients treated with erlotinib, 38% had squamous carcinoma and 47% had adenocarcinoma (including bronchioloaveolar type) whereas these cancers were 43% and 44% respectively for patients receiving placebo. Median PFS was significantly improved in the erlotinib group, 2.8 months compared to 2.6 in the placebo group (HR 0.71; $p < 0.0001$). Improved PFS was reported both in patients with adenocarcinoma and squamous carcinoma. Tumor samples were obtained from all 899 patients for biomarker analyses, including EGFR protein overexpression (by immunohistochemistry; IHC), increased EGFR copy number (by FISH) and EGFR and KRAS mutations (by DNA sequencing).[44] The only biomarker predictive for PFS outcome was the presence of an EGFR mutation (median PFS with erlotinib 45 versus 13 weeks with placebo, HR 0.10, 95% CI: 0.04, 0.25). Median OS was 12 months in the erlotinib group versus 11 months in the placebo group (HR 0.81; $p = 0.0088$). The OS HR for EGFR IHC-positive tumors was 0.77 (95% CI: 0.64, 0.93) versus IHC-negative tumors 0.91 (95% CI: 0.59, 1.38). Patients with adenocarcinoma had an OS HR of 0.77 (95% CI: 0.61, 0.97) but patients with squamous carcinoma had an OS HR of 0.86 (95% CI: 0.68, 1.10).[52, 53]

Non-small Cell Lung Cancer Second/Third Line Therapy—A double blind trial was conducted in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen to compare erlotinib at a dose of 150 mg daily, with placebo (2:1 ratio).[54] Fifty percent of the patients had adenocarcinoma and 30% had squamous carcinoma. The median OS was 6.7 months versus 4.7 months for erlotinib versus placebo (HR 0.73; $p < 0.001$) and median PFS was 2.2 months versus 1.8 months for erlotinib versus placebo (HR 0.59; $p < 0.001$). The ORR was 8.9% versus 0.9% ($p<0.001$).

Pancreatic Cancer—Erlotinib in combination with gemcitabine as first-line treatment was evaluated in a phase 3 double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable, or metastatic pancreatic cancer.[9] Patients were randomized to erlotinib (100 or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine (1000 mg/m^2 IV given during cycle 1 on days 1, 8, 15, 22, 29, 36 and 43 of an 8-week cycle, and in cycle 2 and subsequent cycles on days 1, 8 and 15 of a 4-week cycle. Although insufficient patients (n=48) were treated in the 150-mg erlotinib combination arm to draw conclusions, OS was significantly prolonged on the 100 mg-erlotinib plus gemcitabine arm; 6.4 compared to 6 months (HR 0.81, $p = 0.028$). PFS was also significantly longer with

erlotinib plus gemcitabine; 3.8 months versus 3.5 months (HR 0.76; p = 0.006). There was no significant difference in ORR between the arms, 8.6% versus 7.9% (p = 0.87).[9, 55]

Adverse Reactions—The most common adverse reactions (>20%) from a pooled analysis of all four indications summarized above were rash, diarrhea, anorexia, fatigue, dyspnea, cough, and nausea and vomiting. [9] Rash(14%) and dyspnea (8%) were the reported grade 3/4 adverse events (>5%) in patients with EGFR mutations treated with erlotinib while rash (6%) was the grade 3/4 adverse event (>5%) in those receiving maintenance erlotinib therapy.[9] Grade 3/4 adverse events (>5%) reported in patients receiving second/third line erlotinib treatment for advanced NSCLC were dyspnea (28%), fatigue (18%), anorexia (9%), rash (8%), and diarrhea (6%). Grade 3/4 adverse events (>5%) in patients with pancreatic cancer receiving erlotinib treatment were fatigue (16%), infection (13%), abdominal pain (9%), nausea and vomiting (7%), and anorexia (6%).[9]

7.10 Gefitinib (Iressa; AstraZeneca)

Gefitinib inhibits cell-surface tyrosine kinases including EGFR. This agent is indicated for patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel therapy who have benefited from prior gefitinib (did you mean to say another agent here…not sure this makes sense…indicated in patients who have previously had it?) therapy, but not as first-line therapy for patients with EGFR mutations.[56] The recommended daily dose of gefitinib is 250 mg with or without food and it is available as a 250-mg tablet.

Chemotherapy Pretreated, not Enriched Population—A phase 3 study of gefitinib as second- or third-line treatment was conducted with 1,692 patients with locally advanced or metastatic NSCLC.[57] Patients were randomly assigned (2:1) to gefitinib (250 mg/day) or placebo. At median follow up of 7.2 months there was no significant difference in median survival for the overall population (5.6 months for gefitinib and 5.1 months for placebo; HR 0.89; p = 0.087) or for the 812 patients with adenocarcinoma (6.3 months versus 5.4 months; HR 0.84; p = 0.089). However, median OS was significantly longer in the gefitinib-treated group than the placebo group in never-smokers (8.9 versus 6.1 months, HR 0.67; p = 0.012) and Asian patients (9.5 versus 5.5 months, HR 0.66; p=0.01).

First Line Single-agent Treatment in Enriched Populations—For the IPASS (*IRESSA Pan-Asia Study*), 1,217 patients were randomly assigned to receive either 250-mg gefitinib or chemotherapy with carboplatin plus paclitaxel.[56] Patients were Asian, had adenocarcinoma, and were either nonsmokers (those who had smoked more than 100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤ 10 pack-years of smoking). For the entire cohort, progression-free survival was significantly better for patients treated with gefitinib than chemotherapy; the 12-month PFS rate was 25% versus 7% (HR 0.74). There was no significant difference in OS, possibly due to patient crossover at disease progression—median OS was 18.8 months for the gefitinib-treated patients versus 17.4 months for those treated with the combination (HR 0.90; 95% CI: 0.79, 1.02).[58] EGFR mutations were present in 60% of the 437 patients evaluated for the mutation. For these patients, PFS was significantly prolonged following gefitinib treatment (median 9.5 months versus 6.3 months for those receiving chemotherapy, HR 0.48). However, OS was not increased because 64 % of the chemotherapy-treated patients subsequently crossed over to gefitinib at disease progression (median 22 months in both treatment groups, HR 1.00). The ORR was 71% with gefitinib versus 47% with chemotherapy in the mutation-positive subgroup (p < 0.001).[59] For the patients without EGFR mutations, PFS was significantly shorter for those treated with gefitinib than chemotherapy (median 1.5 months versus 6.5 months; HR 2.85; 95% CI:

2.05, 3.95) but the difference in OS was not considered significant (median 11.2 months versus 12.7 months, HR 1.18).

First-line Treatment in Combination with Chemotherapy—Two large trials designated INTACT *(Iressa Survival Evaluation in Lung Cancer*) were conducted in chemotherapy-naïve patients with stage III and IV NSCLC. For INTACT-1, 1,093 patients were randomized to receive 250 or 500 mg gefitinib daily or placebo in combination with gemcitabine and cisplatin. For INTACT-2, 1, 037 patients received gefitinib as above but the chemotherapy regimen was carboplatin and paclitaxel. Adding gefitinib therapy did not increase or improve tumor response rates, TTP, or OS for either chemotherapy regimen.[60, 61]

Adverse Reactions—The most common adverse reactions (>20%) in the phase 3 trial of patients with locally advanced or metastatic NSCLC study were rash and diarrhea [57] and there were no grade 3/4 adverse events (>5%) in the gefitinib arm. The most common adverse reactions (>20 %) in the gefitinib-treated arm of the IPASS trial were rash, diarrhea, dry skin, and anorexia but there were no grade 3/4 adverse events (>5%) in these patients. [56]

7.11 Lapatinib (Tykerb; GlaxoSmithKline)

Lapatinib inhibits the intracellular tyrosine kinase domains of both ErbB1 and ErbB2. This drug is approved for use in combination with capecitabine for patients with advanced or metastatic HER2-positive breast cancer who have received anthracycline, taxane, and trastuzumab, and in combination with letrozole for treatment-naïve HER2-positive and ER/PR-positive postmenopausal women.[62] The recommended dose for patients with advanced or metastatic HER2-positive breast cancer is 1,250 mg orally once daily on days 1-21 continuously in combination with capecitabine at 2,000 mg/m^2/day (every 12 hours) on days 1-14 in 21-day cycles. The recommended dose for hormone receptor positive, HER2-positive metastatic breast cancer is 1,500 mg administered orally once daily continuously in combination with 2.5 mg daily letrozole. Lapatinib is available as a 250-mg tablet to be taken without food once daily.

HER2-positive Metastatic Breast Cancer, in Combination with Capecitabine—A phase 3 trial was conducted in HER2-positive patients with locally advanced or metastatic breast cancer who had progressed after treatment with anthracyclines, taxanes, and trastuzumab. [62] Patients were randomized to receive a combination of lapatinib (1,250 mg once daily continuously) plus capecitabine (2,000 mg/m^2/day on days 1-14 in 21-day cycles), or capecitabine alone (2,500 mg/m^2/day on days 1-14 in 21- day cycles); a total of 399 patients were enrolled. Median TTP was 6.2 months versus 4.3 months for patients receiving the combination and capecitabine, respectively (HR 0.57; p = 0.00013). The ORR was 22% in the combination group versus 14% in patients receiving capecitabine alone (p=0.09).[63] OS data were not mature at the time of efficacy analysis; however, based on the TTP data, patients receiving capecitabine alone were allowed to cross over to the combination. Analysis of the survival data after patients were followed for an additional 2 years revealed a median OS of 17 months for patients treated with lapatinib plus capecitabine versus 15 months for the capecitabine-alone group (HR 0.89; p = 0.276).[62, 64]

Hormone receptor-positive, HER2-positive Metastatic Breast Cancer—The combination of lapatinib and letrozole was evaluated in a double-blind, placebo-controlled study of 1,286 postmenopausal women with ER-positive and/or PR-positive metastatic breast cancer who had not received prior therapy for metastatic disease.[39] Some 642

patients were randomized to receive the combination of lapatinib (1,500 mg once daily) plus letrozole (2.5 mg once daily) and 644 were randomized to receive letrozole (2.5 mg once daily). Of the 219 patients (17% of all treated) with HER2-positive tumors, the combination of lapatinib and letrozole improved PFS to 8.2 months from 3 months for letrozole alone (HR 0.71; $p = 0.019$). The response rate for the combination agents was 28% compared to 15% for letrozole alone ($p = 0.21$). There was no improvement in either PFS or ORR for patients with HER2-negative tumors.

Adverse Reactions—The most common (>20%) adverse reactions during treatment with the combination of lapatinib and capecitabine were diarrhea, HFS, nausea, rash, vomiting, and fatigue.[62] Grade 3/4 adverse events (>5%) in the patients treated with lapatinib were diarrhea (14%) and HFS (12%). The most common (≥20%) adverse reactions during treatment with the lapatinib plus letrozole combination were diarrhea, rash, nausea, and fatigue, while diarrhea (10%) was the only grade 3/4 adverse event >5%.[62]

7.12 Vemurafenib (Zelboraf; Roche)

Vemurafenib inhibits some mutated forms of the B-RAF serine/threonine kinase, including BRAFV600E and related kinases such as C-RAF, A-RAF, wild-type B-RAF, SRMS, ACK1, MAP4K5, and FGR. Vemurafenib is approved for patients with unresectable or metastatic melanoma with B-RAFV600E mutations that have been detected by the FDA-approved Cobas® 4800 BRAF V600 Mutation Test.[13] The recommended dose is 960 mg orally BID with doses taken 12 hours apart with or without food but with a glass of water, and it is available as a 240-mg tablet.

In an open-label phase 3 trial in treatment-naïve patients with metastatic melanoma harboring a BRAFV600E mutation, 337 patients were randomized to receive vemurafenib (960 mg twice daily) and 338 patients were randomized to receive dacarbazine 1(000 mg/m^2 IV on day 1 of every 3-week cycle).[65] The confirmed, investigator-assessed best ORR was 48.4% (95% CI: 41.6, 55.2) in patients treated with vemurafenib compared to 5.5% (95% CI: 2.8, 9.3) in patients receiving dacarbazine. The median OS was 9.6 months (not reached) in patients treated with vemurafenib versus 7.9 months in those treated with dacarbazine (HR 0.44; $p < 0.0001$). Median PFS was also significantly longer in the vemurafenib arm (5.3 months) than the dacarbazine arm (1.6 months) (HR 0.26; $p < 0.0001$).

Adverse Reactions—The most common adverse events reported in the trial (≥ 20%) were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, hyperkeratosis, diarrhea, headache, skin papilloma, squamous cell carcinoma of the skin, and keratoacanthoma[65] Grade 3/4 adverse events (>5%) were squamous cell carcinoma of the skin, keratoacanthoma (22%), and rash(8%).[13]

7.13 Vismodegib (Erivedge; Genentech)

Vismodegib is approved for patients with metastatic or locally advanced basal cell carcinoma that has recurred following surgery and for patients who are not candidates for surgery or radiation.[14] The drug inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction. The recommended dose of vismodegib is 150 mg orally once daily taken with or without food; it is available as a 150-mg capsule.

In an open-label study in patients with either metastatic or locally advanced basal cell carcinoma (BCC), the response rate in 33 patients with metastatic BCC was 30% (95% CI: 16, 48; $p = 0.001$) and 64% of patients had stable disease; of 63 patients with locally advanced BCC, the response rate was 43% (95% CI: 31, 56; $p < 0.001$), 38% had stable

disease, and 21% achieved CR. The median duration of response was 7.6 months in both BCC cohorts. [66]

Adverse Reactions—Adverse events reported in more than 20% of the patients on these trials were muscle spasms, alopecia, dysgeusia, weight loss, loss of appetite, nausea, diarrhea, and fatigue; grade 3/4 adverse events (>5%) were weight loss (7.2%) and fatigue (5.1%).[14]

7.14 Ruxolitinib (Jakafi; Incyte)

Ruxolitinib inhibits Janus Associated Kinases (JAKs) 1 and 2, which mediate the signaling of cytokines and growth factors that are important both for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, followed by activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Ruxolitinib is approved for patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.[67] The starting dose is 20 mg BID for patients with a platelet count greater than 200,000/mcL and 15 mg BID for patients with a platelet count between 100,000/mcL and 200,000/mcL. Dosing should be modified for thrombocytopenia: complete blood counts should be monitored every 2 to 4 weeks on treatment until doses are stabilized, then as clinically indicated. The dose can be increased to 25 mg BID in patients who tolerate the drug well. If there is no reduction in splenomegaly or improvement in symptoms after 6 months, further treatment with ruxolitinib should be stopped. Drug is available as 5, 10, 15, 20, and 25 mg tablets.

Two randomized phase 3 studies have been conducted in patients with myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia-myelofibrosis).[68, 69] In both studies, eligible patients had palpable splenomegaly at least 5 cm below the costal margin and were classified as intermediate 2 (2 prognostic factors) or high (3 or more prognostic factors) risk based on the International Working Group Consensus Criteria (IWG). Study endpoints included the percentage of patients with at least a 35% reduction in spleen volume at weeks 24 and 48. In the first of these trials, a double-blind study of 309 patients randomized to ruxolitinib or placebo, [68] 41.9% of the patients in the ruxolitinib group achieved a 35% reduction in splenic volume at week 24 compared to 0.7% in the placebo group ($p < 0.001$). There was also a greater than 50% improvement in the total symptom score at 24 weeks in 45.9% of the patients who received ruxolitinib compared to 5.3% of the patients who received placebo ($p < 0.001$).

In the second study, an open-label trial of 219 patients with myelofibrosis, 28% of the patients treated with ruxolitinib had at least a 35% reduction in spleen volume at week 48 whereas none of the patients receiving best available therapy achieved this endpoint ($p < 0.001$).[69] Patients treated with ruxolitinib had an improvement in overall quality-of-life measures and a reduction in the symptoms associated with their disease, but no effect on OS has yet been demonstrated.

Adverse Reactions—The most common hematologic adverse reactions (> 20%) were thrombocytopenia and anemia.[68, 69] The most common non-hematologic adverse reactions (>10%) were bruising, dizziness, and headache, whereas fatigue (5.2%) was the only grade 3/4 non-hematologic drug-related adverse event.[67]

Kinase Inhibitors for CML—Five KIs are approved for patients with CML (Table 12). Three separate randomized clinical trials demonstrated that nilotinib or dasatinib yielded

10% or greater frequent complete cytogenetic remissions (CCyR) and major molecular responses (MMR) by 12 months, as well as fewer progressions to accelerated-phase (AP) or blast-phase (BP) disease compared with imatinib. [71-73] However, no randomized trial to date has shown an overall survival benefit from treatment with nilotinib or dasatinib over imatinib. Of the four second-generation TKIs approved for patients with resistant CP-CML (nilotinib, dasatinib, bosutinib, and ponatinib), ponatinib appears to be unique in that it is effective across known Abl mutations including T315I. The five TKIs approved for CML do not appear to have overlapping side effects, which allows a patient to be switched to another TKI in the event that drug-related toxicities become intolerable. This phenomenon is likely due to the different spectrum of kinases inhibited by each TKI beyond their common target, Abl.

7.15 Imatinib (Gleevec; Novartis)

Imatinib inhibits Bcr-Abl, the constitutively active tyrosine kinase created by the Philadelphia chromosome abnormality, as well as the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF) c-Kit. Imatinib is approved for patients with newly diagnosed CML or for those with disease that has progressed following IFN-α therapy for Philadelphia chromosome-positive CML (Ph+ CML) in CP-stage disease at 400 mg/day, in AP-and BP- stage disease at 600 mg/day; in c-Kit-positive unresectable and/or metastatic malignant GIST at 400 mg/day; for the adjuvant treatment of adult patients following resection of c-Kit-positive GIST at 400 mg/day; in relapsed or refractory Ph+ acute lymphoblastic leukemia at 600 mg/day; in myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements at 400 mg/day; in aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown at 100 mg/day or 400 mg/day; in adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase; for patients with HES and/or CEL who are FIP1L1-PDGFRa fusion kinase negative or unknown at 100 mg/day or 400 mg/day; and for adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) at 800 mg/day.[4] Imatinib should be taken with food and a large glass of water but the tablets (100 and 400 mg) can be dissolved in water or apple juice. The 400 and 600 mg doses are administered once daily whereas the 800 mg dose is administered twice a day at 400 mg.

Unresectable and/or Malignant Metastatic Gastrointestinal Stromal Tumors— A meta-analysis was performed of data from two open-label, phase 3 studies in a total of 1,640 patients with unresectable or metastatic malignant GIST randomized 1:1 to receive either 400 mg (n=818) or 800 mg (n=822). [70][71, 72] Median OS and ORR for patients on the two doses were similar in that the median OS was 49 months for the 400-mg group and 48.7 months for the 800-mg group, while the ORR was 51% and 54%, respectively.

Adjuvant Treatment of Gastrointestinal Stromal Tumors—A double blind, placebo-controlled, trial was conducted in 713 patients randomized to imatinib (400 mg/day) or placebo for 12 months—patients were required to have measurable tumors of >3 cm.[4] Patients on the placebo arm were allowed to cross over to imatinib at disease recurrence.[73] Eight percent of patients receiving imatinib and 20% of patients on placebo had recurrence-free survival (RFS) events, i.e., tumor recurrence or death, at the interim analysis median follow up at 20 months (HR 0.35; $p < 0.0001$). By the median follow up at 50 months, there were 21% RFS events in the imatinib arm compared to 28% events in the placebo arm, HR of 0.718 (95% CI: 0.531, 0.971) and 26 (7%) and 33 (9%) deaths in the imatinib and placebo arms, respectively, HR of 0.816 (95% CI: 0.488, 1.365).

A second open-label, phase 3 trial in the adjuvant setting randomized adult patients to either 12 or 36 months of imatinib treatment at 400 mg/day. Eligible patients had one of the following: tumor diameter > 5 cm with mitotic count >5/50 by high power field (HPF); tumor diameter >10 cm and any mitotic count; tumor of any size with mitotic count >10/50 HPF; or tumors that had ruptured into the peritoneal cavity.[4] Median follow-up was 42 months. There were 42% RFS events in the 12-month arm and 25% RFS events in the 36-month arm. Patients treated for 36 months had significantly prolonged RFS over the shorter period, HR of 0.46 (95% CI: 0.32, 0.65; $p < 0.0001$); 5-year RFS events were 65.6% versus 47.9%, respectively. Treatment for 36 rather than 12 months significantly prolonged OS with a HR of 0.45 (95% CI: 0.22, 0.89; $p = 0.0187$). Treating these patients with imatinib for up to 3 years is therefore recommended.[74]

Newly- Diagnosed Chronic Phase Chronic Myeloid Leukemia—A randomized, open-label, phase 3 study was conducted in 1,106 patients with newly diagnosed Ph+ CML in chronic phase (CP-CML) to compare single-agent imatinib with the combination of IFN-α plus cytarabine (Ara-C).[4] Patients were crossed over to the alternative treatment arm at disease progression. At 84 months, the estimated OS was 86.4% in the imatinib arm versus 83.3% in the IFN-α combination arm ($p = 0.073$; HR 0.75, 95% CI: 0.547, 1.028), but any benefit in OS was offset by a 90% crossover rate. The complete cytogenetic response rates for patients on the imatinib and IFN-α combination arms were 74.7% versus 6.5%.[75, 76]

Adverse Reactions—The most frequently reported adverse reactions for imatinib (>30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain.[4] Grade 3/4 adverse reactions (>10%) in advanced GIST trials were edema (13%), fatigue (12%), and abdominal pain (14%). There were no grade 3/4 adverse reactions (>5%) in adjuvant GIST trials whereas the grade 3/4 adverse reaction (>5%) in trials of patients with newly diagnosed CML was musculoskeletal pain (5.4%).[4]

7.16 Dasatinib (Sprycel; Bristol-Myers Squibb)

Dasatinib inhibits Bcr-Abl, SRC family, c-Kit, EPHA2, and PDGFRβ kinases. Dasatinab is approved for patients with newly diagnosed or imatinib-resistant/intolerant CP-CML at a dose of 100 mg daily and for patients with AP, BP-CML, or resistant/intolerant Ph+ ALL at 140 mg daily.[8] The drug is taken orally with or without food and is available at 20, 50, 70, 80, 100, and 140 mg tablets.

Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia—A total of 519 adult patients with newly diagnosed CP-CML were randomized to receive either dasatinib 100 mg once daily or imatinib 400 mg once daily on a randomized, open-label trial.[77] The rate of confirmed complete cytogenic response measured within 12 months was 76.8% for dasatinib and 66.2% for imatinib ($p=0.007$).

Resistant or Intolerant Chronic Myeloid Leukemia in Chronic Phase—Patients with imatinib-resistant/intolerant CP-CML (n=670) were randomized to receive dasatinib at doses and schedules of 100 mg once daily, 50 mg BID, 140 mg once daily, or 70 mg BID. [78] The 167 patients randomized to receive 100 mg dasatinib achieved a PFS of 57% at 5 years. The OS for all patients was 78% and the overall rate of transformation to advanced disease was 5%. The complete cytogenetic response rate was 50% at 2 years. In an exploratory analysis, 42% and 60% of patients had Bcr-Abl levels ≤ 10% (International Scale, IS) at 1 and 3 months, respectively.

Adverse Reactions—The most common non-hematologic adverse reactions (>20%) in patients with newly diagnosed or resistant/intolerant CML were fluid retention, diarrhea, and

headache.[77] There were no grade 3/4 non-hematologic adverse reactions (>5%) in patients with newly diagnosed CP-CML whereas grade 3/4 hypophosphatemia (10%) was reported in the patients with resistant CP-CML.[8]

7.17 Nilotinib (Tasigna; Novartis)

Nilotinib inhibits the autophosphorylation of Bcr-Abl, PDGFR, c-Kit, CSF-1R, and DDR1 kinases. Nilotinib is approved for patients with newly diagnosed Ph+ CP-CML at 300 mg BID and for patients with resistant or intolerant Ph+ CP or AP-CML at 400 mg BID.[10] This agent should be taken on an empty stomach and is available as 150 and 200 mg capsules.

Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase—A phase 3, open-label study randomized patients 1:1:1 to receive nilotinib at either 300 mg BID (n=282) or 400 mg BID (n=281) or imatinib (n=283).[79] By 12 months, patients on the 300-mg nilotinib arm achieved an 80% complete cytogenetic response compared to 65% for those on the imatinib arm (p=0.001). By 24 months, significantly more patients receiving nilotinib had achieved a major molecular response (Bcr-Abl transcript levels on the IS of 0.1% or less by realtime quantitative PCR of peripheral blood) compared to imatinib (71% with 300-mg nilotinib, 67% with 400-mg nilotinib, and 44% with imatinib; $p < 0.0001$). Significantly more patients in the nilotinib groups also achieved a complete molecular response, defined as a reduction of Bcr-Abl IS levels to ≤ 0.0032%, than did patients in the imatinib group (26% with 300-mg nilotinib, 21% with 400-mg nilotinib, and 10% with imatinib; $p \leq 0.0004$). After 24 months, there were fewer CML-related deaths in the nilotinib groups than in the imatinib group: 5 on 300-mg nilotinib, 3 on 400-mg nilotinib, and 10 on imatinib.

Resistant or Intolerant Chronic Myeloid Leukemia in Chronic Phase—An open-label phase 2 study of nilotinib was conducted in 321 patients to evaluate the 400 mg BID dose in this population.[80] Fifty-nine percent of patients achieved a major cytogenetic response and 44% achieved a complete cytogenetic response. Of the patients achieving complete cytogenetic response, 56% had a major molecular response. The cytogenetic response was durable in that 84% of these patients maintained the response through 24 months. OS at 24 months was 87%.

Adverse Reactions—The most commonly reported non-hematologic adverse reactions (>20%) in patients with newly diagnosed CP-CML were rash, pruritus, headache, nausea, fatigue, myalgia, and nasopharyngitis; however there were no grade 3/4 non-hematologic adverse reactions (>5%) in these patients. [10] The most commonly reported non-hematologic adverse reactions (>20%) in patients with resistant or intolerant CP-CML were rash, pruritus, and nausea; while grade 3/4 non-hematologic adverse reactions (>5%) were elevated lipase (18%), hypophosphatemia (17%), hyperglycemia (12%), and hyperbilirubinemia (7%).[10]

7.18 Bosutinib (Bosulif; Pfizer)

Bosutinib, which inhibits Bcr-Abl kinase and Src-family kinases, is approved for patients with chronic, accelerated, or blast-phase Ph+ CML who are resistant to or intolerant of prior therapy.[5] Bosutinib is available as 100 and 500 mg tablets. The dose is 500 mg orally once daily with food. The dose can be escalated to 600 mg daily if patients have not achieved a complete hematologic response by 8 weeks, or a complete cytogenetic response by 12 weeks providing that there are no adverse reactions greater than grade 3. In a phase 1/2 study of 288 patients with imatinib-resistant (n = 200) or imatinib-intolerant (n = 88) CML and no other previous kinase inhibitor exposure, 31% of patients achieved a major cytogenetic

response at 24 weeks.[81] After a median follow up of 24.2 months, 53% of the patients had a major cytogenetic response and 41% had a complete cytogenetic response; some 64% percent of patients achieving a complete cytogenetic response had a major molecular response. At 2 years, PFS and OS were 79% and 92%, respectively. Responses were reported in patients with all known types of Bcr-Abl mutations with the exception of T315I.

Adverse Reaction—The most common adverse reactions (> 20%) are diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, and fatigue.[5] Grade 3/4 non-hematologic adverse reactions (>5%) of CP-CML were diarrhea (9%), rash (8%), and elevated ALT (7%).[5]

7.16 Ponatinib (Iclusig;ARIAD)

Ponatinib is approved for chronic, accelerated, or blast phase CML that is resistant or intolerant to prior tyrosine kinase inhibitor therapy and Ph+ acute lymphoblastic leukemia (Ph+ ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. This agent inhibits ABL, T315I-mutant ABL, VEGFR, PDGFR, FGFR, EPH receptors, SRC family kinases, KIT, RET, TIE2, and FLT3. The drug is available as 15 and 45 mg tablets and is administered orally at a dose of 45 mg once daily, with or without food.

A multicenter, single-arm trial of 449 patients resistant or intolerant (R/I) to imatinib, dasatinib, or nilotinib, or who had a confirmed T315I mutation. Patients were assigned to one of five cohorts: CP-CML R/I (n=203), CP-CML T315I (n=64), AP-CML (n=83), BP-CML (n=62), or Ph+ALL (n=32). In the CP-CML cohort, 54% of patients had a major cytogenetic response and 44% achieved a complete cytogenetic response at a median follow-up of 10 months. Seventy percent of patients with CP-CML with T315I mutation achieved a major cytogenetic response; the median duration of response had not been reached at the time of analysis. For the AP-CML, BP-CML, and Ph+ ALL cohorts, major hematologic responses were observed in 52%, 31%, and 41% of the patients, respectively. Median durations of major hematologic response in patients with AP-CML, BP-CML and Ph+ ALL were 9.5 months, 4.7 months and 3.2 months, respectively. The estimated (Kaplan-Meier) probability of responders maintaining the primary endpoint at one year was reported as 91% in the CP-CML, 42% in the AP-CML, and 35% in the BP-CML/Ph+ALL cohorts. [82]

Adverse Reaction—The most common non-hematologic adverse reactions from this clinical trial (> 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia. [82] Grade 3/4 non-hematologic adverse reactions (>5%) in the CP-CML cohort were hypertension (39%), arterial ischemia (7%), and abdominal pain (10%). [82]

8 Conclusion

KIs can offer efficacious therapy along with the advantage of daily oral administration. However, this route of administration raises concerns about patient compliance, drug interactions, and the management of chronic toxicities.[7] The practitioner needs to consider the proper dose based on indication, organ function, interactions with concurrent medications and food, as well as adherence from the patient's standpoint. Appreciable fluctuations in drug exposures can occur with food and concomitant medications. To minimize unwanted side effects and to maximize desired efficacy, the practitioner needs to educate the patient on the importance of consistent dosing, on how to take the drug to comply with the correct dosing regimen, and on expected common side effects. It is important to share this information with other specialists given the current practice of multispecialty patient care. The number of FDA-approved oral KIs is expected to increase,

as will the indications for these approved agents, emphasizing the importance of remaining up-to-date with possible drug interactions. Because many KIs share similar but complicated dosing regimens, we highlighted common aspects of KI use in this review as a quick reference guide for practitioners.

There has been a remarkable increase in the development of new therapies for cancer. These developments, while exciting, bring their own challenges in continuing to provide optimum oncology care for the community. Keeping abreast of new developments and establishing basic principles of practice by understanding the way KIs are developed in early trials and current FDA recommendations are both essential to ensure the best care of our patients.

Acknowledgments

We would like to thank Heather Gorby, SAIC-Frederick, Inc., for editorial assistance in the preparation of this manuscript.

References

1. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science. 2002; 298(5600):1912–34. Epub 2002/12/10. [PubMed: 12471243]
2. Gotink KJ, Verheul HM. Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action? Angiogenesis. 2010; 13(1):1–14. Epub 2009/12/17. [PubMed: 20012482]
3. Danielson PB. The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. Curr Drug Metab. 2002; 3(6):561–97. Epub 2002/10/09. [PubMed: 12369887]
4. FDA/Center for Drug Evaluation Research. Label information for Gleevec [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2003. [updated 2003 Apr 18; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021588s024lbl.pdf
5. FDA/Center for Drug Evaluation Research. Label information for Bosulif [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Sep 4; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203341lbl.pdf
6. FDA/Center for Drug Evaluation Research. Label information for Stivarga [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Sep 27; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203085lbl.pdf
7. Kang SP, Ratain MJ. Inconsistent labeling of food effect for oral agents across therapeutic areas: differences between oncology and non-oncology products. Clin Cancer Res. 2010; 16(17):4446–51. Epub 2010/08/26. [PubMed: 20736327]
8. FDA/Center for Drug Evaluation Research. Label information for Sprycel [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2006. [updated 2011 Oct 7; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021986s009s010lbl.pdf
9. FDA/Center for Drug Evaluation Research. Label information for Tarceva [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Apr 17; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021743s017lbl.pdf
10. FDA/Center for Drug Evaluation Research. Label information for Tasigna [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2007. [updated 2012 Dec 20; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022068s011lbl.pdf
11. Pavlovsky C, Egorin MJ, Shah DD, Beumer JH, Rogel S, Pavlovsky S. Imatinib mesylate pharmacokinetics before and after sleeve gastrectomy in a morbidly obese patient with chronic myeloid leukemia. Pharmacotherapy. 2009; 29(9):1152–6. Epub 2009/08/25. [PubMed: 19698017]

12. FDA/Center for Drug Evaluation Research. Label information for Inlyta [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Jan 27; cited 2013 Feb 8] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202324lbl.pdf
13. FDA/Center for Drug Evaluation Research. Label information for Zelboraf [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2011. [updated 2011 Aug 8; cited 2013 Feb 8] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429s000lbl.pdf
14. FDA/Center for Drug Evaluation Research. Label information for Erivedge [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2013 Jan 30; cited 2013 February 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203388lbl.pdf
15. Flockhart, D. Cytochrome P450 drug interaction table [homepage on the Internet]. Indianapolis, IN: Indiana University School of Medicine; 2007. [updated 2011 May 17; cited 2013 Feb 5] Available from: http://medicine.iupui.edu/clinpharm/ddis/
16. FDA/Center for Drug Evaluation Research. Label information for Votrient [homepage on the Internet]. Silver Spring, MD: 2009. [updated 2012 Nov 15; cited 2013 February 10] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022465s013lbl.pdf
17. FDA/Center for Drug Evaluation Research. Label information for Xalkori [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2011. [updated 2012 Feb 24; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s003lbl.pdf
18. FDA/Center for Drug Evaluation Research. Label information for Sutent [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Nov 16; cited 2013 Feb 12] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021938s021s022s023lbl.pdf
19. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012:1–207. Epub 2012/09/13. [PubMed: 22967432]
20. FDA/Center for Drug Evaluation Research. Label information for Nexavar [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2011. [updated 2011 Oct 14; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021923s012lbl.pdf
21. Kollmannsberger C, Bjarnason G, Burnett P, Creel P, Davis M, Dawson N, et al. Sunitinib in metastatic renal cell carcinoma: recommendations for management of noncardiovascular toxicities. Oncologist. 2011; 16(5):543–53. Epub 2011/04/15. [PubMed: 21490127]
22. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003; 13(1):3–126. Epub 2003/03/11. [PubMed: 12625976]
23. Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA. 1990; 263(11):1529–32. Epub 1990/03/16. [PubMed: 2308185]
24. Brown RL. Tyrosine kinase inhibitor-induced hypothyroidism: incidence, etiology, and management. Target Oncol. 2011; 6(4):217–26. Epub 2011/11/22. [PubMed: 22101606]
25. Maitland ML, Bakris GL, Black HR, Chen HX, Durand JB, Elliott WJ, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst. 2010; 102(9):596–604. Epub 2010/03/31. [PubMed: 20351338]
26. Food and Drug Administration. Drug development and drug intereactions [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2011. [updated 2011 Sep 16; cited 2013 Feb 12] Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
27. Food and Drug Administration. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs [homepage on the

Internet]. Silver Spring, MD: Food and Drug Administration; 2005. [updated 2005 Oct; cited 2013 Feb 21] Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf

28. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. Scientific World Journal. 2012; 2012:212178. Epub 2012/05/18. [PubMed: 22593664]
29. Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2003. [updated 2003 May; cited 2013 Feb 12] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf
30. Patel H, Egorin MJ, Remick SC, Mulkerin D, Takimoto HM, Doroshow JH, et al. Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): Implications for chemotherapy dosing. American Society of Clinical Oncology Annual Meeting: Journal of Clinical Oncology. 2004 Abstract #6041.
31. Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired renal function - study design, data analysis, and impact on dosing and labeling [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 1998. [updated 1998 May cited 2013 Feb 12] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072127.pdf
32. FDA/Center for Drug Evaluation Research. Label information for Caprelsa [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2011. [updated 2012 Oct 9; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022405s003lbl.pdf
33. FDA/Center for Drug Evaluation Research. Label information for Cometriq [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Nov 29; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203756lbl.pdf
34. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011; 378(9807):1931–9. Epub 2011/11/08. [PubMed: 22056247]
35. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28(6):1061–8. Epub 2010/01/27. [PubMed: 20100962]
36. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012; 379(9829):1879–86. Epub 2012/05/19. [PubMed: 22595799]
37. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359(4):378–90. Epub 2008/07/25. [PubMed: 18650514]
38. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009; 27(20):3312–8. Epub 2009/05/20. [PubMed: 19451442]
39. Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009; 27(33):5538–46. Epub 2009/09/30. [PubMed: 19786658]
40. FDA/Center for Drug Evaluation Research. Label information for Sutent [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2006. [updated 2012 Nov 16; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021938s021s022s023lbl.pdf
41. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of

imatinib: a randomised controlled trial. Lancet. 2006; 368(9544):1329–38. Epub 2006/10/19. [PubMed: 17046465]

42. Demetri GD, Garrett CR, Schoffski P, Shah MH, Verweij J, Leyvraz S, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res. 2012; 18(11): 3170–9. Epub 2012/06/05. [PubMed: 22661587]
43. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(22):3584–90. Epub 2009/06/03. [PubMed: 19487381]
44. Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clin Oncol. 2012; 30(12):1371–7. Epub 2012/03/21. [PubMed: 22430274]
45. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011; 364(6):501–13. Epub 2011/02/11. [PubMed: 21306237]
46. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381(9863):303–12. Epub 2012/11/28. [PubMed: 23177514]
47. Schoffski, P.; Elisei, R.; Muller, S.; Brose, MS.; Shah, AM.; Licitra, LS., et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documents RECIST progression at baseline. American Society of Clinical Oncology Annual Meeting: Journal of Clinical Oncology; 2012; Abtract 5508
48. Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012; 30(2):134–41. Epub 2011/10/26. [PubMed: 22025146]
49. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012; 13(10):1011–9. Epub 2012/09/08. [PubMed: 22954507]
50. Shaw, AT.; Kim, DW.; Nakagawa, K., editors. European Society of Medical Oncology. 2012. Phase III randomized study of crizotinib versus pemetrexed or docetaxel chemotherapy in advanced, ALK-positive non-small cell lung cancer (NSCLC).
51. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012; 13(3):239–46. [PubMed: 22285168]
52. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010; 11(6):521–9. Epub 2010/05/25. [PubMed: 20493771]
53. Brugger W, Triller N, Blasinska-Morawiec M, Curescu S, Sakalauskas R, Manikhas GM, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. J Clin Oncol. 2011; 29(31):4113–20. Epub 2011/10/05. [PubMed: 21969500]
54. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353(2):123–32. Epub 2005/07/15. [PubMed: 16014882]
55. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007; 25(15):1960–6. Epub 2007/04/25. [PubMed: 17452677]
56. FDA/Center for Drug Evaluation Research. Label information for Iressa [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2003. [updated 2005 Jun 17; cited

2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021399s008lbl.pdf

57. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005; 366(9496):1527–37. Epub 2005/11/01. [PubMed: 16257339]
58. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361(10):947–57. Epub 2009/08/21. [PubMed: 19692680]
59. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011; 29(21):2866–74. Epub 2011/06/15. [PubMed: 21670455]
60. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. J Clin Oncol. 2004; 22(5):777–84. Epub 2004/03/03. [PubMed: 14990632]
61. Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. J Clin Oncol. 2004; 22(5):785–94. Epub 2004/03/03. [PubMed: 14990633]
62. FDA/Center for Drug Evaluation Research. Label information for Tykerb [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2007. [updated 2012 Feb 14; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022059s013lbl.pdf
63. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006; 355(26):2733–43. Epub 2006/12/29. [PubMed: 17192538]
64. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010; 15(9):924–34. Epub 2010/08/26. [PubMed: 20736298]
65. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364(26):2507–16. Epub 2011/06/07. [PubMed: 21639808]
66. Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. N Engl J Med. 2012; 366(23):2171–9. [PubMed: 22670903]
67. FDA/Center for Drug Evaluation Research. Label Information for Jakafi [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2011. [updated 2012 Jun 21; cited 2013 Feb 11] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202192s001lbl.pdf
68. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012; 366(9):799–807. Epub 2012/03/02. [PubMed: 22375971]
69. Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012; 366(9):787–98. Epub 2012/03/02. [PubMed: 22375970]
70. Gastrointestinal Stromal Tumor Meta-Analysis Group. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a metaanalysis of 1,640 patients. J Clin Oncol. 2010; 28(7):1247–53. Epub 2010/02/04. [PubMed: 20124181]
71. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008; 26(4):626–32. Epub 2008/02/01. [PubMed: 18235122]

72. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004; 364(9440):1127–34. Epub 2004/09/29. [PubMed: 15451219]

73. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373(9669):1097–104. Epub 2009/03/24. [PubMed: 19303137]

74. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schutte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012; 307(12):1265–72. Epub 2012/03/29. [PubMed: 22453568]

75. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003; 348(11):994–1004. Epub 2003/03/15. [PubMed: 12637609]

76. Deininger, M.; O'Brien, SG.; Guilhot, F.; Goldman, JM.; Hochhaus, A.; Hughes, TP., et al. International randomized study of interferon versus STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. American Society of Hematology Annual Meeting and Exposition: Blood; 2009; p. 126

77. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010; 362(24):2260–70. Epub 2010/06/08. [PubMed: 20525995]

78. Shah, NP.; Kantarjian, H.; Kim, DW.; Hochhaus, A.; Saglio, G.; Guilhot, F., et al. Six-year (yr) follow-up of patients (pts) with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukemia (CML-CP) receiving dasatinib. American Society of Clinical Oncology Annual Meeting: Journal of Clinical Oncology; 2012; Abstract #6506

79. Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011; 12(9):841–51. Epub 2011/08/23. [PubMed: 21856226]

80. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood. 2011; 117(4):1141–5. Epub 2010/11/26. [PubMed: 21098399]

81. Cortes JE, Kantarjian HM, Brummendorf TH, Kim DW, Turkina AG, Shen ZX, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011; 118(17):4567–76. Epub 2011/08/26. [PubMed: 21865346]

82. FDA/Center for Drug Evaluation Research. Label information for Ponatinib [homepage on the Internet]. Silver Spring, MD: Food and Drug Administration; 2012. [updated 2012 Dec 17; cited 2013 May 28] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf

Table 1

FDA-approved oral kinase inhibitors are listed with indications in parentheses.

FDA Approved Year (New)	Agent (Indication)
2001 (1)	Imatinib (CML)
2002 (0)	Imatinib (advanced GIST)
2003 (1)	Gefitinib
2004 (1)	Erlotinib (lung)
2005 (1)	Erlotinib (pancreas)
	Sorafenib (RCC)
2006 (2)	Dasatinib (2nd line)
	Sunitinib (RCC, GIST)
2007 (2)	Lapatinib, Nilotinib (2nd line)
	Sorafenib (HCC)
2008 (0)	Imatinib (adjuvant GIST)
2009 (1)	Pazopanib (RCC)
2010 (0)	Dasatinib (1st line)
	Nilotinib (1st line)
2011 (4)	Crizotinib
	Ruxolitinib
	Sunitinib (pNET)
	Vandetanib
	Vemurafenib
2012 (4)	Axitinib
	Bosutinib
	Cabozantinib
	Pazopanib (sarcoma)
	Regorafenib (CRC)
	Vismodegib
	Ponatinib
2013 (0)	Regorafenib (GIST)
	Erlotinib (1st line, EFGR mutated)

Abbreviations: CML, chronic myelogenous leukemia; CRC, colorectal carcinoma; GIST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; pNET, pancreatic neuroendocrine tumor; EGFR, epithelial growth factor receptor.

Table 2

Targets inhibited by kinase inhibitors. Data are from each KI package insert; KIs that are not known to inhibit multiple kinases are not listed.

	Agent												
Kinase Inhibitor	**Regorafen ib**	**Pon atin ib**	**Dasat inib**	**Soraf enib**	**Vemura fenib**	**Vandet anib**	**Caboza ntinib**	**Pazop anib**	**Sunit inib**	**Nilot inib**	**Bosut inib**	**Imati nib**	**Crizot inib**
PDGFR	×	×	×	×				×	×	×		×	
c-Kit	×	×	×	×			×	×	×	×		×	
VEGFR	×	×		×		×	×	×	×				
RET	×	×		×		×	×		×				
Abl	×	×	×							×	×	×	
Abl T315I		×											
EGFR						×							
EPHR	×	×	×			×							
BRAFV60 0E	×			×	×								
CRAF(raf-1)	×			×	×								
Src		×	×			×					×		
BRAF				×	×								
CSF-1R									×	×			
DDR	×									×			
FGFR	×	×						×					
FLT3		×		×			×		×				
Hck			×								×		
Lck			×					×					
TIE2	×	×				×	×						
ACK1					×								
Alk													×
ARAF					×								
AXL							×						
BRK						×							
c-Fms								×					
FGR					×								
FYN			×										
Itk								×					
Jak													
Lyn											×		
MAP4K5					×								

	Agent												
Kinase Inhibitor	**Regorafen ib**	**Pon atin ib**	**Dasat inib**	**Soraf enib**	**Vemura fenib**	**Vandet anib**	**Caboza ntinib**	**Pazop anib**	**Sunit inib**	**Nilot inib**	**Bosut inib**	**Imati nib**	**Crizot inib**
MET							×						×
Ptk5	×												
ROS1													×
Sapk2	×												
SCF												×	
Smoothened SRMS					×								
Trk2A	×												
TRKB							×						
Yes			×										

Abbreviations: PDGFR, platelet derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; RET, rearranged during transfection; EGFR, epithelial growth factor receptor; EPHR, ephrin receptor; SRC, rous sarcoma oncogene cellular; CSF-1R, colony stimulating factor 1 receptor; DDR, discoidin domain receptor; FGFR, fibroblast growth factor receptor; FLT3, Fms-like tyrosine kinase 3; Lck, lymphocyte-specific protein tyrosine kinase; Abl, Ableson leukemia oncogene; Jak, Janus-family tyrosine kinase; ACK1, activated CDC42 kinase 1; Alk, anaplastic lymphoma kinase; BRK, breast tumor kinase; c-Fms, cellular homolog of feline sarcoma virus; FGR, feline sarcoma viral; Itk, IL2-inducible T-cell kinase; MAP4K5, mitogen-activated protein kinase; Sapk2, stress-activated protein kinase; SCF, Skp, Cullin, F-box containing complex; SRMS, src-related kinase; TRKB, tyrosine-related kinase B; Yes; Yamaguchi sarcoma virus oncogene.

Table 3

Examples of medications that strongly induce CYP3A4.

Type of Medication	Name
Antibiotics	Rifampin (its derivatives)
Anticonvulsants	Phenytoin
	Phenobarbital
	Carbamezepine (its derivatives)
Glucocorticoids	Prednisone (>10 mg)
	Methylprednisolone (>8 mg)
	Dexamethasone (>1.5 mg)
HIV Antivirals	Efavirenz
	Nevirapine
Miscellaneous	St. John's
	Wort Modafinil
	Pioglitazone, Troglitazone

Table 4

Examples of medications and foods that strongly or moderately inhibit CYP3A4.

Type of Medication	Name
Antibiotics	Clarithromycin
	Telithromycin (Azithromycin; weak inhibitor)
Antifungals	Itraconazole
	Ketoconazole
	Voriconazole
HIV Protease Inhibitors	Ritonavir
	Indinavir
	Saquinavir
	Nelfinavir
	Amprenavir
	Lopinavir
Moderate CYP3A4 inhibitors	Erythromycin
	Fluconazole
	Aprepitant
	Verapamil
	Diltiazem
	Grapefruit and grapefruit juice

Table 5

Examples of medications that are substrates for CYP enzymes with narrow therapeutic windows.

Type of Medication	Name	Adverse Reaction
Antiarrhythmic	Bepridil	Risk of QT interval prolongation and Torsade de Pointes
	Flecainide	
	Lidocaine	
	Mexiletine	
	Amiodarone	
	Quinidine	
	Propafenone	
Ergot Derivatives	Dihydroergotamine	Risk of severe vasospasm
	Ergonovine	Risk of peripheral or cerebral ischemia
	Ergotamine	
	Methylergonovine	
Immune Modulators	Cyclosporine	Risk of nephrotoxicity
	Tacrolimus	Risk of neurotoxicity
	Sirolimus	
Miscellaneous	Quetiapine	Increased toxicity
	Risperidone	
	Clozapine	
	Atomoxetine	
Neuroleptics	Pimozide	Risk of QT prolongation

Table 6

KI interactions with drugs and food are listed. In general, when antacids are used, avoid concurrent intake with KIs to maximize KI absorption.

Kinase Inhibitor	Food Effect	CYP 3A4 inducer	CYP 3A4 Inhibitor	Effect on Concurrent Medications	Proton Pump Inhibitor	Statin	Warfarin
Axitinib	No	Decrease KI level; avoid inducer	Increase KI level; Reduce KI dose	Does not inhibit CYP3A4	No adjustment		
Bosutinib	With food	Decrease KI level; avoid inducer	Increase KI level; Avoid inhibitor		Decrease KI level; use antacid, H2 2 hr later		
Cabozantinib	Empty Stomach	Decrease KI level; avoid inducer	Increase KI level; Avoid inhibitor	CYP3A4 substrate increase			
Crizotinib	No	Decrease KI level; avoid inducer	Increase KI level; Avoid inhibitor	CYP3A4 substrate increase			
Dasatinib	No	Decrease KI level; increase KI dose	Increase KI level; Reduce KI dose	CYP3A4 substrate increase	Do not use PPI, H2; use antacid 2 hr later	Simvastatin's AUC increase	
Erlotinib	Empty stomach	Decrease KI level; increase KI dose	Increase KI level; Reduce KI dose	CYP3A4 substrate increase	Do not use PPI; take erlotinib 10 hr later or 2 hr before H2; use antacid 2 hr later		High INR
Gefitinib	No	Decrease KI level; increase dose to 500 mg	Increase KI level; Avoid inhibitor		H2 reduced AUC		
Imatinib	With food	Decrease KI level; increase KI dose	Increase KI level; Avoid inhibitor	CYP3A4 substrate increase		Simvastatin's AUC increase	
Lapatinib	Empty stomach	Decrease KI level; increase KI dose	Increase KI level; Reduce KI dose	CYP3A4 substrate increase	Esomeprazole did not reduce KI level		
Nilotinib	Empty stomach	Decrease KI level; avoid inducer	Increase KI level; Reduce KI dose	CYP3A4 substrate increase	Decrease KI level;use antacid, H2, 2 hr later; gastrectomy decrease KI level		No change
Pazopanib	Empty Stomach	Decrease KI level; avoid inducer	Increase KI level; Reduce KI dose	CYP3A4 substrate change			No change
Regorafenib	With food	Decrease KI level; avoid inducer	Increase KI level; Avoid inhibitor	CYP3A4 substrate increase			
Ruxolitinib	No	No adjustment	Increase KI level; Reduce KI dose				
Sorafenib	Empty stoma ch	Decrease KI level; avoid inducer	Ketoconazole, no effect	Not inhibit CYP3A4			
Sunitinib	No	Decrease KI level; increase KI dose	Increase KI level; Reduce KI dose	No effect on major CYP			
Vandetanib	No	Decrease KI level; avoid inducer	Itraconazole, no effect	Avoid; QT prolonging/ar rhythmic			

Kinase Inhibitor	Food Effect	CYP 3A4 inducer	CYP 3A4 Inhibitor	Effect on Concurrent Medications	Proton Pump Inhibitor	Statin	Warfarin
Vemurafenib	No	Decrease KI level; avoid inducer	Increase KI level; Avoid inhibitor	CYP3A4 substrate change			Warfarin AUC 18% increase
Vismodegib	No	No effect	No effect		PPI, H2, and antacid may decrease KI level		
Ponatinib	No	avoid inducer	Increase KI level; Reduce to 30mg	No effect on major CYP	Not evaluated; antiacid may reduce KI level		

Abbreviations: AUC, area under the curve; H2, Histamine H2 receptor blocker; HR, hour; KI, kinase inhibitor

Table 7

Major adverse reactions associated with KIs are listed. Incidence is from across all FDA indications of each KI using the highest percent reported and landmark studies that lead to KI approval by FDA. Percent may be different from smaller phase 2 studies.

Kinase Inhibitor	Black Box Warning	Fatal Hepatic Failure	Grade 3/4 AST/ALT	Grade 3/4 Total Bilirubin	Any Grade QT Prolongation	Grade 3 QT Prolongation	Tors ades
Axitinib	None		<1%				
Bosutinib	None		7%	1%	<10%	0.2%	
Cabozantinib	Perforation, fistula, or hemorrhage		6%			None	
Crizotinib	None		7%		3.5%	1.3%	
Dasatinib	None		<1%	1%		1%	
Erlotinib	None		1% NSCLC, 13%) Pancreatic	<1% NSCLC 10% Pancreatic			
Gefitinib	None						
Imatinib	None		3%	1.1%			
Lapatinib	Hepatotoxicity	Few deaths	5%	4%			
Nilotinib	QT prologation, torsades		4%	4%	4.1%	<1%	
Pazopanib	Hepatotoxicity	0.2%	12%	3%		2%	<1%
Regorafenib	Hepatotoxicity	0.3%-0.8%	6%	13%			
Ruxolitinib	None		1.3%				
Sorafenib	None				Rare		
Sunitinib	Hepatotoxicity	0.3%	5%	1%			<0.1 %
Vandetanib	QT prologation, torsades		2%	0%	14%	8%	Few cases
Vemurafenib	None		2.8%	1.9%			
Vismodegib	Embryo-fetal death or severe birth defects						
Ponatinib	Arterial thrombosis Hepatotoxicity	3 fatal cases	8%	1%	Mostly ≤20ms changes		

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; NSCLC, non-small cell lung carcinoma.

Table 8

General eligibility criteria used for early phase trials in drug development are listed. ECG QTc was not required for every drug development trial.

Eligibility Criteria	Value
Absolute Neutrophil Count	≥1,500/μL
Platelet Count	≥100,000/μL
Total Bilirubin	≤1.5 × institutional ULN
AST/ALT	≤2.5 × ULN, if liver metastasis, ≤5 × ULN (Patients who have both bilirubin >ULN and AST/ALT >ULN were not generally eligible in early phase drug trials)
Creatinine or Creatinine	≤1.5 × ULN
Clearance	≥60 mL/minute/1.73m^2 if creatinin≥ 1.5 × ULN
Urinalysis Protein	≤1+, If ≥2+, 24-hr protein should be < 1 g (or protein/creatinine ratio <1);usually needed for antiangiogenetic KIs
ECG QTc	≤ 450 ms for males, ≤ 470 ms for females

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; KI, kinase inhibitor; LLN, lower limit of normal; ULN, upper limit of normal.

Curr Probl Cancer. Author manuscript; available in PMC 2014 May 01.

Table 9

Dose modification according to organ dysfunction and metabolism are listed. Half life is measured in hours for all drugs except vandetanib and vismodegib (days).

	Child-Pugh Classification			Renal Impairment			Single Dose Half Life (hours)	Hepatic Excretion	Renal Excretion
Kinase Inhibitor	**A**	**B**	**C**	**Mild**	**Moderate**	**Severe (not including HD)**			
Axitinib	No adjustment	reduce dose		No adjustment	No adjustment	No adjustment	2.5-6	41%	23%
Bosutinib	200 mg	200 mg	200 mg	No adjustment	No adjustment	Do not use	22.5	91.3%	3%
Cabozantinib		Do not use	Do not use	No adjustment	No adjustment		55	54%	27%
Crizotinib				No adjustment	No adjustment		42	63%	22%
Dasatinib	No adjustment	No adjustment	No adjustment				3~5	85%	4%
Erlotinib	No adjustment	No adjustment	Use caution				36.2	83%	8%
Gefitinib	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment		48	86%	4%
Imatinib	No adjustment	No adjustment	Decrease dose by 25%	≤600 mg	≤ 400 mg; reduce by 50%	100 mg	17.1	68%	13%
Lapatinib	No adjustment	No adjustment	Reduce dose				14	Most	<2%
Nilotinib	Reduce dose	Reduce dose	Reduce dose	No adjustment			17(Multi-day dosing)	93%	
Pazopanib	No adjustment	Reduce to 200mg	Do not use	No adjustment	No adjustment		30.9	Most	<4%
Regorafenib	No adjustment	No adjustment	Do not use	No adjustment	Do not use	Do not use	28	71%	19%
Ruxolitinib	Reduce dose	Reduce dose	Reduce dose	No adjustment	Reduce dose	Reduce dose	3	22%	74%
Sorafenib	No adjustment	No adjustment		No adjustment	No adjustment	No adjustment	25-48	77%	19%
Sunitinib	No adjustment	No adjustment		No adjustment	No adjustment	No adjustment	40-60	61%	16%
Vandetanib		Do not use	Do not use	No adjustment	200 mg	200 mg	19 days	44%	25%
Vemurafenib	No adjustment	No adjustment		No adjustment	No adjustment		57	94%	1%
Vismodegib							12 days	82%	4.4%
Ponatinib	Not studied	avoid	avoid	Not studied	avoid	avoid	24	87%	5%

Abbreviations: HD, hemodialysis.

Table 10

NCI-Organ Dysfunction Working Group liver and renal dysfunction classification table.

Group	TB Value	AST Value
Normal	≤ ULN and	≤ULN
Mild	1-1.5 × ULN or	> ULN
Moderate	1.5-3 × ULN and	Any
Severe	3-10 × ULN and	Any

NCI-ODWG Renal Dysfunction Classification	
Group	**Creatinine Clearance**
Normal	≥ 60 mL/min
Mild	40-59 mL/min
Moderate	20-39 mL/min
Severe	< 20 mL/min

Abbreviations: AST, aspartate aminotransferase; TB, total bilirubin; ULN, upper limit of normal.

Table 11

Common adverse reactions associated with KIs with anti-angiogenic properties. Incidence is from all FDA indications for each KI using the highest percent reported and landmark studies that lead to FDA approval. Percent may be different from smaller phase 2 studies. Grade 2 cardiac dysfunction is defined in CTCAE v4 as symptoms of cardiac dysfunction or ≥ 15% absolute decline in LVEF compared to baseline or a decline in LVEF of ≥ 10% compared to baseline that is also below the lower limit of normal.

Kinase Inhibitor	Axitinib	Cabozantinib	Pazopanib	Regorafenib	Sunitinib	Sorafenib	Vandetanib
No. targets	1	8	7	14	6	8	7
HTN (all grades)	40%	33%	42%	30% CRC 59% GIST	34%	9% HCC 17% RCC	33%
HTN Grade 3/4	16%	8%	7%	8% CRC 28%GI ST	13% RCC 4% GIST	4%	9%
Cardiac Dysfunction			EF drop ≥ grade 2; 11% sarcoma	Ischemia 1.2%	EF drop ≥ grade 2; 11% GIST, 27% RCC	Ischemia 2.7%	Few cases
EF monitor			Patient at risk, i.e., prior doxorubicin	Not required	Patient at risk		
Hypothyroidism (all grades)	19%)	N/A	7%	4.2% CRC 18% GIST	4% GIST 16% RCC	Uncommon	N/A
Proteinuria (all grades)	11%)	2%	9%	60% CRC 33% GIST	Few cases		10%
ALT Elevation	All grade 22%	all grade 86%, grade 3/4 6%	Grade 2≥ 18%	All grade 45% Grade 3/4 6%	All grade 51%, grade 3/4 3%	liver dysfunction 11% not specified as ALT	51%
Pre-surgery	Stop 24 hr before	Stop 28 d before	Stop 7 d before	Stop 14 d before	Physician discretion		Physician discretion
Arterial Thromboembolism	1~2%	2%	2~3%		Few cases	Uncommon	Few cases
VTE	3%	6%	5%		3%	Uncommon	
Any hemorrhage			13% RCC 22%o Sarcoma	21%	37% RCC, 18% GIST	18%	
Grade 3/4	1%	3%	Grade 4 3%	2%	4~7%	5%	
Hemorrhage			RCC Grade 4 1% Sarcoma				
QTc Prolongation			QTc ≥ 500ms; 2%			Rare	14%
Torsades			<1%		< 0.1%		grade 3/4; 8%, few torsades cases
Hand Foot Syndrome (all grades)	27%	50%	6%	45% CRC 67% GIST	14% GIST, 29% RCC	21% HCC, 30% RCC	Few cases

N/A; Non-applicable due to total thyroidectomy in most patients. Abbreviations: d, day; CTCAE, Common Terminology Criteria for Adverse Events; LVEF, left ventricular ejection fraction, CRC; colorectal cancer, GIST; gastrointestinal stromal tumor.

Curr Probl Cancer. Author manuscript; available in PMC 2014 May 01.

Table 12

Five Kinase Inhibitors for CML. CML is classified by phase, CP, AP, BP, or by number of treatment lines, i.e., newly diagnosed (new) or resistant or intolerant (R/I). New CP = newly diagnosed chronic phase, R/I CP= refractory or intolerant chronic phase, CCyR=complete cytogenetic response, MCyR= major cytogenetic response, CHR=complete hematologic response. Serious fluid retention= pleural, pericardial, peritoneal effusions. CHF=congestive heart failure.

	Imatinib	**Dasatinib**	**Nilotinib**	**Bosutinib**	**Ponatinib**
CP	1st line	1st, 2nd, 3rd line	1st, 2nd, 3rd line	2nd, 3rd line	2nd, 3rd line
AP	1st line	2nd, 3rd line	2nd, 3rd line	2nd, 3rd line	2nd, 3rd line
BP	1st line	2nd, 3rd line	not studied	2nd, 3rd line	2nd, 3rd line
Ph+ALL	Refractory ALL (first line with concurrent chemo)	2nd, 3rd line (first line with concurrent chemo)	not studied	not studied	2nd, 3rd line
T315I	resistant	resistant	resistant	resistant	sensitive
New CCyR	75% at 84 months	77%) vs 66%at 12 months£	80% vs 65% at 12 months£	not indicated	not indicated
imatinib R/I CP,MCyR	NA	63% at 22 months	51% at 18 mos	27% at 5.5 months€; (as 3rd line)	49% at 10 months
AP, CHR	38% at 18 months	47% at 6 months	30% at 18 mos	30% at 11 months€	47% at 10 months
BP, CHR	7% at 18 months	17-21% at 6 months	not studied	15% at 11 months€	21% at 10 months
food	with	without	without	with	with/without
serious fluid retention	G1-4 7% in new CP	G1-4 14% in new CP	G1-4 1% in new CP	G3≥ 3% in R/I all phases	10% in R/I all phases G3≥ 1% in R/I CP
all Grade CHF	0.7%in new CP	2%in new CP			6% in R/I
G3-4 lipase			7% in new CP 18% in R/I CP check monthly	8% in R/I CP	15% in combined R/I, AP, BP, ALL check biweekly × 2 months then monthly

NA=not applicable. €=at data cut off time, otherwise all other months are at median duration of treatment. £=compared to imatinib.