Oncology Oral, Hematologic Cancers Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
acalabrutinib (Calquence®)[1]	AstraZeneca	▪ Treatment of adults with mantle cell lymphoma (MCL) treated with ≥ 1 prior therapy* ▪ Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
bosutinib (Bosulif®)[2]	Pfizer	▪ Newly diagnosed chronic phase (CP) Ph+ CML ▪ Treatment of chronic, accelerated, or blast phase Ph+ chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy
busulfan (Myleran®)[3]	Aspen/Prasco LA	▪ Palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia†
chlorambucil (Leukeran®)[4]	Aspen/Prasco LA	▪ Treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas, including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease; chlorambucil is not curative in any of these disorders but may produce clinically useful palliation
dasatinib (Sprycel®)[5]	Bristol-Meyers Squibb	▪ Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib (Gleevec) ▪ Treatment of adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy ▪ Newly diagnosed adult patients with Ph+ CML in chronic phase ▪ Treatment of pediatric patients with Ph+ CML in chronic phase ▪ Treatment of pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy
duvelisib (Copiktra®)[6]	Verastem	▪ Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after ≥ 2 prior therapies ▪ Relapsed or refractory follicular lymphoma (FL) after ≥ 2 prior systemic therapies*
enasidenib (Idhifa®)[7]	Celgene	▪ Relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation, as determined with an FDA-approved test‡
fedratinib (Inrebic®)[8]	Celgene	▪ Intermediate-2 or high-risk primary or secondary post-polycythemia vera or post-essential thrombocythemia myelofibrosis (MF)
gilteritinib (Xospata®)[9]	Astellas	▪ Relapsed or refractory adults with AML with a FLT3 mutation, as detected by an FDA-approved test‡
glasdegib (Daurismo™)[10]	Pfizer	▪ In combination with low-dose cytarabine, for the treatment of newly diagnosed AML in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy

ALL = acute lymphoblastic leukemia; cGVHD = chronic graft versus host disease; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous (myeloid) leukemia; FL = follicular lymphoma; GIST = gastrointestinal stromal tumors; MCL = mantle cell lymphoma; MF = myelofibrosis; MZL = marginal zone lymphoma; Ph+ = Philadelphia chromosome positive; SLL = small lymphocytic lymphoma; TKI = tyrosine kinase inhibitor

* Indication approved under accelerated approval based on select clinical markers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

† Busulfan intravenous is FDA approved for use in combination with cyclophosphamide prior to allogeneic bone marrow transplantation; oral busulfan may sometimes be utilized off-label as part a preparatory regimen for hematopoietic stem cell transplant. The use of busulfan as a preparatory regimen for bone marrow transplantation will not be covered in this review.

‡ A list of Food and Drug Administration (FDA)-approved companion diagnostics can be found at https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
hydroxyurea (Hydrea®)[11]	generic, Bristol-Myers Squibb	▪ Resistant CML ▪ Locally advanced squamous cell carcinomas of the head and neck (excluding lip), in combination with concurrent chemoradiation‖
ibrutinib (Imbruvica®)[12]	Pharmacyclics	▪ Mantle cell lymphoma (MCL) in patients who have received ≥ 1 prior therapy* ▪ CLL/ SLL ▪ CLL/ SLL with 17p deletion ▪ Waldenström's macroglobulinemia ▪ Marginal zone lymphoma (MZL) requiring systemic therapy and patient has had prior anti-CD20-based therapy* ▪ Chronic graft versus host disease (cGVHD) after failure of ≥ 1 line of systemic therapy
idelalisib (Zydelig®)[13]	Gilead	▪ Relapsed chronic CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities¶ ▪ Relapsed follicular B-cell non-Hodgkin's lymphoma in patients who have received ≥ 2 prior systemic therapies*,¶ ▪ Relapsed SLL in patients who have received ≥ 2 prior systemic therapies*,¶
imatinib (Gleevec®)[14]	generic, Novartis	▪ Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase ▪ Patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy ▪ Adult patients with relapsed or refractory Ph+ ALL ▪ Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy ▪ Adult patients with myelodysplastic/ myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements as determined with an FDA-approved test‡ ▪ Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation, as determined with an FDA-approved test or with c-Kit mutational status unknown‡ ▪ Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who are FIP1L1-PDGFRα fusion kinase-negative or unknown ▪ Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP) ▪ Patients with Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) ▪ Adjuvant treatment of adult patients following resection of Kit (CD117)-positive GIST

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‡ A list of Food and Drug Administration (FDA)-approved companion diagnostics can be found at https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

‖ Hydroxyurea is also available as a 200 mg, 300 mg, and 400 mg capsule under the brand name Droxia®. Droxia is indicated to reduce the frequency of painful crises and need for blood transfusions in patients with sickle cell anemia who have recurrent moderate to painful crises. Droxia will not be included in this review.

¶ Idelalisib (Zydelig) is not recommended and is not indicated for first-line treatment for any patient. Idelalisib (Zydelig) is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL.

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
ivosidenib (Tibsovo®)[15]	Agios	▪ Adult patients with relapsed or refractory AML with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation, as detected by an FDA-approved test‡ ▪ Adult patients with newly diagnosed AML who are ≥ 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy with a susceptible IDH1 mutation, as detected by an FDA-approved test‡
ixazomib (Ninlaro®)[16]	Millennium	▪ In combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received ≥ 1 prior therapy
lenalidomide (Revlimid®)[17]	Celgene	▪ In combination with dexamethasone for the treatment of multiple myeloma ▪ As maintenance therapy for multiple myeloma following autologous hematopoietic stem cell transplantation (auto-HSCT) ▪ Treatment of transfusion-dependent anemia due to low-or intermediate-1-risk myelodysplastic syndromes associated with a deletion of 5q cytogenetic abnormality with or without additional cytogenetic abnormalities ▪ Treatment of mantle cell lymphoma after relapse or disease progression after 2 prior therapies, 1 of which included bortezomib ▪ In combination with a rituximab product for the treatment of previously treated FL ▪ In combination with a rituximab product for the treatment of previously treated MZL
melphalan (Alkeran®)[18]	generic, Apopharma	▪ Palliative treatment of multiple myeloma ▪ Palliation of non-resectable epithelial carcinoma of the ovary
mercaptopurine (Purixan®)[19,20]	generic (tablets); Nova (suspension)	▪ ALL as a component of a combination maintenance therapy regimen
midostaurin (Rydapt®)[21]	Novartis	▪ Newly diagnosed AML that is FLT3 mutation-positive as detected by an FDA-approved test‡, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation** ▪ Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia
nilotinib (Tasigna®)[22]	Novartis	▪ Accelerated phase and chronic phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib (Gleevec) ▪ Newly diagnosed adult and pediatric patients ≥ 1 year of age with Ph+ CML in chronic phase ▪ Treatment of chronic phase Ph+ CML with resistance or intolerance to prior tyrosine kinase inhibitor (TKI) therapy in pediatric patients ≥ 1 year of age
panobinostat (Farydak®)[23]	Novartis/Secura	▪ Treatment of multiple myeloma in combination with bortezomib and dexamethasone in patients who have received ≥ 2 prior regimens, including bortezomib and an immunomodulatory agent*

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* Indication approved under accelerated approval based on select clinical markers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

‡ A list of Food and Drug Administration (FDA)-approved companion diagnostics can be found at https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

**Midostaurin (Rydapt) is not indicated as a single-agent induction therapy for the treatment of patients with AML.

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
pomalidomide (Pomalyst®)[24]	Celgene	▪ For use in combination with dexamethasone for patients with multiple myeloma who have received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy ▪ For the treatment of adults with acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART), as well as for the treatment of KS in adults who are human immunodeficiency virus (HIV)-negative*
ponatinib (Iclusig®)[25]	Millennium	▪ Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) ▪ Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ALL for whom no other TKI is indicated††
procarbazine (Matulane®)[26]	Leadiant	▪ For use in combination with other anticancer drugs for the treatment of stage 3 and stage 4 Hodgkin's disease; used as part of the MOPP regimen (nitrogen mustard, vincristine, procarbazine, prednisone)
ruxolitinib (Jakafi®)[27]	Incyte	▪ Intermediate or high-risk MF, including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF ▪ Treatment of polycythemia vera in patients who have had an inadequate response to or are intolerant of hydroxyurea ▪ Treatment of steroid-refractory acute graft versus host disease (GVHD) in adult and pediatric patients ≥ 12 years of age
selinexor (Xpovio™)[28]	Karyopharm	▪ In combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma (RRMM) who have received ≥ 4 prior therapies and whose disease is refractory to ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody* ▪ Treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after ≥ 2 lines of systemic therapy*
thalidomide (Thalomid®)[29]	Celgene	▪ Treatment of newly diagnosed multiple myeloma in combination with dexamethasone ▪ Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL)‡‡ ▪ Prevention and suppression of cutaneous manifestations of ENL recurrence as maintenance therapy

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* Indication approved under accelerated approval based on select clinical markers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

†† Ponatinib (Iclusig) is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

‡‡ Thalidomide is not indicated as monotherapy for ENL treatment in the presence of moderate to severe neuritis.

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
thioguanine (Tabloid®)[30]	Aspen/Prasco LA	▪ For remission induction and remission consolidation of acute nonlymphocytic leukemias[§§]
tretinoin[31]	generic	▪ For remission induction in patients with acute promyelocytic leukemia (APL), FAB classification M3 characterized by the presence of the t(15;17) translocation and/or presence of the PML/RARα gene who are refractory to, have relapsed from, or have a contraindication to anthracycline chemotherapy[‖‖]
venetoclax (Venclexta®)[32]	AbbVie	▪ Treatment of CLL or SLL in adult patients ▪ In combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy[*]
vorinostat (Zolinza®)[33]	Merck, Sharp & Dohme	▪ Treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients who have progressive, persistent, or recurrent disease on or following 2 systemic therapies
zanubrutinib (Brukinsa™)[34]	Beigene	▪ Treatment of adult patients with mantle cell lymphoma (MCL) who have received ≥ 1 prior therapy[*]

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* Indication approved under Accelerated Approval based on select clinical markers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

§§ Use of thioguanine (Tabloid) is not recommended for use during maintenance therapy of acute nonlymphocytic leukemias or in other similar long-term continuous treatments due to high risk of liver toxicity. Response rates vary with age and the prior treatments; combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone. Thioguanine is not effective for chronic lymphocytic leukemia, Hodgkin's lymphoma, multiple myeloma or solid tumors. Although thioguanine has activity in the treatment of CP-CML, more objective responses are observed with other agents.

‖‖ Tretinoin is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with tretinoin.

Due to the infrequency of their usage in modern day chemotherapeutic regimens, oral busulfan, procarbazine, melphalan, and thioguanine will not be discussed in detail in this therapeutic class review.

Many of the hematologic malignancies included in this therapeutic class review also have extensive parenteral drug therapy options in addition to the oral agents included in this review. This review will focus on the role of oral agents in the management of these diseases.

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OVERVIEW

Leukemias

Acute Lymphocytic Leukemia (ALL)[35,36]

ALL is the most common form of childhood leukemia, with nearly 60% of patients diagnosed before the age of 20. Approximately 28% of cases of ALL are diagnosed at age 45 or older, with 12% of cases diagnosed at 65 years or older. Overall survival (OS) outcomes for children with ALL have improved dramatically in the last decades such that 5-year OS is estimated to be 89% in children. Unfortunately, adolescents and adults do not fare as well with current therapies, and the current survival in this group is only 20% to 40%. Aside from patient age, prognosis is also influenced by cytogenetic markers, including Philadelphia chromosome positive (Ph+) which has historically been associated with a poorer prognosis in ALL. Standard therapy for the treatment of ALL is usually separated into phases. These phases often include induction, consolidation, and maintenance. Daily administration of oral mercaptopurine (Purixan) is often included as part of a backbone treatment in the maintenance phase of treatment.

Philadelphia chromosome positive (Ph+) ALL[37,38]

Ph+ ALL is rare in pediatric cases of ALL, occurring in approximately 2% of cases. In contrast, approximately 25% of adult cases of ALL are Ph+. The 1.2020 National Comprehensive Cancer Network (NCCN) guidelines recommend incorporation of a tyrosine kinase inhibitor (TKI) in the frontline regimen for Ph+ ALL as an established standard of care for adolescents/young adults and adult patients. The TKI may be combined with either chemotherapy or corticosteroids depending on the patient's age and comorbidities for patients with Ph+ ALL. Imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), and ponatinib (Iclusig) have all been studied in combination with chemotherapy as part of induction, as well as maintenance regimens, for Ph+ ALL in both adolescents/young adults and adult patients. The NCCN ALL guidelines also note bosutinib (Bosulif) is an option but state there is limited data for that particular TKI in Ph+ ALL. Mutation testing for the ABL gene should be considered as this mutation can confer greater resistance or susceptibility to a particular TKI. Pediatric patients with Ph+ ALL are also candidates for TKI therapy. The 2.2020 NCCN guidelines for pediatric ALL specifically list combined treatment regimens containing imatinib or dasatinib. A study by the Children's Oncology Group (COG) utilizing imatinib for children with Ph+ ALL demonstrated a 5-year event-free survival of 70% (standard error, ± 12%) which is superior to historical controls prior to the introduction of imatinib.[39]

Acute Myeloid Leukemia (AML)[40,41]

AML is the most common form of acute leukemia among adults. The median age at diagnosis is 67 years with 54% of patients diagnosed at age 65 and older while approximately 30% are diagnosed at age 75 and above. Cytogenetic analysis is of great importance with AML and provides information regarding the patient's overall prognosis and may guide treatment decisions.

The 3.2020 NCCN guidelines regarding treatment of adult patients with AML largely divide the treatment options into 2 age groups, patients < 60 years of age and patients ≥ 60 years of age. Of the orally targeted therapies, only midostaurin (Rydapt) is recommended by the NCCN guidelines for use in both these groups of patients. Oral midostaurin in combination with cytotoxic chemotherapy is

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recommended as part of standard induction, consolidation, and post-remission therapies for patients with FLT3-mutated AML (all category 2A).

The NCCN guidelines include enasidenib (Idhifa), glasdegib (Daurismo), ivosidenib (Tibsovo), and venetoclax (Venclexta) in the management AML only for those patients who are ≥ 60 years of age. In this population, patients who are candidates for intensive remission induction therapy and who also have unfavorable risk cytogenetics may receive venetoclax in combination with hypomethylating agents (HMA) (e.g., decitabine, azacitidine) or cytarabine (all category 2A). Patients aged ≥ 60 years who are not candidates for intensive remission induction or who decline intensive remission and are without actionable mutations may be treated with a combination of HMA or low dose cytarabine (LDAC) along with venetoclax (all venetoclax regimens category 2A, preferred) or glasdegib plus LDAC among other options (category 2A). Venetoclax plus HMA is also listed as an option along with single agents enasidenib or ivosidenib for IDH2-mutated or IDH1-mutated AML, respectively (all category 2A). For post-induction therapy in patients who have a response to lower intensity therapy, the lower intensity regimen should be continued, including enasidenib (IDH2-mutated), ivosidenib (IDH1-mutated), venetoclax with either a HMA or LDAC, or glasdegib with LDAC (all category 2A).

For patients with relapsed/refractory AML who have IDH1 or IDH2 mutations, therapy with single agents enasidenib or ivosidenib, respectively, may be utilized (category 2A), and for patients with FLT3 mutations, gilteritinib (Xospata) is a category 1 recommendation. The guidelines note that these drugs increase the risk for differentiation syndrome and hyperleukocytosis which may require treatment with hydroxyurea and corticosteroids to mitigate. The NCCN guidelines note that in the event of relapsed/refractory disease after completion of consolidation, targeted therapies may be restarted if the drugs were not administered continuously and not stopped due to the development of clinical resistance.

In 2020, the American Society of Hematology published guidelines for the treatment of newly diagnosed AML in older adults.[42] This guideline examined questions around the role of treatment for older adults with AML and the intensity and length of treatment in this patient population. The general conclusion of the panel of experts was that for older adults, treatment is recommended over best supportive care, and more-intensive therapy is recommended over less-intensive therapy when it is tolerable to the patient. Specific recommendations pertaining to patients who are not appropriate for intensive antileukemic therapy but who are able to receive treatment include a recommendation of monotherapy (e.g., glasdegib, venetoclax) over combination therapy (conditional recommendation based on low certainty). The guidelines further note that when these patients choose combination therapy, there is evidence to support the use LDAC in combination with glasdegib and HMA in combination with venetoclax.

Acute Promyelocytic Leukemia (APL)[43]

APL is a subtype of AML. While APL is an aggressive subtype of AML, advancements in treatment, including the introduction of tretinoin, also known as all-trans retinoic acid (ATRA), have greatly improved survival in this disease. ATRA in conjunction with other agents, most commonly arsenic trioxide IV, constitute the preferred regimens for APL induction therapy. The median age of APL diagnosis (age 44 years) is younger than the median age of diagnosis for other subtypes of AML. APL is identified by the translocation of the PML gene on chromosome 15 to the RARA gene on chromosome 17, which is referred to as either t(15;17) or APL with PML-RARA. The use of tretinoin causes cells expressing PML-RARA to undergo differentiation to mature neutrophils at a rate higher than normal

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cells. Peripheral blood neutrophils that express PML-RARA rearrangements have been shown to differentiate to normal neutrophils during treatment with tretinoin.[44] Treatment with ATRA plus arsenic is associated with a risk for differentiation syndrome which may be characterized by fever, shortness of breath, and pleural or pericardial effusions. Patients at high risk for differentiation syndrome (initial WBC > 10,000 cells/mcL) should begin prophylaxis with corticosteroids with the initiation of treatment. If prophylaxis is not initiated at outset, dexamethasone should be introduced as soon as the patient develops any signs or symptoms of respiratory compromise. Another unique feature of APL compared to other subtypes of AML is the high risk of coagulopathy, which has been associated with a very high rate of early mortality in APL patients. As this is a curable disease, it is imperative to start treatment with oral tretinoin as soon as a presumptive diagnosis of APL is made, without waiting for molecular testing or cytogenetics in order to decrease the risk of early death due to coagulopathy.

Chronic Myeloid Leukemia (CML)[45,46]

CML comprises 15% of all adult leukemias, and while the median age at diagnosis is 67 years, CML does occur in all age groups, including pediatric patients. Most patients with CML possess a gene mutation called the Philadelphia (Ph) chromosome. In this genetic abnormality, a translocation of chromosome 9 and chromosome 22 occurs [t(9,22)]. As a result, the breakpoint cluster region (BCR) gene from chromosome 22 is fused with the ABL gene on chromosome 9, and this is referred to as the BCR-ABL1 fusion gene.

Three phases are used to classify CML: these are chronic phase (CP), accelerated phase (AP), and blast phase (BP). While most patients are diagnosed in chronic phase, without treatment, CP-CML will eventually progress to AP-CML in about 3 to 5 years. Prior to the introduction of TKI therapies, allogeneic hematopoietic stem cell transplant (HSCT) was often utilized in suitable CML patients as a potentially curative option. However, in the era of TKI therapy, allogeneic HSCT is no longer recommended as a first-line therapy and is usually reserved for CML patients who are either refractory or resistant to TKI therapy or who present with blast phase at diagnosis. Although not definitively curative, the introduction of TKI therapy has radically changed the clinical course of CML. The primary goal of TKI therapy in CP-CML patients is to prevent progression to AP-CML or BP-CML. Life expectancy for patients with CP-CML who are managed on a TKI now approaches that of age-matched controls.

There are currently 3 generations of TKIs marketed for use in CML patients. The original, first generation TKI is imatinib. Second generation TKIs include dasatinib, nilotinib, and bosutinib. The only third generation TKI currently on the market is ponatinib; however, the use of ponatinib is limited to select patients due to the risk of serious adverse effects.

For patients newly diagnosed with Philadelphia chromosome-positive CML (Ph+ CML) in the chronic phase, the 2.2021 NCCN clinical guidelines recommend first determining the patient's risk score (low, intermediate, or high risk), which aids in selection of appropriate TKI therapy. The Sokal, Hasford (Euro), or EUTOS long-term survival (ELTS) risk scoring systems are recommended. For low-risk score patients, imatinib (at a dose of 400 mg daily), dasatinib, nilotinib, and bosutinib are all NCCN category 1, preferred recommendations. For patients with an intermediate or high-risk score, all the second generation TKIs, dasatinib, nilotinib, and bosutinib are category 1, preferred recommendations. While utilization of imatinib 400 mg daily is an NCCN 2A, other recommended, option in this setting, the second generation TKIs are preferred over imatinib because long-term follow-up data from large clinical trials have shown higher rates of molecular response and lower risk of disease progression with

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second generation TKIs compared to imatinib in intermediate- and high-risk score patients. This is especially relevant in young women for whom the goal of achieving a deep and rapid molecular response may facilitate eventual discontinuation of TKI therapy for family planning purposes.

Clinical response in CML is measured by standardized hematologic, cytogenetic, and molecular indices. Hematologic response is defined as the normalization of peripheral blood counts. Cytogenetic responses are defined by the percent of cells that are Ph+ in a bone marrow biopsy sample. Complete cytogenetic response (CcyR) is defined as the elimination of all Ph+ cells from the sample, while major cytogenetic response (McyR) is defined as fewer than 35% Ph+ cells seen in the sample. Molecular response, as measured by quantitative reverse-transcription polymerase chain reaction (qPCR) standardized across different laboratories using the International Scale (IS), is the most sensitive test to monitor disease status.

The preferred method for monitoring response to TKI therapy is by qPCR (IS) and should be conducted every 3 months after initiating TKI treatment for at least 2 years. Patients who continue to show > 10% BCR-ABL1 (IS) 3 months after starting TKI therapy should first be evaluated for compliance and/or possible drug interactions. Once compliance has been confirmed and drug interactions have been ruled out, the drug treatment options are to switch to an alternate TKI or continue the same TKI. Patients who were receiving imatinib may also receive a dose increase of imatinib (as tolerated to a maximum of 800 mg daily). The NCCN guidelines note that some patients who fail to achieve < 10% BCR-ABL1 (IS) at 3 months may still achieve a decline to < 10% BCR-ABL1 (IS) by 6 months and those patients tend to have favorable outcomes. Therefore, patients who have demonstrated a > 50% BCR-ABL1 (IS) decline from baseline, but who are still minimally above the 10% threshold at 3 months, may be well served by not making drastic changes to the treatment strategy at this juncture. Patients who continue to have > 10% BCR-ABL1 (IS) at 6 months or beyond should be switched to an alternate TKI and evaluated for allogeneic HSCT. Mutational analysis should also be considered as it may provide information regarding specific point mutations that may be affected by a TKI. For example, dasatinib, nilotinib, and bosutinib are effective against most mutations resistant to imatinib. The T315I mutation confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib, while ponatinib is indicated for the treatment of patients with T315I mutations. The NCCN guidelines contain a list of contraindicated mutations to specific TKIs. Patients found to have these mutations should NOT receive treatment with bosutinib, dasatinib, or nilotinib in the second-line setting. Only ponatinib has no contraindicated mutations listed. Patients who progress to AP-CML while receiving TKI therapy have a worse prognosis than patients who present with AP-CML. In AP-CML, TKI selection is based on prior therapy and/or BCR-ABL mutation profile.

In recent years, studies have examined the feasibility of discontinuing TKI therapy for patients with CP-CML who have maintained a sustained a deep molecular response. Several trials have shown that approximately 40% of patients with a deep and stable molecular response who discontinue imatinib remain disease-free and are described as having treatment-free remission (TFR). Discontinuation of second generation TKIs, including dasatinib and nilotinib, has been studied in the STOP 2G-TKI trial.[47] TFR rates at 48 months after TKI discontinuation in this trial were 53.57% (95% confidence interval [CI], 40.5% to 66.65%). No patients experienced progression to AP-CML while off therapy, and all relapsing patients regained major molecular response (MMR) after restarting therapy. The NCCN guidelines list several criteria which all should be met for a patient to be considered for TKI discontinuation. These include adult patients with no prior history of AP-CML or BP-CML who have had a stable molecular

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response (BCR-ABL1 ≤ 0.01% IS) for ≥ 2 years as documented on ≥ 4 tests, performed ≥ 3 months apart. The guidelines also outline a monitoring schedule that should be conducted indefinitely after discontinuation of TKI therapy.

Due to the relative rarity of CML diagnoses in pediatric patients, there are no evidence-based guidelines specifically addressing the management of pediatric patients with CML. Protocols often follow a similar treatment schema as those utilized in adult patients. Imatinib has been approved for use in newly diagnosed pediatric patients with CP-CML for more than a decade, and both nilotinib and dasatinib subsequently received approval for the treatment of newly diagnosed pediatric patients with CP-CML.

Lymphomas

Hodgkin Lymphoma (HL)[48]

HL is most commonly diagnosed in patients who are between 15 and 30 years of age. There are several different subtypes of HL, and staging ranges from early stage favorable to advanced stage disease. HL is now curable in ≥ 80% of patients. Given the high cure rates, treatment decisions are now made with considerable consideration given to avoiding long-term toxicity with the prescribed regimen. Historically, a standard regimen for the treatment of HL in adults was MOPP (mechlorethamine, vincristine, prednisone, and procarbazine). However, MOPP has been largely replaced in the front-line setting by other regimens that carry a lower risk of sterility and secondary leukemias. The most common front-line chemotherapy regimen for adults (pediatric protocols may differ) is now ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). Other commonly utilized regimens include Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone) or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

Non-Hodgkin's Lymphomas (NHL)[49,50]

Lymphomas are a heterogeneous group of malignancies that originate in the immune cells (predominantly B-cells and T-cells) of the lymphoid tissue. Leukemias and lymphomas are similar diseases with overlapping characteristics. Most lymphomas involve tumor invasion of the lymph nodes and other tissues, while the malignant clone in most leukemias predominates in the bone marrow. The most common presentation of lymphoma is that of a solid tumor, but NHL can also present as circulating tumor cells in the peripheral blood. NHLs are further classified into distinct clinical entities based on morphology, immunophenotype, genetic features, and clinical features. B-cell lymphomas are the most common type of NHL and comprise about 85% to 90% of all NHLs. All of the NHLs in this review, with the exception of cutaneous T-cell lymphoma (CTCL), are classified as mature B-cell lymphomas. These include chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), marginal zone lymphoma (MZL), and mantle cell lymphoma (MCL).

Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)[51,52]

CLL is classified as NHL and is the most prevalent adult leukemia in Western countries. It is generally a disease of the elderly, usually diagnosed around the age of 70 years. A small percentage of patients undergo Richter's transformation of their disease to an aggressive non-Hodgkin's lymphoma. The treatment of CLL is highly individualized as some patients may only require observation and other

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patients may be candidates for cytotoxic or biologic therapies. CLL and SLL are different manifestations of the same disease. In CLL, a significant portion of the abnormal lymphocytes are in the blood as well as in the bone marrow. In SLL, there is a relative lack of abnormal lymphocytes in the blood; instead, abnormal lymphocytes are found predominantly in the lymph nodes, bone marrow, and other lymphoid tissues. In the 1950s and 1960s, alkylating agents, including chlorambucil (Leukeran) combined with corticosteroids, became the standard of care for patients requiring treatment for CLL. The role of chlorambucil in the current day management of CLL is either as monotherapy in older, unfit patients or combined with anti-CD20 antibodies.

Cytogenetic abnormalities (including del13q, del11q, or del17p) detected in patients with CLL are of prognostic significance. In addition, immunoglobulin heavy-chain variable (IGHV) mutational status is an important predictor of survival outcomes. Unmutated IGHV is associated with poor prognosis compared with mutated IGHV. These genetic characteristics, as well as age and comorbidities, are factors utilized in selecting the choice of therapy for patients with CLL. The current NCCN guidelines stratify treatment selection based on the presence or absence of del(17p), which is associated with unfavorable outcomes. Patients with del(17p) have an approximate 32-month overall survival, while standard risk CLL patients may have an overall survival approaching 10 years.[53] Therefore, the intensity of treatment regimens, as well as whether the treatment is being utilized in the first-line setting or for relapsed/ refractory disease, varies accordingly.

The NCCN V4.2020 first-line therapy recommendations include monotherapy with ibrutinib (Imbruvica) as a preferred, category 1 recommendation for all CLL patients without del(17p) in both the first-line setting and in relapsed/refractory disease regardless of age or comorbidities. In addition, acalabrutinib (with or without obinutuzumab) and venetoclax plus obinutuzumab are both NCCN category 2A, preferred options regardless of age or comorbidities for first-line therapy of patients without del(17p) as well. Chlorambucil monotherapy is a category 3 NCCN recommendation for first-line therapy in patients with significant comorbidities or ≥ 65 years of age. When chlorambucil is combined with obinutuzumab, it is a category 2A recommendation in patients unable to tolerate purine analogs, those with significant comorbidities, or those aged ≥ 65 years. Lenalidomide maintenance may be considered for high-risk patients after first-line therapy.

For relapsed/refractory disease in patients without del(17p), ibrutinib monotherapy, acalabrutinib monotherapy, and venetoclax plus rituximab are all category 1, preferred treatment options regardless of age or comorbidities. The combination of idelalisib plus rituximab or duvelisib are category 2A, preferred regimens in this same patient population. Idelalisib monotherapy, venetoclax monotherapy, and lenalidomide with or without rituximab are category 2A recommendations as well. Lenalidomide is recommended for post second-line maintenance therapy (category 2A).

For CLL patients who harbor the del(17p) cytogenetic mutation, ibrutinib, acalabrutinib with or without obinutuzumab, and venetoclax plus obinutuzumab are all category 2A, preferred therapies for first-line treatment.

For the treatment of relapsed/refractory disease in patients with del17p, ibrutinib, acalabrutinib, venetoclax plus rituximab are all category 1, preferred treatments. Idelalisib plus rituximab, duvelisib and single agent venetoclax are category 2A, preferred regimens. Other recommended regimens according to the NCCN guidelines include monotherapy with idelalisib and lenalidomide with or without rituximab.

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Diffuse Large B cell lymphoma (DLBCL)[54]

DLBCLs are the most common type of lymphoma and account for 30% of all NHL. There are several subtypes of DLBCL, including DLBCL arising from follicular lymphoma (FL). Some patients with FL may undergo conversion to more aggressive lymphomas, such as DLBCL, and this risk increases over time; about 30% of FL patients convert to a more aggressive lymphoma at 10 years post-FL diagnosis.

The B-cell lymphoma NCCN guidelines V4.2020 list selinexor (Xpovio) as an option for DLBCL not otherwise specified, including DLBCL arising from FL after at least 2 prior systemic therapies (category 2A).

Follicular Lymphoma (FL)[55,56]

FL is the most common subtype of indolent NHL. Indolent lymphomas make up about 25% to 40% of all NHL, and 70% of all indolent lymphomas are FL. Due to the indolent nature of FL, the median survival is approximately 8 to 10 years.

The B-cell lymphoma NCCN guidelines V4.2020 list lenalidomide plus rituximab as a category 2A, preferred regimen in both the first-line setting and the second- or subsequent-line therapy. Chlorambucil (Leukeran), with or without rituximab (category 2A), is listed as a first- or second-line or subsequent therapy option for the elderly or infirm patients with FL. Idelalisib or duvelisib are second-line or subsequent therapy options (category 2A) for FL patients who are relapsed/refractory after 2 prior therapies.

Mantle Cell Lymphoma (MCL)[57,58]

MCL, while technically classified as an aggressive lymphoma, possesses characteristics of both indolent and aggressive NHLs. The median overall survival is approximately 3 years, but there is no evidence of a survival plateau, which is similar to indolent lymphomas. The chromosomal translocation t(11;14) is usually present in MCL. MCL is highly resistant to conventional chemotherapy and yet displays an aggressive disease course.

The B-cell lymphoma NCCN guidelines V4.2020 indicate that lenalidomide plus rituximab (category 2A) is one of several regimens that may be utilized for induction therapy when a less aggressive regimen is indicated. In the second-line setting, patients who achieved a near complete response (CR) to induction therapy and are planning to proceed to HSCT, lenalidomide with or without rituximab is a preferred regimen. For other patients in the second-line setting, all of Bruton tyrosine kinase (BTK) inhibitors, including acalabrutinib, ibrutinib (with or without rituximab), and zanubrutinib, as well as lenalidomide with or without rituximab, are listed as preferred options (all category 2A).

Marginal Zone Lymphoma (MZL)[59]

MZLs account for approximately 10% of all NHLs and are generally divided into 3 subtypes, nodal MZL, splenic MZL, and the most common subtype, mucosa-associated lymphoid tissue (MALT lymphoma). Lenalidomide plus rituximab is an NCCN category 2B recommendation for first-line therapy of MZLs. For elderly or infirm patients, chlorambucil with or without rituximab may also be utilized in the first-line setting (category 2A). Both lenalidomide with or without rituximab and ibrutinib as a single agent are NCCN V4.2020 category 2A, preferred recommendations for second- and subsequent-line therapy of MZL. Idelalisib or duvelisib may be used in the second- and subsequent-line of marginal zone lymphoma in patients who are relapsed/refractory after 2 prior therapies.

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Cutaneous T-cell Lymphoma (CTCLs)[60]

CTCLs are a group of NHLs that primarily develop in the skin and sometimes progress to involve lymph nodes, blood, and visceral organs. The annual incidence of CTCL is estimated to be 9.6 per 1 million persons. Mycosis fungoides (MF) is the most common type of CTCL, accounting for about 50% to 70% of CTCL cases, while Sézary syndrome (SS) accounts for 1% to 3% of cases. MF is an extranodal NHL of mature T-cells with primary cutaneous involvement and is characterized as an indolent neoplasm. SS is an erythrodermic leukemic variant of CTCL and is characterized by significant blood involvement and lymphadenopathy. Median survival can range from 1.5 years to 10 years depending on certain prognostic indicators, including patient age, lymph node, or visceral (stage IV) disease, and peripheral blood involvement. The 2.2020 NCCN guidelines for primary cutaneous lymphomas recommend vorinostat (Zolinza) as a category 2A, preferred choice for those patients requiring systemic therapy of CTCLs, including MF or SS.

Dermatofibrosarcoma protuberans[61]

Dermatofibrosarcoma protuberans is an uncommon tumor that arises in the dermis layer of the skin. The 1.2020 NCCN guidelines no longer recommend consideration of imatinib in the adjuvant setting for patients with positive margins post-resection; however, neoadjuvant imatinib may be considered in cases where the disease is unresectable. For recurrent disease, imatinib may be considered for unresectable disease or if unacceptable function or cosmetic outcomes would occur with resection. Imatinib may also be utilized in the setting of metastatic disease (all category 2A recommendations). The guidelines also state that tumors lacking the t(17;22) translocation may not respond to imatinib. Molecular analysis of a tumor using cytogenetics may be useful prior to starting imatinib therapy in these patients.

Gastrointestinal Stromal Tumors (GIST)[62]

The 2.2020 NCCN guidelines for soft tissue sarcomas recommend imatinib for patients with GIST that is definitively unresectable, recurrent, or metastatic (category 1). Imatinib is also recommended in the postoperative setting for patients with GIST who have been completely resected but have a significant risk of recurrence and did not receive preoperative imatinib (category 2A). In patients who were completely resected after the receipt of preoperative imatinib, adjuvant therapy may be continued (category 2A). Imatinib may also be utilized in patients with persistent gross residual disease after surgery (category 2A). Mutational testing is strongly recommended because patients with advanced GISTs have different responses to imatinib based on detectable mutations. While most KIT and PDGFRA mutations are associated with a response to imatinib, certain variants have a much lower response rate to imatinib; a higher dose of imatinib may be warranted in these patients. If neither KIT nor PDGFRA mutations are present, the likelihood of response to imatinib is < 50%. According to the guidelines, preoperative imatinib may prohibit accurate assessment of recurrence risk, and, therefore, imatinib should only be considered in the neoadjuvant setting if surgical morbidity would be reduced by downstaging the tumor (category 2A). In addition, testing the tumor for mutation status is recommended prior to starting preoperative imatinib to ensure the tumor has a genotype that is likely to respond to treatment. Maximal response may require 6 months or more of imatinib treatment to occur.

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Graft versus Host Disease (GVHD)[63,64,65]

Graft versus host disease (GVHD) is an immune-mediated disease that can result following complications of HSCT which the transplanted cells (graft) recognize the recipient's body as foreign. Organ systems most commonly impacted by acute GVHD (aGVHD) include the skin, GI tract, and liver. The American Society for Blood and Marrow Transplantation (re-named The American Society for Transplantation and Cellular Therapy [ASTCT] in 2019) published a clinical practice guideline in 2012 around the first- and second-line treatment of aGVHD.[66] These guidelines state that corticosteroids are the standard of care for the initial treatment of aGVHD and note that the literature does not support the choice of any specific agent for secondary therapy of aGVHD. These guidelines were published prior to the May 2019 FDA approval of ruxolitinib (Jakafi) for the treatment of corticosteroid-refractory aGVHD in adult and pediatric patients ≥ 12 years of age. In 2019, the NCCN published their first set of clinical practice guidelines around HSCT. These guidelines address the clinical severity grading and the treatment of GVHD. The NCCN guidelines concur with the ASTCT guidelines that there is insufficient evidence to recommend a particular systemic agent over any other for patients with steroid-refractory aGVHD.

Chronic GVHD (cGVHD) is generally an extension of acute GVHD that often develops more than 100 days after transplant, but it can also occur in those without acute GVHD. Symptoms include ocular manifestations (e.g., burning, irritation, photophobia, pain), oral or gastrointestinal (GI) manifestations (e.g., food sensitivity, oral dryness, pain, weight loss), respiratory manifestations (e.g., wheezing, dyspnea, cough), and neuromuscular manifestations (weakness, neuropathic pain, muscle cramps). The National Institutes of Health (NIH) has developed criteria to assist in diagnosis of cGVHD. Corticosteroids are most commonly the initial systemic therapy choice for most patients with moderate to severe cGVHD. Adjunctive supportive care may also be used (e.g., artificial tears, artificial saliva). Ibrutinib was the first drug approved for cGVHD in patients who have failed ≥ 1 systemic treatment, but many other therapies have been used off-label and for primary or secondary therapy (e.g., low-dose methotrexate, mycophenolate mofetil [CellCept], sirolimus [Rapamune]). The NCCN guidelines also cite a lack of high-quality evidence for the second-line treatment of cGVHD, and they do not prefer a specific therapy but rather encourage enrollment in a clinical trial.

Kaposi Sarcoma[67]

Kaposi sarcoma (KS) is a malignancy of the endothelial cells and is characterized by cutaneous red or brown papules, often seen on the lower extremities. There are 4 types of KS. Classic KS presents with cutaneous lesions but follows an indolent course. It is most common in elderly patients of Mediterranean, Eastern European, Middle Eastern, and/or Jewish descent. Endemic KS tends to be more aggressive than classic KS and occurs in younger patients (< 40 years old), as well as in children in equatorial Africa. The third type of KS is iatrogenic and occurs in the setting of patients taking immunosuppressive therapy (e.g., organ transplant recipients). The fourth type of KS is seen in patients infected with the human immunodeficiency virus (HIV). In these patients, KS is considered to be an acquired immune deficiency syndrome (AIDS)-defining cancer. The risk for developing KS is estimated to be approximately 498-fold higher in HIV-positive patients compared to the general United Stated (US) population. Due to the improved treatment options available to AIDS patients, the incidence of this cancer has been declining.

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The NCCN V3.2020 guidelines for AIDS-related KS list pomalidomide (Pomalyst) as a preferred systemic therapy option for patients with relapsed/refractory disease and note that pomalidomide has been FDA approved for the treatment of adult patients with AIDS-related KS after failure of highly active antiretroviral therapy.

Multiple Myeloma (MM)[68,69,70]

Multiple myeloma is a malignant neoplasm of plasma cells that results in accumulation of plasma cells in bone marrow, which can lead to hypercalcemia, renal insufficiency, anemia, and lytic bone lesions. This constellation of effects is often referred to by the acronym "CRAB" and is likely an indicator of end organ dysfunction associated with MM. Immunoglobulin, produced by plasma cells, results in the diagnostic M-protein spike seen in most MM patients through plasma or urine electrophoresis. Multiple myeloma accounts for approximately 17% of all hematologic malignancies in the US, and the median age of diagnosis is 69 years. Multiple myeloma is sensitive to a variety of cytotoxic agents, but the disease is not considered curable with currently available drug therapy. The clinical course of MM usually involves initial responses to chemotherapy, but these responses may be transient; thus, re-treatment with multiple rounds of therapy with different agents may be required to treat relapse. The 5-year survival rate has increased in recent years to over 50% due to newer and more effective treatments.[71] Overall survival now is estimated to be 8 to 10 years among patients with standard-risk disease, but it is significantly lower in patients that exhibit high-risk features.[72]

Initial therapy decisions regarding the primary treatment of MM are stratified by whether the patient is a candidate for future autologous HSCT. In transplant-eligible patients, the use of stem cell depleting therapies is avoided.

For transplant-eligible patients, the 3 drug regimen of bortezomib/lenalidomide/dexamethasone is an NCCN V1.2021 category 1, preferred recommendation for initial therapy. Other NCCN recommended regimens that may be considered for primary therapy of MM in transplant candidates include carfilzomib/lenalidomide/dexamethasone or daratumumab/lenalidomide/bortezomib/dexamethasone (both category 2A) or ixazomib/lenalidomide/dexamethasone (category 2B). Classified as useful in certain circumstances, bortezomib/thalidomide/dexamethasone is a category 1 recommendation. Other regimens classified as useful in certain circumstances and rated as category 2A include daratumumab/lenalidomide/bortezomib/dexamethasone, ixazomib/cyclophosphamide/dexamethasone, cyclophosphamide/lenalidomide/dexamethasone, daratumumab/bortezomib/thalidomide/dexamethasone or dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib. The NCCN guidelines state a preference for 3-drug regimens over 2-drug regimens as the standard of care for primary treatment. However, patients who could not be considered for initiation of treatment with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance status improves.

The joint American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) clinical practice guideline for the treatment of multiple myeloma notes that for transplant-eligible patients the optimal regimen and number of cycles remains unproven, but at least 3 to 4 cycles of induction therapy with an immunomodulatory drug, a proteasome inhibitor, and steroids is advised prior to stem cell harvest. Lenalidomide is an NCCN preferred, category 1 recommendation for maintenance therapy for potential transplant candidates, while ixazomib also is a category 1 recommendation but is not preferred. Bortezomib/lenalidomide may be useful in certain circumstances in the maintenance setting of

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patients who are potential transplant candidates. The ASCO/CCO guideline notes a minimum of 2 years of maintenance therapy is associated with improved survival and recommends this duration of therapy whenever possible (evidence quality: high, benefit outweighs harm; strength of recommendation: strong).

For patients who are non-transplant candidates, the combination regimens of bortezomib/ lenalidomide/dexamethasone, lenalidomide/low-dose dexamethasone, and daratumumab/ lenalidomide/dexamethasone are all designated preferred, category 1 NCCN recommendations for primary therapy. Other recommended regimens utilized as primary therapy in non-transplant candidates include ixazomib/lenalidomide/dexamethasone (category 2A), carfilzomib/lenalidomide/ dexamethasone (category 2A), or daratumumab/bortezomib/melphalan/prednisone (previously category 2A, now category 1). Cyclophosphamide/lenalidomide/dexamethasone (category 2A) may be useful in certain circumstances for myeloma patients who are not transplant candidates. The ASCO/CCO guideline notes initial treatment of non-transplant eligible patients should include, at a minimum, a immunomodulatory agent or proteasome inhibitor plus a steroid, if possible, and continuous therapy should be offered over fixed-duration therapy (evidence quality: high, benefit outweighs harm; strength of recommendation: strong).

Single-agent lenalidomide is the preferred oral drug treatment for maintenance therapy of MM (category 1), and bortezomib/lenalidomide may be useful in certain circumstances (category 2A).

The ASCO/CCO guideline recommends all patients with relapsed myeloma who are exhibiting symptoms should be treated immediately and that triplet therapy should be administered on first relapse, contingent upon the patient's tolerance. Triplet therapy is defined as a regimen with 2 novel agents (proteasome inhibitors, immunomodulatory drugs, or monoclonal antibodies) (evidence quality: high, benefit outweighs harm; strength of recommendation: strong). The NCCN also lists preferred regimens for the treatment of progressive or relapsed myeloma. Many of these combinations include a backbone of lenalidomide and dexamethasone combined with either a proteasome inhibitor (bortezomib [category 2A], carfilzomib [category 1], or ixazomib [category 1]) or daratumumab (category 1). Additional NCCN preferred regimens for previously treated myeloma patients include ixazomib/pomalidomide/dexamethasone (category 2A) or bortezomib/pomalidomide/dexamethasone (category 1), both of which were previously rated as other recommended regimens and are now NCCN preferred regimens. Finally, isatuximab-irfc/pomalidomide/dexamethasone is a category 1, preferred regimen for patients with previously treated multiple myeloma. Panobinostat/bortezomib/ dexamethasone is not listed as a preferred regimen for previously treated MM patients but does have an NCCN category 1 rating. Panobinostat- and pomalidomide-based regimens are also included in several regimens listed by the NCCN as other recommended regimens or as useful in certain circumstances for patients with previously treated multiple myeloma (all category 2A, except lenalidomide or pomalidomide combined with dexamethasone, which are both category 1 recommendations). Single agent lenalidomide or pomalidomide may be considered for steroid-intolerant individuals in the setting of previously treated multiple myeloma (category 2A). Selinexor combined with dexamethasone is a category 2A recommendation that is listed as useful in certain circumstances and is indicated for patients who have received ≥ 4 prior therapies and whose disease is refractory to ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

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Myelodysplastic Syndromes[73]

Myelodysplastic syndromes are associated with profound cytopenias and patients are subject to the morbidity associated with refractory anemia, neutropenia, and thrombocytopenia. According to the 2.2020 NCCN guidelines, there are numerous categories/subtypes of myelodysplastic syndromes. One of these subtypes, chronic myelomonocytic leukemia (CMML), may be associated with a 5q32 translocation. In this particular subset of patients, those identified to possess a platelet derived growth factor beta (PDGFRβ) gene rearrangement may respond well to treatment with imatinib.

Within the spectrum of myelodysplastic syndromes (MDS), the del(5q) syndrome is recognized by the World Health Organization (WHO) as a separate MDS category. This disorder generally has a relatively good prognosis and is highly responsive to lenalidomide therapy.

Myelofibrosis (MF)[74]

The diagnosis of MF is based on the 2017 WHO diagnostic criteria and requires patients to meet 3 major criteria and ≥ 1 minor criterion that are a combination of clinical, laboratory, cytogenetics, and molecular tests. One of the major criteria is the presence of a pathogenetic mutation such as JAK2. These patients may also have palpable splenomegaly, anemia, night sweats, weight loss, unexplained fever, and diffuse bone pain. According to the 1.2020 NCCN guidelines, treatment with ruxolitinib is recommended for lower-risk MF patients who are symptomatic (category 2A), while ruxolitinib (category 2A) or fedratinib (category 2B) may be utilized in patients who have higher-risk MF and who are not transplant candidates, have symptomatic anemia, and have a platelet count > 50,000/mm^3. Fedratinib may be used for patients who were previously treated with ruxolitinib and either had no response or a loss of response (category 2A). Patients should be monitored for clinically meaningful response of their symptoms.

Polycythemia Vera (PV)[75]

Polycythemia vera, along with myelofibrosis and essential thrombocythemia are hematopoietic diseases collectively termed myeloproliferative neoplasms (MPN). There are approximately 148,000 patients in the US with PV. The OS of patients diagnosed with a MPN is significantly worse than that of matched controls, and these diseases may transform into a more aggressive blastic MPN or AML, both of which are associated with a poor prognosis. JAK2 V617F mutations occur in > 90% of patients with PV. The NCCN V1.2020 guidelines for the management of PV recommend ruxolitinib for high risk patients (age ≥ 60 years and/or prior history of thrombosis) who have had an inadequate response or lack of response to antiplatelet therapies, phlebotomy to maintain hematocrit < 45%, and preferred treatment with hydroxyurea.

Systemic Mastocytosis

Systemic mastocytosis is 1 of 3 subtypes of mastocytosis. It is defined as an accumulation of mast cells in one or more organs and may include skin involvement. Systemic mastocytosis is the most common form diagnosed in adults. The other 2 types are cutaneous mastocytosis, which is limited to the skin and most frequently occurring in children, and mast cell sarcoma, which presents as a solitary mass but is extremely rare in humans. In 2017, the World Health Organization (WHO), removed mastocytosis as 1 of the subtypes of myeloproliferative neoplasms and listed it as a separate disease entity.

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The NCCN guidelines V1.2020 list imatinib as a treatment for aggressive systemic mastocytosis in certain circumstances (only if KIT D816V mutation negative or unknown or if eosinophilia is present with FIP1L1-PDGFRA fusion gene).

Waldenström's Macroglobulinemia[76]

Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) is a B-cell disorder presenting as bone marrow infiltration with lymphoplasmacytic cells that are CD19+, CD20+, and CD22+. The 1.2021 NCCN guideline recommends treating only those patients who are symptomatic. These symptoms may include hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, and cytopenias. Ibrutinib with or without rituximab is listed as an option for primary treatment (category 1), and ibrutinib with or without rituximab is a category 1, preferred regimen for use in patients who have received previous therapies for Waldenström's macroglobulinemia. Up to 40% of WM patients may have recurrent mutations in the CXCR4 gene and certain CXCR4 mutations may confer resistance to ibrutinib; therefore, the NCCN guidelines recommend consideration of CXCR4 gene mutation testing for patients being initiated on ibrutinib therapy.

No current US guidelines exist for the treatment of erythema nodosum leprosum, hypereosinophilic syndrome, or chronic eosinophilic leukemia.

PHARMACOLOGY[77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104]

Traditional cytotoxic chemotherapy agents interfere with DNA synthesis and replication largely by targeting rapidly proliferating cells. These types of traditional cytotoxic chemotherapy agents lack selectivity for tumor cells and are lethal to both tumor and normal cells. Although the rapid proliferation of most types of cancer lends some degree of selectivity for malignant cells, the selectivity is incomplete and dose-limiting damage to normal cells also occurs. Traditional cytotoxic chemotherapy agents in this review include busulfan, chlorambucil, thioguanine, procarbazine, melphalan, hydroxyurea, and mercaptopurine.

Hydroxyurea acts as a ribonucleotide reductase inhibitor, which is the rate-limiting enzyme of DNA synthesis. Hydroxyurea inhibits ribonucleotide reductase by binding to the M2 subunit and disrupting the iron complex. Hydroxyurea exerts its effects on cells in the S-phase, especially in cells rapidly synthesizing DNA.

Melphalan, chlorambucil (Leukeran), and busulfan (Myleran) are all alkylating agents and their cytotoxicity appears to be related to interstrand cross-linking with DNA.

The precise mode of cytotoxicity associated with procarbazine has not been clearly defined. It appears to inhibit protein, RNA, and DNA synthesis possibly by inhibiting transmethylation during RNA replication.

Mercaptopurine and thioguanine (Tabloid) are purine analogs that are closely related in both their chemical structure and their functioning. These purine analogs substitute for the purine base guanine in RNA and DNA creating "false" base pairs. Similar to other antimetabolites, these drugs are most active in the S-phase of the cell cycle. The net effect of these purine base substitutions is a blockade of the synthesis and utilization of the purine in the DNA replication process.

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Thalidomide (Thalomid) and its analogues, lenalidomide (Revlimid) and pomalidomide (Pomalyst), are classified as immunomodulatory agents. These agents inhibit the secretion of pro-inflammatory cytokines and increase the secretion of anti-inflammatory cytokines by monocytes. In addition, these agents possess antiangiogenic properties and antineoplastic activity.[105] Thalidomide, the original prototype drug in this class, inhibits angiogenesis due to inhibition of basic fibroblast growth factor (bFGF) and selectively reduces levels of tumor necrosis factor alpha (TNF-alpha) by accelerating the degradation of TNF-alpha messenger RNA encoding protein. Thalidomide also increases levels of interleukin-2 (IL-2) and interferon-gamma, augments natural killer-like activity, and inhibits IL-12 production.

Lenalidomide inhibits the phosphorylation of Akt in response to bFGF, thus reducing malignant transformation and invasiveness by reducing cell growth, migration, and survival. Lenalidomide also appears to cause cytogenetic changes that correlate with hematologic response in patients with MDS.

Pomalidomide inhibits the proliferation of hematopoietic tumor cells and induces apoptosis.

Tretinoin is not a cytotoxic agent; rather, it induces cytodifferentiation of acute promyelocytic leukemia (APL) cells. Tretinoin produces an initial maturation of the primitive promyelocytes derived from the leukemic clone thus allowing repopulation of the bone marrow with normal hematopoietic cells. The exact mechanism of action of tretinoin in APL is unknown.

The remaining agents included in this review are broadly classified as biologic response modifiers or signal transduction inhibitors. Many of these specifically inhibit a variety of tyrosine kinases. Advances in molecular biology, as well as the decoding of the human genome, have identified a number of pathways and potential targets related specifically to cancer cell growth and survival. Signal transduction inhibitors target intracellular signal transduction pathways. These signal transduction pathways are known to lead to uncontrolled cellular growth and proliferation, tumor metastasis, and prevention of apoptosis in malignant cells. Protein kinase inhibitors function by binding to the adenosine triphosphate (ATP) binding site found on receptor and non-receptor tyrosine kinase proteins. If the ATP binding site is occupied by a protein kinase inhibitor, ATP is unable to bind and, hence, cannot donate a phosphate group to the protein residue on the substrate and activate the target protein. Therefore, activation of downstream signaling pathways that could lead to uncontrolled tumor cell growth and differentiation are inhibited. Agents included in this review that can be classified as signal transduction inhibitors include acalabrutinib (Calquence), bosutinib (Bosulif), dasatinib (Sprycel), duvelisib (Copiktra), enasidenib (Idhifa), fedratinib (Inrebic), gilteritinib (Xospata), glasdegib (Daurismo), imatinib (Gleevec), ivosidenib (Tibsovo), nilotinib (Tasigna), ponatinib (Iclusig), ruxolitinib (Jakafi), ibrutinib (Imbruvica), ixazomib (Ninlaro), midostaurin (Rydapt), venetoclax (Venclexta), idelalisib (Zydelig), and zanubrutinib (Brukinsa). Selinexor (Xpovio) is a nuclear export inhibitor.

Ixazomib (Ninlaro) is a reversible proteasome inhibitor that has been shown to induce apoptosis of multiple myeloma cells.

Ibrutinib (Imbruvica) inhibits Bruton's tyrosine kinase (BTK), a signaling molecule within the B-cell antigen receptor (BCR) that regulates mechanisms of B-cells including proliferation, differentiation, apoptosis, and cell migration.[106] Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Acalabrutinib (Calquence) also inhibits BTK-mediated activation of downstream signaling proteins by forming a covalent bond with a cysteine residue in the BTK active site. Zanubrutinib (Brukinsa) also inhibits BTK via formation of a covalent

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bond in the kinase's active site. As a BTK inhibitor, zanubrutinib has demonstrated the ability to inhibit B-cell proliferation and decrease tumor growth in malignant cell lines.

Ruxolitinib (Jakafi), an oral kinase inhibitor, inhibits Janus associated kinases (JAKs) JAK1 and JAK that mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Similarly, fedratinib (Inrebic) inhibits JAK2 and FMS-like tyrosine kinase 3 (FLT3); it is considered JAK2 selective. Myelofibrosis (MF) is a myeloproliferative neoplasm associated with dysregulated JAK1 and JAK2 signaling.

Midostaurin (Rydapt) inhibits multiple receptor tyrosine kinases including wild type FLT3, FLT3 mutant kinases (ITD and TKD), KIT (wild type and D816V mutant), PDGFRα/β, and members of the serine/ threonine kinase PKC (protein kinase C) family. Midostaurin activity in FLT3-associated AML is likely a result of inhibition FLT3 receptor signaling and cell proliferation and induction of apoptosis in leukemic cells expressing ITD and TKD mutant FLT3 receptors or overexpressing wild type FLT3 and PDGF receptors. Midostaurin also has been shown to inhibit KIT signaling, cell proliferation, and histamine release to induce apoptosis in mast cells resulting in a therapeutic effect for aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, and mast cell leukemia. Gilteritinib inhibits several TKIs, including FLT3.

Enasidenib (Idhifa) inhibits the isocitrate dehydrogenase 2 (IDH2) enzyme which leads to decreased 2-hydroxyglutarate (2-HG) levels and induces myeloid differentiation towards mature myeloid cells in patients with IDH2-mutated AML. Similarly, ivosidenib (Tibsovo) inhibits the isocitrate dehydrogenase 1 (IDH1) enzyme in a similar fashion, also leading to decreased 2-HG levels and induction of myeloid cell differentiation to mature myeloid cells in patients with IDH1-mutated AML.

Glasdegib (Daurismo) is a small molecule, hedgehog pathway inhibitor. It acts by binding to and inhibiting the transmembrane protein smoothened (SMO), which is a part of the hedgehog signal transduction cascade.

Venetoclax (Venclexta) inhibits BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been seen in CLL cells. This overexpression of BCL-2 in CLL helps to potentiate tumor cell survival and has been associated with resistance to other therapies. Venetoclax (Venclexta) helps restore apoptosis in malignant cells.

Idelalisib (Zydelig) and duvelisib (Copiktra) inhibit phosphatidylinositol 3-kinase (PI3K), expressed in both normal and malignant B-cells inducing apoptosis and inhibiting proliferation. Idelalisib and duvelisib inhibit several cell signaling pathways, including B-cell receptor (BCR) signaling. Treatment of lymphoma cells with idelalisib results in inhibition of chemotaxis and adhesion and reduced cell viability. Treatment of leukemia cells with duvelisib results in inhibition of growth and reduced cell viability.

Selinexor (Xpovio) reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). Cell cycle arrest and apoptosis of cancer cells occur as a result of this process.

Vorinostat (Zolinza) and panobinostat (Farydak), while not classified as a signal transduction inhibitors, are also broadly classified as a biologic response modifiers. Vorinostat (Zolinza) inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2, HDAC3 (Class I), and HDAC6 (Class II). Panobinostat (Farydak) is a pan-histone deacetylase (HDAC) inhibitor. These enzymes catalyze the removal of acetyl

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groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an over expression of HDACs or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypo acetylation of core nucleosomal histones.[107]

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PHARMACOKINETICS[108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140]

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active metabolites	Elimination (%)	Effect of High Fat Meal (%)
acalabrutinib (Calquence)	0.6-2.8 (6.9 active metabolite)	97.5	CYP3A: major Glutathione conjugation, amide hydrolysis: minor	ACP-5862	Feces: 84 Urine: 12	AUC: None Cmax: ▼ 73
bosutinib (Bosulif)	22.5	94	CYP3A4	None	Feces: 91.3 Urine: 3	AUC: ▲1.7 fold Cmax: ▲1.8 fold
busulfan (Myleran)	2.6	32	Extensive metabolism by enzymatic activity	none with cytotoxic activity	Urine: < 2	Not available
chlorambucil (Leukeran)	1.5	99	oxidative degradation	phenylacetic acid mustard	Urine: 20-60	AUC: ▼20 Cmax: ▼55
dasatinib (Sprycel)	3-5	96	CYP3A4	Yes	Feces: 85 Urine: 4	AUC: ▲ 14
duvelisib (Copiktra)	4.7	> 98%	CYP3A4	nr	Feces: 79 Urine: 14	AUC: ▼6 Cmax: ▼37
enasidenib (Idhifa)	≈190	96-98	Hepatic by multiple CYP enzymes and UGTs	Yes (AGI-16903)	Feces: 89 Urine: 11	Not available
fedratinib (Inrebic)	41, 114 (biphasic disposition)	92	CYP3A4, CYP2C19, flavin-containing monooxygenase 3 (FMO3)	nr	Feces: 77 Urine: 5	AUC: ▲ 24 Cmax: ▲ 14
gilteritinib (Xospata)	113	94	CYP3A4	Yes (M17, M16, M10)	Feces: 64.5 Urine: 16.4	AUC: ▼< 10 Cmax: ▼26
glasdegib (Daurismo)	17.4	91	CYP3A4: major CYP2C8, UGT1A9: minor	nr	Feces: 42 Urine: 49	AUC: ▼16 Cmax: ▼31
hydroxyurea (Hydrea)	4	Not described	Hepatic; not fully characterized	None	Urine: 80	None
ibrutinib (Imbruvica)	4-6	97	CYP3A4: major CYP2D6: minor	PCI-45227	Feces:80 Urine: 10	AUC: ▲2 fold Cmax: ▲2-4 fold
idelalisib (Zydelig)	8	84	UGT1A4: minor	None	Feces: 78 Urine: 14	AUC: ▲1.4 fold

nr = not reported

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Pharmacokinetics (continued)

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active metabolites	Elimination (%)	Effect of High Fat Meal (%)
imatinib (Gleevec)	18	95	CYP3A4: major CYP1A2, 2D6, 2C9, 2C19: minor	N-demethyl derivative (half-life 40 hours)	Feces: 68 Urine: 13	None
ivosidenib (Tibsovo)	93	92-96	CYP3A4: major N-dealkylation, hydrolytic pathways: minor	None	Feces: 77 Urine: 17	AUC: ▲25 Cmax: ▲98
ixazomib (Ninlaro)	9.5 days	99	multiple CYP enzymes (3A4, 1A2, 2B6,2C8,2D6,2C19,2C9)	nr	Urine:62 Feces:22	AUC: ▼ 28 Cmax: ▼ 69
lenalidomide (Revlimid)	3-5	30	Limited metabolism	None	Urine: 90	AUC: ▼20 Cmax: ▼50
melphalan (Alkeran)	1.5	53 to 92	Hydrolysis	None	Urine: 10	AUC: ▼36 to 54
mercaptopurine (generic tablet, Purixan)	2 (suspension)	19	Methylation Oxidation	6-thioguanine nucleotides (6-TGNs)	Urine: 46	None
midostaurin (Rydapt)	19	99.8	CYP3A4	CGP62221 CCP52421	Feces: 95% Urine: 4%	nr
nilotinib (Tasigna)	17	98	Oxidation and hydroxylation	None	Feces: 93	AUC: ▲ 82
panobinostat (Farydak)	37	90	Oxidation, reduction, hydrolysis, glucuronidation, CYP3A	None	Urine:29-51 Feces: 44-77	AUC: ▼ 16 Cmax: ▼ 44
pomalidomide (Pomalyst)	9.5	12 to 44	CYP1A2 CYP3A4	None	Urine: 73 Feces: 15	nr
ponatinib (Iclusig)	24	99	CYP3A4 CYP2C8	None	Feces: 87 Urine: 5	None
procarbazine (Matulane)	7 min (parent; once reaches plasma)	Not described	Auto-oxidation	nr	Urine: 70	nr
ruxolitinib (Jakafi)	3	97	CYP3A4	Yes	Feces: 22 Urine: 74	AUC: ▲ 4 Cmax: ▼ 24

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Pharmacokinetics (continued)

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active metabolites	Elimination (%)	Effect of High Fat Meal (%)
selinexor (Xpovio)	6-8	95	CYP3A4, UDP-glucuronosyltransferases (UGTs), glutathione S-transferases (GSTs)	nr	nr	None
thalidomide (Thalomid)	5.5-7.3	55-66	Limited metabolism	None	Feces < 2 Urine: 93.6	Tmax ▲to 6 hours
tretinoin	0.5-2	> 95	CYP enzymes	None	Feces: 31 Urine: 63	nr
venetoclax (Venclexta)	26	> 99	CYP3A4/5	M27	Feces: > 99.9	AUC ▲
vorinostat (Zolinza)	2	71	Glucuronidation and hydrolysis followed by β oxidation	None	Urine: < 1	AUC: ▲1.3 fold
zanubrutinib (Brukinsa)	2-4	94	CYP3A	None	Feces: 87 Urine: 8	none

nr = not reported

Genetic polymorphism of mercaptopurine metabolism / variability in mercaptopurine metabolism is 1 of the major causes of interindividual difference in systemic exposure to the drug and its active metabolites. Mercaptopurine activation occurs via hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and several enzymes to form 6-thioguanine nucleotides (6-TGNs). The cytotoxicity of mercaptopurine is due, in part, to the incorporation of 6-TGN into DNA. Mercaptopurine is inactivated via 1 major pathway. One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-6-MP. TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. For Caucasians and African Americans, approximately 0.3% (1:300) of patients have 2 non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have 1 TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with 2 functional alleles. Homozygous-deficient patients (2 non-functional alleles), if given usual doses of mercaptopurine, accumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to mercaptopurine toxicity. Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active thioguanine nucleotides than people with normal TPMT activity and are more likely to experience mercaptopurine toxicity. TMPT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity.

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CONTRAINDICATIONS/WARNINGS[141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168]

There are no contraindications with acalabrutinib (Calquence), dasatinib (Sprycel), duvelisib (Copiktra), enasidenib (Idhifa), glasdegib (Daurismo), ibrutinib (Imbruvica), imatinib (Gleevec), ivosidenib (Tibsovo), ixazomib (Ninlaro), panobinostat (Farydak), ponatinib (Iclusig), ruxolitinib (Jakafi), selinexor (Xpovio), vorinostat (Zolinza), or zanubrutinib (Brukinsa).

Bosutinib (Bosulif), gilteritinib (Xospata), hydroxyurea, idelalisib (Zydelig), melphalan, thalidomide (Thalomid), midostaurin (Rydapt), chlorambucil (Leukeran), lenalidomide (Revlimid), tretinoin, and mercaptopurine are contraindicated in patients with hypersensitivity to the active drug or any of the components.

Chlorambucil should not be used in patients whose disease has demonstrated prior resistance to the drug. There may be cross-sensitivity (skin rash) between chlorambucil and other alkylating agents.

Hydroxyurea is contraindicated in patients with marked bone marrow depression (WBC < 2.5 x 10^9/L) or thrombocytopenia (platelets < 100,000/mm^3) or severe anemia.

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

Neither mercaptopurine nor melphalan should be used in patients whose disease has demonstrated prior resistance to the drug. There is usually complete cross-resistance between mercaptopurine and thioguanine.

Nalidixic acid is contraindicated in patients undergoing concomitant therapy with melphalan or other alkylating agents because of reports of serious gastrointestinal (GI) toxicity, such as hemorrhagic ulcerative colitis or intestinal necrosis.

Pomalidomide (Pomalyst) is contraindicated in females who are pregnant and in patients with severe hypersensitivity (e.g., angioedema, anaphylaxis) to pomalidomide or any of the excipients contained within the product.

The use of venetoclax (Venclexta) with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.

Boxed Warnings

Thalidomide (Thalomid), glasdegib (Daurismo), lenalidomide (Revlimid), and pomalidomide (Pomalyst) all have a boxed warning regarding pregnancy/embryo-fetal toxicity. Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects, even after a single dose. Thalidomide, lenalidomide, and pomalidomide are all contraindicated in females who are pregnant. Pregnancy must be excluded before starting treatment and patients receiving glasdegib, thalidomide, lenalidomide, or pomalidomide must use 2 reliable methods of contraception while taking these medications. Mortality at or shortly after birth has been reported in about 40% of infants exposed to thalidomide. Females of reproductive potential taking glasdegib should utilize effective contraception during treatment and for a minimum of 30 days following the final dose; males with female partners of reproductive potential are recommended to use condoms during glasdegib therapy and for a minimum of 30 days following the final dose. Chlorambucil is probably mutagenic and teratogenic in human and produces human infertility. Melphalan is leukemogenic in humans and

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produces chromosomal aberrations *in vitro* and *in vivo* and, therefore, should be considered potentially mutagenic in humans. Tretinoin carries a high risk of teratogenic effects and women should have a negative pregnancy test prior to initiating whenever a delay in therapy is possible. If tretinoin represents the best available treatment for a pregnant woman or a woman of childbearing potential, the patient should receive full information and warnings regarding the risk to the fetus.

Chlorambucil can severely suppress bone marrow function and is a known carcinogen in humans.

Enasidenib (Idhifa), gilteritinib (Xospata), and ivosidenib (Tibsovo) carry boxed warnings for differentiation syndrome with and without concomitant hyperleukocytosis, which is associated with rapid proliferation and differentiation of myeloid cells. Symptoms include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. This can be fatal if it is not treated; if suspected, corticosteroids and hemodynamic monitoring should be initiated until symptom resolution. Hospitalization may be required. If severe symptoms occur (e.g., symptoms requiring intubation or ventilator support, renal dysfunction > 48 hours), interrupt enasidenib, gilteritinib, or ivosidenib until symptoms are no longer severe. Differentiation syndrome has been observed as early as 1 day and at up to 5 months following enasidenib initiation, as early as 2 days and up to 75 days following gilteritinib initiation, and as early as 1 day and up to 3 months after ivosidenib initiation. In November 2018, the FDA issued a Safety Announcement, warning healthcare providers of the risk of differentiation syndrome with enasidenib, noting that they should also be aware of this risk with other agents associated with differentiation syndrome.[169]

Fedratinib (Inrebic) carries a boxed warning for encephalopathy, including Wernicke's, as this has been reported in patients using fedratinib. Thiamine levels should be assessed prior to initiation, during treatment, and when clinically indicated. Fedratinib should be discontinued if encephalopathy is suspected. Parenteral thiamine should also be administered when indicated.

Idelalisib (Zydelig) has a boxed warning regarding fatal and/or serious toxicities, including hepatotoxicity (14% incidence), diarrhea/colitis (14% to 19% incidence), pneumonitis (4% incidence), fatal and/or serious infections (21% to 36%), and intestinal perforation. Duvelisib (Copiktra) also has a boxed warning regarding fatal and/or serious toxicities, including infections (31% incidence), diarrhea/colitis (18% incidence), cutaneous reactions (5% incidence), and non-infectious pneumonitis (5% incidence).

Melphalan and tretinoin carry boxed warnings regarding the fact they should only be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. In the case of melphalan, there is a risk of severe bone marrow suppression with resulting infection or bleeding that may occur. For tretinoin, patients with APL are at high risk in general and can have severe adverse reactions to tretinoin; the physician must be experienced in the management of patients with acute leukemia, and tretinoin should be initiated in a facility with adequate services to monitor drug tolerance and support a patient compromised by drug toxicity, including respiratory compromise.

Nilotinib's (Tasigna) labeling has a boxed warning related to QT prolongation and sudden deaths. Use of nilotinib is associated with prolongation of the QT interval. For this reason, nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or in patients experiencing long QT syndrome. Before initiating therapy with nilotinib, hypokalemia and hypomagnesemia must be corrected, and monitoring of these electrolytes is recommended. Concomitant use of medications associated with QT

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prolongation and strong inhibitors of the CYP3A4 enzyme system should be avoided in patients taking nilotinib. Food should not be consumed 2 hours before or 1 hour after the dose is taken due to increased bioavailability when taken with food. An ECG should be obtained at baseline, 1 week after treatment has started, and periodically thereafter, to monitor the QTc. ECGs should also be obtained after any changes in dosage. A dose reduction of nilotinib is recommended in patients with hepatic impairment. In an ongoing study of 867 patients, there were 5 sudden deaths reported in patients receiving treatment with nilotinib. Possible abnormalities in ventricular repolarization are suspected of contributing to these reported deaths given their early occurrence relative to the start of therapy with nilotinib.

Panobinostat's (Farydak) boxed warning describes potentially fatal toxicities, including severe diarrhea and cardiac toxicities. Severe diarrhea occurred in 25% of patients treated with panobinostat during the clinical trials. Potential cardiac toxicities include ischemic events and severe arrhythmias. Electrocardiogram (ECG) and electrolytes should be monitored at baseline and periodically throughout treatment as indicated.[170]

Ponatinib (Iclusig) has a boxed warning regarding the risk of arterial occlusion, venous thromboembolism, heart failure, and hepatotoxicity. Arterial occlusion has occurred in 35% of ponatinib-treated patients, including fatal myocardial infarction (MI), stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Venous thromboembolism has occurred in 6% of ponatinib-treated patients. Patients should be monitored for evidence of thromboembolism and vascular occlusion. Ponatinib should be interrupted or stopped immediately for vascular occlusion. Heart failure, including fatalities, occurred in 9% of ponatinib-treated patients. Patients should have cardiac function monitored. Ponatinib should be interrupted or stopped for new or worsening heart failure. Hepatotoxicity, liver failure, and death have occurred in ponatinib-treated patients. Patients should have hepatic function monitored and ponatinib should be interrupted if hepatotoxicity is suspected.[171]

Thalidomide, lenalidomide, and pomalidomide all have a boxed warning regarding the risk of venous thromboembolism, both deep vein thrombosis (DVT) and pulmonary embolism (PE). Prophylaxis with an anticoagulation agent is recommended for patients receiving thalidomide- or lenalidomide-based therapies.[172] Lenalidomide also includes a boxed warning related to the risk of arterial thromboembolism, MI, and stroke in patients with multiple myeloma receiving lenalidomide in conjunction with dexamethasone.

Lenalidomide also has a boxed warning regarding hematologic toxicity as it can cause significant neutropenia and thrombocytopenia.

Approximately 25% of patients with APL who are treated with tretinoin experience a syndrome called the retinoic acid-APL (RA-APL) syndrome, which is characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure. RA-APL has been fatal in some patients with multi-organ failure, and some patients have required mechanical ventilation. The syndrome usually occurs during the first month of treatment with some cases reported following the first dose of tretinoin. High-dose steroids (dexamethasone 10 mg intravenously [IV] every 12 hours for 3 days) should be initiated promptly at first suspicion of RA-APL syndrome.

Approximately 40% of tretinoin-treated patients will develop rapidly evolving leukocytosis and patients

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who present with a high WBC at diagnosis (> 5 x 10^9/L) have an increased risk. Consideration may be given to adding an anthracycline to tretinoin therapy on day 1 or 2 for patients presenting with a high WBC count or if the WBC count rises during the first month of treatment.

Selected Warnings and Recommended Monitoring

Drug	Selected Warnings	Recommended Monitoring
acalabrutinib (Calquence)	Serious and opportunistic infections, hemorrhage (fatal and serious), infections, cytopenias, second primary malignancies (most commonly skin cancer), atrial fibrillation and flutter	Signs/symptoms of infection; signs/symptoms of bleeding: consider withholding acalabrutinib for at least 3 to 7 days pre- and post-surgery, depending on the type of surgery and risk of bleeding; consider prophylaxis for opportunistic infections according to standard of care; complete blood count (CBC) regularly; signs/symptoms of atrial fibrillation, such as palpitations, lightheadedness, syncope, or new onset dyspnea; protect from sun exposure to limit skin cancer and monitor for skin cancers
bosutinib (Bosulif)	GI toxicity, myelosuppression, hepatotoxicity, fluid retention, embryo-fetal toxicity, renal toxicity, Stevens-Johnson syndrome (SJS), cardiac failure and left ventricular dysfunction	CBC, liver function tests (LFTs) and bilirubin monthly for 3 months, renal function at baseline and during therapy, signs/ symptoms of cardiac failure
chlorambucil (Leukeran)	Myelosuppression; seizures; infertility; secondary malignancies, including leukemias; skin rash progressing to erythema multiforme, toxic epidermal necrolysis (TEN), or SJS	CBC weekly, WBC 3 or 4 days after each CBC for the first 3 to 6 weeks of therapy
dasatinib (Sprycel)	Myelosuppression occurs earlier and more frequently in patients with advanced phase CML or Ph+ ALL compared to chronic phase CML; bleeding related events (mostly associated with severe thrombocytopenia); fluid retention; QT prolongation; cardiac ischemic events, congestive heart failure, left ventricular dysfunction, myocardial infarction (MI), arrhythmias, palpitations, peripheral arterial occlusive disease, transient ischemic attacks (TIAs), pulmonary arterial hypertension; embryo-fetal toxicity; severe dermatologic toxicity, including SJS and erythema multiforme, tumor lysis syndrome; adverse bone growth and development in pediatric patients; nephrotic syndrome	CBC every 2 weeks for 12 weeks then every 3 months thereafter for patients in chronic phase CML; CBC should be monitored weekly for the first 2 months and then monthly thereafter for patients with advanced phase CML or Ph+ALL; symptoms of pleural effusion or other fluid retention, such as new or worsened dyspnea on exertion or at rest or pleuritic chest pain; ECG, signs/symptoms cardiac dysfunction/cardiopulmonary disease; electrolyte levels; CBC before starting each round of chemotherapy and as indicated, as well as every 2 days until recovery during the chemotherapy consolidation blocks for pediatric patients with Ph+ ALL
duvelisib (Copiktra)	Infections, diarrhea/colitis, cutaneous reactions, pneumonitis, hepatotoxicity, neutropenia, embryo-fetal toxicity,	Signs/symptoms of infection; new or worsening diarrhea; new or worsening skin reactions; new or worsening pulmonary signs or symptoms; hepatic function; neutrophil count every 2 weeks for the first 2 months, weekly in patients with grade 3 or 4 neutropenia, and until resolution
enasidenib (Idhifa)	Differentiation syndrome, embryo-fetal toxicity	Assess blood counts and blood chemistries for leukocytosis and tumor lysis syndrome prior to the initiation; monitor at a minimum of every 2 weeks for at least the first 3 months during treatment

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Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
fedratinib (Inrebic)	Anemia, thrombocytopenia, GI toxicity, hepatic toxicity, elevated amylase and/or lipase	CBC, amylase, lipase, and hepatic function at baseline periodically and as clinically indicated; signs and symptoms of GI toxicity (consider antiemetics, antidiarrheals, and/or supportive measures)
gilteritinib (Xospata)	Differentiation syndrome, posterior reversible encephalopathy syndrome (PRES), prolonged QT interval, pancreatitis, embryo-fetal toxicity	Signs and symptoms of differentiation syndrome; signs and symptoms of PRES (e.g., seizure, altered mental status); ECG before starting therapy, on days 8 and 15 of cycle 1, and before starting the next 2 cycles; monitor and correct hypokalemia and hypomagnesemia before starting and during treatment; signs and symptoms of pancreatitis
glasdegib (Daurismo)	Embryo-fetal toxicity, QTc interval prolongation	Assess pregnancy status prior to starting and recommend contraception; avoid breastfeeding and donating blood; monitor ECG and electrolytes
hydroxyurea	Bone marrow suppression, most commonly leukopenia, which is more likely to occur in patients who previously received radiation therapy (RT) or cytotoxic chemotherapy; exacerbation of post irradiation erythema; pancreatitis and hepatotoxicity and sometimes fatal hepatic failure have occurred in human immunodeficiency virus (HIV)-infected patients treated with hydroxyurea and anti-retroviral therapy; macrocytosis; secondary leukemias; cutaneous vasculitis toxicities; embryo-fetal toxicity; avoid use of live vaccines; interference with uric acid, urea, or lactic acid assays is possible, rendering falsely elevated results of these parameters; pulmonary toxicity	CBC with differential, renal function, signs and symptoms of pulmonary toxicity (e.g., pyrexia, cough, dyspnea)
ibrutinib (Imbruvica)	Hemorrhage, infections, progressive multifocal leukoencephalopathy (PML), cytopenias, cardiac arrhythmias, atrial fibrillation, hypertension, second primary malignancies, embryo-fetal toxicity, tumor lysis syndrome	Signs/symptoms of bleeding or infection: consider withholding ibrutinib for at least 3 to 7 days pre- and post-surgery, depending on the type of surgery and risk of bleeding; signs/symptoms of atrial fibrillation, such as palpitations, lightheadedness, or new onset dyspnea: CBC monthly, blood pressure; increased risk opportunistic infections: consider prophylaxis according to standard of care

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Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
idelalisib (Zydelig)	Hepatotoxicity, severe diarrhea or colitis, pneumonitis, fatal and/or serious infections, intestinal perforation, severe cutaneous reactions including fatal cases of SJS and TEN, anaphylaxis, neutropenia, embryo-fetal toxicity	Liver function (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months and then every 1 to 3 months thereafter; development of severe diarrhea; colitis; pulmonary symptoms including cough, dyspnea, hypoxia; development of severe skin reactions; signs and symptoms of infection, CBC
imatinib (Gleevec)	Myelosuppression (anemia, neutropenia, thrombocytopenia); hemorrhage; fluid retention and edema; severe congestive heart failure (CHF) and left ventricular dysfunction; severe hepatotoxicity (some fatal); hypereosinophilic cardiac toxicity; GI disorders; dermatologic toxicities including erythema multiforme and SJS; embryo-fetal toxicity; growth retardation in children and pre-adolescents; dizziness blurred vision, or somnolence which may impact ability to drive a car or operate machinery; hypothyroidism; tumor lysis syndrome; renal toxicity	CBC, weight, signs/symptoms of fluid retention, signs/symptoms of cardiac failure, LFTs, ECG, serum troponin, thyroid function tests, growth monitoring in children, renal function at baseline and during therapy
ivosidenib (Tibsovo)	Differentiation syndrome, QTc Interval prolongation, Guillain-Barre' syndrome	CBC with differential, weight, blood pressure, serum creatinine after initiation of drug to monitor for differentiation syndrome, ECGs, electrolytes, signs and symptoms of motor and/or sensory neuropathy
ixazomib (Ninlaro)	Thrombocytopenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy, peripheral edema, rash, hepatotoxicity, embryo-fetal toxicity, thrombotic microangiopathy (some fatal)	Platelet counts at least monthly; consider more frequent platelet count monitoring during the first 3 cycles of treatment; symptoms of neuropathy; LFTs; signs and symptoms of thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS)

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Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
lenalidomide (Revlimid)	Embryo-fetal toxicity; hematologic toxicity; venous and arterial thromboembolism, including deep vein thrombosis (DVT), pulmonary embolism (PE), MI, and stroke (CVA); increased mortality in patients with CLL; development of second primary malignancies (mainly AML and MDS); increased mortality of patients with multiple myeloma when pembrolizumab is added to a thalidomide analogue plus dexamethasone; increased risk of early death in patients with MCL; hepatotoxicity; angioedema and serious dermatologic reactions including SJS and TEN, and drug reaction with eosinophilia and systemic symptoms (DRESS); tumor lysis syndrome; tumor flare reaction; impaired stem cell mobilization; thyroid dysfunction, including both hypothyroidism and hyperthyroidism, hypersensitivity	Attempt to minimize all modifiable risk factors for thromboembolic events (e.g., hyperlipidemia, hypertension, smoking); monitor for signs of infection and advise patients to observe for bleeding or bruising; weekly pregnancy tests during the first month and then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles; CBC weekly for first 8 weeks and then at least monthly thereafter (MDS), CBC weekly for first 2 cycles then on days 1 and 15 of cycle 3 and then monthly thereafter (MM), CBC weekly for first 28 days, every 2 weeks during cycles 2 to 4 and then monthly thereafter (MCL); thromboprophylaxis is recommended; monitor for signs and symptoms of thrombotic events; monitor for development of second primary malignancies; LFTs; signs of angioedema; exfoliative or bullous rash or other severe cutaneous reactions; signs/ symptoms of tumor lysis syndrome; signs and symptoms of thyroid dysfunction
melphalan	Bone marrow suppression, secondary malignancies, anaphylaxis, impairment of fertility	CBC with differential
mercaptopurine (Purixan)	Bone marrow suppression resulting in anemia, leukopenia, thrombocytopenia or any combination of these; life-threatening infections and bleeding; hepatotoxicity; immunosuppression; embryo-fetal toxicity; treatment related malignancies associated with immunosuppressive therapy including skin cancers (melanoma and non-melanoma), sarcomas, and uterine cervical cancer *in situ*, also including lymphoproliferative disorders such as Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (these appear to be related to the degree and duration of immunosuppression); macrophage activation syndrome (MAS), particularly with off-label use in disorders such as inflammatory bowel disease	CBC; consider thiopurine-S-methyltransferase (TPMT) testing and NUDT15 genotyping in any patient with unexpectedly severe myelosuppression; monitor serum transaminase levels, alkaline phosphatase, and bilirubin levels at weekly intervals when first beginning therapy and at monthly intervals thereafter; monitor and promptly treat infections such as EBV and CMV as these are known triggers for MAS
midostaurin (Rydapt)	Embryo-fetal toxicity, pulmonary toxicity including interstitial lung disease and pneumonitis	Signs or symptoms of interstitial lung disease or pneumonitis

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Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
nilotinib (Tasigna)	Myelosuppression; QT prolongation; sudden deaths; hemorrhage; cardiac and arterial vascular occlusive events; electrolyte abnormalities; fluid retention, including effusions; hepatotoxicity and hepatic impairment; pancreatitis and elevated serum lipase; embryo-fetal toxicity; drug interactions with strong inhibitors or inducers of CYP3A4; take without food as food greatly increases bioavailability; capsules contain lactose; tumor lysis syndrome; sudden deaths have been reported in nilotinib (Tasigna); exposure of nilotinib (Tasigna) is reduced in patients with total gastrectomy, adverse bone growth and development in pediatric patients	CBC every 2 weeks for the first 2 months and monthly thereafter; ECG at baseline and 7 days after initiation; chemistry panel plus phosphate, magnesium, and calcium levels; serum lipase, LFTs monthly or as indicated; cardiovascular status and cardiovascular risk factors; lipid profile, serum glucose; QT interval in patients with hepatic impairment; signs/symptoms of severe fluid retention; shortness of breath; growth and development in pediatric patients; BCR-ABL transcript levels with FDA-approved test
panobinostat (Farydak)	Severe diarrhea, cardiac ischemia, arrhythmias, hemorrhage, hepatotoxicity, embryo-fetal toxicity, myelosuppression, infections, hepatotoxicity	Patient hydration status and electrolyte blood levels at baseline and weekly; ECG at baseline and periodically as clinically indicated; CBC at baseline and weekly during treatment; signs/symptoms of infection; liver function prior to treatment and regularly during treatment; women should use effective contraception while taking and for at least 1 month after last dose, while men should use condoms while on treatment and for at least 6 months after the last dose of panobinostat
pomalidomide (Pomalyst)	Embryo-fetal toxicity; hematologic toxicity; hepatotoxicity; venous and arterial thromboembolism; dizziness and confusional state; neuropathy; risk of second primary malignancies; tumor lysis syndrome; hypersensitivity reactions; increased mortality in combination with pembrolizumab and dexamethasone for MM; angioedema; hypersensitivity (angioedema, anaphylaxis); serious and potentially fatal dermatologic/cutaneous reactions (including SJS, TEN, and DRESS)	Weekly pregnancy tests during the first month and then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles, in MM patients assess CBC weekly for first 8 weeks and monthly thereafter, in KS patients assess CBC every 2 weeks for the first 12 weeks and monthly thereafter, signs and symptoms of tumor lysis syndrome, LFTs monthly, signs or symptoms of hypersensitivity, skin rash (including exfoliative or bullous rash)

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Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
ponatinib (Iclusig)	Arterial occlusion, including fatal MI, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease; cardiac vascular occlusion, including coronary artery occlusion and peripheral arterial occlusive events, including fatal mesenteric artery occlusion; digital or distal extremity necrosis requiring amputation; renal artery stenosis and thrombosis; venous thromboembolism, including DVT, PE, superficial thrombophlebitis and retinal vein thrombosis with vision loss; heart failure, hepatotoxicity; hypertension; pancreatitis; peripheral and cranial neuropathy; ocular toxicity; hemorrhage; fluid retention; cardiac arrhythmias; myelosuppression; tumor lysis syndrome; impaired wound healing; GI perforation; embryo-fetal toxicity; increased toxicity in newly diagnosed chronic phase CML; reversible posterior leukoencephalopathy syndrome (RPLS); SJS	LFTs at baseline and then at least monthly, serum lipase every 2 weeks for first 2 months and then monthly thereafter, CBC every 2 weeks for first 3 months and then monthly, blood pressure (BP), signs/symptoms of fluid retention or heart failure or changes in heart rate, arrhythmias, uric acid prior to initiating therapy, evidence of thromboembolism and vascular occlusion, symptoms of neuropathy, comprehensive eye exam at baseline and periodically during treatment
ruxolitinib (Jakafi)	Thrombocytopenia, anemia, neutropenia can occur which can be managed by dose reduction or interruption or transfusion; risk of serious infection-bacterial, mycobacterial, fungal and/or viral infections including tuberculosis, herpes zoster, hepatitis B; active, serious infections should be resolved before initiating ; progressive multifocal leukoencephalopathy (PML), non-melanoma skin cancers, including basal cell, squamous cell, and Merkel cell carcinoma; symptoms including fever, respiratory distress, hypotension, disseminated intravascular coagulopathy (DIC), or multi-organ failure have occurred following discontinuation of ruxolitinib; lipid elevations	CBC at baseline and every 2 to 4 weeks until dose stabilized, then as often as clinically indicated; signs/symptoms of infection; periodic skin examinations; instruct patients not to interrupt or discontinue therapy with ruxolitinib without consulting their physician; assess lipid parameters 8 to 12 weeks following initiation of ruxolitinib; treat according to clinical guidelines for the management of hyperlipidemia
selinexor (Xpovio)	Life-threatening thrombocytopenia, life-threatening neutropenia, severe GI toxicity (nausea/vomiting/diarrhea/anorexia/weight loss), hyponatremia (severe or life-threatening), serious infections (potentially fatal), life-threatening neurological toxicity, embryo-fetal toxicity	CBC with differential, neutrophil counts, standard blood chemistries, body weight, nutritional status, and volume status at baseline and throughout therapy with more frequent monitoring during the initial 3 months of therapy; signs and symptoms of bleeding, infection, or neurological symptoms; nausea and vomiting

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Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
thalidomide (Thalomid)	Embryo-fetal toxicity; venous and arterial thromboembolism; drowsiness and somnolence, peripheral neuropathy; dizziness and orthostatic hypotension; neutropenia; thrombocytopenia; increased HIV viral load; bradycardia; SJS, TEN and DRESS, seizures, tumor lysis syndrome, contraceptive risks, hypersensitivity; increased mortality of patients with multiple myeloma when pembrolizumab is added to a thalidomide analogue plus dexamethasone, increased risk of early death in patients with mantle cell lymphoma	Weekly pregnancy tests during the first month and then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles; signs and symptoms of thromboembolism; monthly exams for signs/symptoms of neuropathy for the first 3 months and then every 6 months thereafter; WBC with differential and platelet counts; consider thiopurine-S-methyltransferase (TPMT) testing and NUDT15 genotyping in any patient with unexpectedly severe myelosuppression as dose reductions may be needed; HIV viral load after first and third months of treatment and every 3 months thereafter in HIV+ patients; live vaccines should be avoided in immunocompromised patients
tretinoin	Retinoic acid-acute promyelocytic leukemia (RA-APL) syndrome, leukocytosis, pseudotumor cerebri, hypercholesterolemia and/or hypertriglyceridemia, elevated LFTs	Signs of fever, dyspnea, weight gain, papilledema, headache, visual disturbances; monitor lipid profiles, LFTs, CBC, coagulation parameters
venetoclax (Venclexta)	Tumor lysis syndrome, neutropenia, infections, embryo-fetal toxicity, increased mortality in combination with bortezomib and dexamethasone in MM (off-label use)	Blood chemistries including uric acid, renal function, CBC assess throughout treatment, signs and symptoms of infections
vorinostat (Zolinza)	PE, DVT, thrombocytopenia (severe thrombocytopenia with GI bleeding when given concomitantly with other HDAC inhibitors such as valproic acid), anemia, hyperglycemia, electrolyte abnormalities, embryo-fetal toxicity	Signs and symptoms of thrombosis, CBC, serum electrolytes, and blood glucose every 2 weeks for first 2 months of therapy and then monthly thereafter; assess electrolytes more often in patients with nausea, vomiting, diarrhea; assess platelet counts more often in patients receiving concurrent HDAC inhibitor therapy
zanubrutinib (Brukinsa)	Hemorrhage, infections (including fatal and serious infections, as well as opportunistic infections), cytopenias, second primary malignancies, cardiac arrhythmias, embryo-fetal toxicity	Signs and symptoms of bleeding; monitor for fever or other signs and symptoms of infection; CBCs during treatment; signs and symptoms of atrial fibrillation and atrial flutter

Risk Evaluation and Mitigation Strategy (REMS)[173,174,175,176,177,178,179]

The ponatinib (Iclusig) REMS program, originally approved in December 2013 to inform prescribers about the approved indications for use and the serious risk of arterial occlusion and vascular thromboembolism associated with ponatinib was discontinued by the FDA in May 2018. After a comprehensive assessment, the FDA determined the REMS communication plan had met its goals.[180]

The idelalisib (Zydelig) and duvelisib (Copiktra) REMS programs were approved in July 2014 and September 2018, respectively, with the FDA approval of these medications. The goal of the idelalisib REMS program is to mitigate the risks of fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious pneumonitis, fatal and/or serious infections, and fatal and serious intestinal perforation associated with idelalisib. The goal of the duvelisib REMS program is to mitigate the risks of fatal and/or serious infections, diarrhea/colitis, cutaneous reactions, and

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pneumonitis associated with duvelisib. The communication plan for both medications includes a REMS letter to oncologists and hematologists who are likely to prescribe the therapy, a REMS fact sheet to be distributed to healthcare providers, a medication guide for patients, and a patient safety information card. Information regarding REMS is available on the Zydelig website, http://www.zydeligrems.com/ and Copiktra website, https://www.copiktrarems.com/.

The panobinostat (Farydak) REMS program was required by the FDA to alert providers to the serious risks of severe diarrhea, which occurred in 25% of panobinostat-treated patients and the risk of cardiac toxicities including severe and fatal cardiac ischemic events as well as arrhythmias which occurred in 12% of panobinostat-treated patients. Providers are advised not to start panobinostat in any patient with a history of recent myocardial infarction (MI), unstable angina, QTcF ≥ 450 msec or clinically significant ST-segment or T-wave abnormalities. The REMS program consists of a fact sheet for healthcare providers, a letter to healthcare providers and a letter to professional societies. Information regarding the REMS program is available on the Farydak website, http://www.farydak-rems.com/index.jsp.

Thalidomide (Thalomid) is available only through a restricted program. The goal of the thalidomide REMS program is to prevent the risk of embryo-fetal exposure to Thalomid and to inform prescribers, patients and pharmacists on the serious risks and safe-use conditions of this medication. The thalidomide program requires that prescribers must be certified with the program and patients must sign a patient-physician agreement form and comply with the REMS requirements. Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements and males must comply with the contraception requirements. Pharmacies must be certified with the program and must dispense only to patients who are authorized to receive thalidomide.

Lenalidomide (Revlimid) is available only through a restricted program. The lenalidomide REMS program requires that prescribers must be certified with the program and patients must sign a patient-physician agreement form and comply with the REMS requirements. Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements and males must comply with the contraception requirements. Pharmacies must be certified with the program and must dispense only to patients who are authorized to receive lenalidomide.

Pomalidomide (Pomalyst) is available only through a restricted program. The pomalidomide REMS program requires that prescribers must be certified with the program and patients must sign a patient-physician agreement form and comply with the REMS requirements. Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements and males must comply with the contraception requirements. Pharmacies must be certified with the program and must dispense only to patients who are authorized to receive pomalidomide.

Further information about the Thalomid, Revlimid, and Pomalyst REMS programs is available at www.CelgeneRiskManagement.com.

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DRUG INTERACTIONS[181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209]

CYP3A4 Substrates – Enzyme Inhibition and Induction

Co-administration of CYP3A4 Inhibitors

When co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, ritonavir, saquinavir, telithromycin), plasma concentrations of ibrutinib (Imbruvica), ruxolitinib (Jakafi), bosutinib (Bosulif), dasatinib (Sprycel), duvelisib (Copiktra), fedratinib (Inrebic), gilteritinib (Xospata), glasdegib (Daurismo), idelalisib (Zydelig), imatinib (Gleevec), ivosidenib (Tibsovo), nilotinib (Tasigna), panobinostat (Farydak), midostaurin (Rydapt), ponatinib (Iclusig), and zanubrutinib (Brukinsa) can potentially increase and the combinations should generally be avoided or used with caution. In addition, patients taking these medications should avoid grapefruit or Seville oranges as it can increase the plasma concentrations of these agents. A dose reduction of fedratinib can be considered as an alternative in those on a strong inhibitor. Selection of an alternate medication with minimal to no enzyme inhibition potential is recommended for ibrutinib. For strong CYP3A4 inhibitors used short-term (7 days or less), consider interrupting ibrutinib therapy. If a moderate CYP3A4 inhibitor must be used, reduce the ibrutinib dose. When ponatinib is administered with strong CYP3A inhibitors, the recommended starting dose of ponatinib (Iclusig) should be reduced. The dose of panobinostat should be reduced to 10 mg when co-administered with strong CYP3A inhibitors. The dose of duvelisib should be decreased if co-administered with a strong CYP3A4 inhibitor. If an alternative agent to the strong CYP3A inhibitor is not available and a patient receiving gilteritinib experiences serious or life-threatening side effects, withhold and decrease the dose of gilteritinib. The dose of zanubrutinib should be decreased if co-administered with moderate or strong CYP3A inhibitors. For use with strong CYP3A inhibitors, the recommended zanubrutinib dose is 80 mg once daily. For coadministration with moderate CYP3A inhibitors, the recommended dose is 80 mg twice daily. Following discontinuation of the CYP3A inhibitor, restart the prior dose of zanubrutinib.

Gilteritinib (Xospata) should not be used in combination with combined P-glycoprotein (P-gp) and strong CYP3A inducers due to the potential for decreased gilteritinib concentrations leading to decreased efficacy.

The use of venetoclax (Venclexta) with strong CYP3A inhibitors is contraindicated during initiation of venetoclax and during the ramp-up phase of therapy. Patients who have been stabilized on a dose of venetoclax (Venclexta) should have their dose reduced by at least 75% when used concomitantly with a strong CYP3A inhibitor. The use of venetoclax with a moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) is not recommended, but if concomitant therapy cannot be avoided, the venetoclax dose should be reduced by 50%. Avoid grapefruit products, Seville oranges, and star fruit during treatment with venetoclax as they contain inhibitors of CYP3A.

When ruxolitinib is administered with strong CYP3A4 inhibitors, a dose reduction should be considered. Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily. The dose of ruxolitinib should be reduced in patients with acute GVHD only when administered with ketoconazole while monitoring blood counts more frequently and adjusting the dose with itraconazole as well if necessary.

Acalabrutinib (Calquence) administration with a strong CYP3A inhibitor may result in increased concentrations of acalabrutinib leading resulting in increased toxicity. This combination should be

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avoided. Dose reduction to 100 mg daily should be considered when acalabrutinib is co-administered with a moderate CYP3A inhibitor.

Alternative therapies that are not strong or moderate CYP3A4 inhibitors should be considered in patients receiving ivosidenib. If the co-administration of a strong CYP3A4 inhibitor is unavoidable, the ivosidenib dose should be reduced to 250 mg once daily.

When pomalidomide is co-administered with a strong CYP1A2 inhibitor (e.g., ciprofloxacin, fluvoxamine) in the presence of a strong CYP3A4/5 and P-glycoprotein (P-gp) inhibitor (e.g., ketoconazole), pomalidomide exposure is increased. However, ketoconazole in the absence of a CYP1A2 inhibitor does not increase pomalidomide exposure. If it is medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, pomalidomide dose should be reduced by 50%.

Patients taking fedratinib (Inrebic) should avoid dual CYP3A4 and CYP2C19 inhibitors; concomitant use has not been evaluated.

Co-administration of CYP3A4 Inducers

Administration of ibrutinib (Imbruvica), bosutinib (Bosulif), dasatinib (Sprycel), duvelisib (Copiktra), glasdegib (Daurismo), venetoclax (Venclexta), imatinib (Gleevec), nilotinib (Tasigna), idelalisib (Zydelig), panobinostat (Farydak), ivosidenib, ixazomib (Ninlaro), midostaurin (Rydapt), acalabrutinib (Calquence), ponatinib (Iclusig), and zanubrutinib (Brukinsa) with potent inducers of CYP3A4 (e.g., dexamethasone, phenytoin, phenobarbital, carbamazepine, rifampin, St. John's wort, rifabutin) may result in decreases in plasma concentrations of these agents. Concurrent use of these medications with strong inducers of CYP3A4 should be avoided or used with caution. If these agents must be used with a CYP3A4 inducer, a dose increase may be considered for some agents (except ponatinib [Iclusig] or zanubrutinib). Concurrent use of glasdegib with moderate CYP3A4 inducers should be avoided; if this is not possible, the dose of glasdegib should be increased, as tolerated, according to dosing instructions provided in the prescribing information. Moderate and strong CYP3A inducers should be avoided in patients receiving zanubrutinib.

Fedratinib (Inrebic) should also be avoided with moderate or strong CYP3A4 inducers; concomitant use has not been evaluated.

Ivosidenib also induces CYP3A4 and may induce CYP2C9. Therefore, ivosidenib may decrease the concentrations of CYP3A4 or CY2C9 substrates. Ivosidenib should not be coadministered with itraconazole or ketoconazole due to the expected loss of antifungal efficacy. Patients may also need to consider alternative methods of contraception if taking ivosidenib with hormonal contraceptives as the concentrations of these drugs may be reduced.

Substrates of CYP3A4, CYP2D6, CYP2C8, CYP2C19

Dasatinib (Sprycel), duvelisib (Copiktra), imatinib (Gleevec), idelalisib (Zydelig), and nilotinib (Tasigna) are also inhibitors of CYP3A4 and, when co-administered with drugs eliminated by this enzyme, they have the potential to increase the plasma concentrations of the CYP3A4 substrates. Caution is advised when using these agents with CYP3A4 substrates that have a narrow therapeutic index (e.g., alfentanil, cyclosporine, ergot alkaloids, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus).

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Coadministration of fedratinib (Inrebic) with drugs that are CYP3A4, CYP2C10, or CYP2D6 substrates may increase the concentrations of the substrates; patients should be monitored for increased adverse effects.

Nilotinib is a competitive inhibitor of CYP2D6. Imatinib may have a weak inhibitor effect on CYP2D6-mediated metabolism and caution is recommended when administering imatinib with CYP2D6 substrates that have a narrow therapeutic window. Nilotinib is also a competitive inhibitor of CYP2C8 and CYP2C9. Panobinostat should not be administered with sensitive CYP2D6 substrates (e.g., dextromethorphan, metoprolol, venlafaxine) or CYP2D6 substrates that have a narrow therapeutic index (e.g., thioridazine, pimozide).

Warfarin

Warfarin is metabolized by CYP2C9 and CYP3A4.

Avoid concomitant use with warfarin with these agents: imatinib (Gleevec) and nilotinib (Tasigna).

Patients receiving warfarin and mercaptopurine, lenalidomide (Revlimid), venetoclax (Venclexta), and vorinostat (Zolinza) should have their international normalized ratios (INRs) monitored closely.

Patients receiving concomitant hydroxyurea, melphalan, or mercaptopurine may have an additive risk of bleeding due to the thrombocytopenic effects of these agents.

P-glycoprotein (P-gp) Inhibitors and Substrates

P-gp Inhibitors

Avoid the use of bosutinib (Bosulif) and venetoclax (Venclexta) with P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quinidine, ranolazine, ticagrelor) as an increase in plasma concentrations may occur. If venetoclax (Venclexta) must be administered in conjunction with a P-gp inhibitor, reduce the dose of venetoclax by at least 50%. Ponatinib (Iclusig), venetoclax, and nilotinib (Tasigna) are also inhibitors of P-gp and therefore have the potential to increase levels of P-gp substrates, and, therefore, should be used with caution on narrow therapeutic index P-gp substrates (e.g., digoxin, everolimus, sirolimus).

P-gp Substrates

Nilotinib (Tasigna) is also a substrate of P-gp. If it is administered with an inhibitor of P-gp, increased concentrations of nilotinib are likely; caution should be exercised.

Lenalidomide is a substrate of P-gp. When digoxin was co-administered with multiple doses of lenalidomide, the digoxin maximum concentration (Cmax) and area under the concentration curve (AUC) were increased by 14%. Periodic monitoring of digoxin plasma levels is recommended.

UGT1A1 and UGT1A9 Substrates

Nilotinib (Tasigna) is a competitive inhibitor of UGT1A1.

Live Vaccines

Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin (BCG; anti-tuberculosis), yellow fever, varicella, and TY21a typhoid vaccines. Induction of immunity to infectious agents or vaccines will likely be subnormal in patients receiving mercaptopurine, melphalan, and hydroxyurea.

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Acetaminophen

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

Antacids

Concomitant administration of dasatinib (Sprycel), acalabrutinib (Calquence), or ponatinib (Iclusig) with antacids may result in reduced systemic exposure of these medications. Therefore, simultaneous administration of these agents with antacids should be avoided. In patients requiring treatment with antacids, the antacid should be given at least 2 hours prior to or 2 hours after the dose of dasatinib or acalabrutinib.

Histamine-2 (H_2) Receptor Blockers/Proton Pump Inhibitors (PPIs)

H_2 receptor blockers and proton pump inhibitors are associated with long-term suppression of gastric acid secretion that may result in reduced systemic exposure of dasatinib (Sprycel), nilotinib (Tasigna), and ponatinib (Iclusig). Concomitant use of H_2 receptor blockers or proton pump inhibitors with these agents is, therefore, not recommended.

Due to the long-lasting effect on gastric acid, concomitant use of proton pump inhibitors with acalabrutinib (Calquence) should be avoided; H2 receptor blockers must be given 2 hours before doses of acalabrutinib.

Concomitant lansoprazole (PPI) decreased bosutinib (Bosulif) Cmax by 46% and AUC by 26% compared to bosutinib alone. Consider using short-acting antacids or H_2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H_2 blocker dosing and bosutinib dosing by more than 2 hours.

H2 blockers such as famotidine and cimetidine may cause additive bradycardia when used with thalidomide.

QT Interval Prolongation

The administration of nilotinib (Tasigna), ivosidenib (Tibsovo), glasdegib (Daurismo), and panobinostat (Farydak) with agents that may prolong the QT interval (e.g., anti-arrhythmics, clarithromycin, methadone, ondansetron) should be avoided.

Cigarette Smoking

Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction.

Other

In HIV-infected patients undergoing therapy with hydroxyurea and didanosine, with or without stavudine, fatal and nonfatal pancreatitis has occurred. Hepatotoxicity and hepatic failure resulting in death have been reported during postmarketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. This combination should be avoided.

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Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

Severe thrombocytopenia and GI bleeding have been reported with concomitant use of vorinostat (Zolinza) and other HDAC inhibitors (e.g., valproic acid). Monitor platelet counts every 2 weeks for first 2 months.

Co-administration of ponatinib and substrates of the ABCG2 transport systems (e.g., methotrexate, imatinib, lapatinib, rosuvastatin, sulfasalazine) may be impacted by ponatinib's inhibition of ABCG2 transporter systems.

Nalidixic acid is contraindicated in patients undergoing concomitant therapy with melphalan or other alkylating agents because of reports of serious GI toxicity, such as hemorrhagic ulcerative colitis or intestinal necrosis.

When allopurinol is co-administered with mercaptopurine, the dose of mercaptopurine must be reduced to one-third to one-quarter of the usual dose to avoid severe toxicity. The dosage of mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression. Enhanced marrow suppression has been noted in some patients also receiving trimethoprim-sulfamethoxazole. There is *in vitro* evidence that aminosalicylate derivatives (e.g., mesalamine or sulfasalazine) may inhibit the TPMT enzyme and should be used with caution in patients receiving concomitant mercaptopurine therapy. Conversely, no dose adjustment is necessary when thioguanine is administered concomitantly with allopurinol.

There is usually complete cross-resistance between mercaptopurine and thioguanine.

Opioids, antihistamines, antipsychotics, antianxiety agents, and other central nervous system (CNS) depressants, including alcohol, when used concomitantly with thalidomide may cause additive sedative effect and should be avoided.

Calcium channel blockers, beta blockers, alpha/beta-adrenergic blockers, digoxin, lithium, tricyclic antidepressants, and neuromuscular blockers should be used with caution in patients receiving thalidomide as they may cause an additive bradycardic effect.

Bortezomib, amiodarone, cisplatin, docetaxel, paclitaxel, vincristine, disulfiram, phenytoin, metronidazole, and alcohol may cause additive peripheral neuropathy when administered with thalidomide.

Hormonal contraceptives increase the risk of venous thromboembolism. It is not known whether concomitant use of these agents with thalidomide further increases the risk of thromboembolism.

Concomitant use of hormonal contraceptives with HIV-protease inhibitors, griseofulvin, modafinil, penicillins, rifampin, rifabutin, phenytoin, carbamazepine, or St. John's wort may reduce the effectiveness of hormonal contraceptives. Therefore, female patients taking thalidomide who require treatment with any of these agents must use 2 other effective methods of contraception.

Erythropoietic agents, estrogen-containing therapies, and other agents may increase the risk of thromboembolism and should be used with caution in multiple myeloma patients receiving thalidomide or lenalidomide and dexamethasone.

Tretinoin should not be administered in combination with vitamin A due to a risk of hypervitaminosis. Caution should be exercised when tretinoin is administered concomitantly with anti-fibrinolytic agents

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such as tranexamic acid, aminocaproic acid, or aprotinin. Avoid the use of tretinoin with other drugs known to cause pseudotumor cerebri/intracranial hemorrhage such as tetracyclines.

Gilteritinib can decrease the efficacy of medications that act on the $5HT_{2b}$ receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline); avoid concurrent use of these medications, if possible.

There are no known drug/drug interactions with chlorambucil (Leukeran), enasidenib (Idhifa), melphalan (Alkeran), or selinexor (Xpovio). Selinexor is a substrate of CYP3A4, UGTs, and GSTs, but no formal drug interaction studies have been conducted.

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ADVERSE EFFECTS[210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237]

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

Drug	Fluid Retention/ Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
acalabrutinib (Calquence) n=124 MCL	nr	31	39	18	19	8	21	nr	46	nr
n=357 (ELEVATE-TN, acalabrutinib alone or with obinutuzumab)	nr	35-39	39-40	25-26	20-22	20	32-37	nr	52-53	5
CLL – previously untreated CLL n=154 (ASCEND, acalabrutinib alone CLL – relapsed or refractory	nr	18	22	9	nr	16	15	nr	47	3.2
bosutinib (Bosulif) n=546 CML – resistant/intolerant to imatinib (Gleevec)	14	82	--	35	46	--	reported	--	27	reported
dasatinib (Sprycel) CML – resistant/intolerant to imatinib (Gleevec)	21-35	18-31	15-33	15-21	18-23	11-26	0-19/3-13	1- < 10	13-74	1- < 10
CML – newly diagnosed (imatinib [Gleevec])	23 (43)	18 (19)	12 (10)	11 (17)	9 (21)	6 (5)	6-12 (12-16)	nr	nr	nr
CML – newly diagnosed chronic phase (imatinib[Gleevec])	38 (45)	22 (23)	14 (11)	14 (18)	10 (25)	8 (8)	7 (12)	nr	nr	nr

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Adverse Effects (continued)

Drug	Fluid Retention / Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
dasatinib (Sprycel)										
Ph+ ALL – resistant or intolerant (adults)	19	31	nr	16	24	19	nr	nr	nr	nr
Ph+ ALL – newly diagnosed with chemotherapy (pediatrics)	47	84	77	68	84	nr	83	93	82	47
duvelisib (Copiktra) n=158 CLL/SLL	11	57	nr	27	23	nr	17	nr	55	nr
duvelisib (Copiktra) n=96 FL	nr	≥ 20	≥ 20	≥ 20	≥ 20	nr	≥ 20	≥ 20	≥ 20	nr
enasidenib (Idhifa)	up to 21	43	nr	reported	50	nr	nr	nr	nr	nr
fedratinib (Inrebic) n=191	nr	66 (16)	9 (1.1)	9 (1.1)	62 (15)	nr	nr	nr	40 (14)	4.2
gilteritinib (Xospata) n=319	40	35	24	36	30	reported	50	41	nr	nr
glasdegib (Daurismo) with cytarabine n=111 (cytarabine only, n=41)	30 (20)	18 (22)	12 (10)	20 (7)	29 (12)	36 (42)	30 (17)	21 (12)	43 (42)	nr
ibrutinib (Imbruvica) cGVHD	12	36	17	12	26	26	14	29	24	nr
ibrutinib (Imbruvica) CLL/SLL	19-22	42-59	12-19	21-27	20-26	reported	25-36	14-21	36-43	14-16

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Adverse Effects (continued)

Drug	Fluid Retention /Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
ibrutinib (Imbruvica) with rituximab (n=352) CLL/SLL (fludarabine + cyclophosphamide + rituximab) (n=158)	28 (17)	53 (27)	40 (27)	49 (29)	40 (64)	31 (8)	61 (35)	22 (8)	26 (51)	42 (22)
ibrutinib (Imbruvica) MCL	35	51	13	25	31	nr	11	17	41	nr
ibrutinib (Imbruvica) MZL	24	43	13	29	25	30	40	17	43	14
ibrutinib (Imbruvica) WM	17	38	14	21	21	28	21	15	21	14
idelalisib (Zydelig) CLL	nr	21 (16)	nr	18 (6)	25 (21)	nr	7 (4)	6 (2)	nr	nr
idelalisib (Zydelig) Indolent NHL	15 (10)	68 (47)	16 (11)	31 (21)	42 (29)	nr	nr	nr	41 (28)	nr
imatinib (Gleevec) CML	61.7-76	43-57	27-36	36-47	49.5-71	28.9-53	38-49/ 9-27	0.1-1	6-42	0.1-1
imatinib (Gleevec) GIST	76.7-86.1	56.2-58.2	19.7-22	38.1-49.8	58.1-64.5	12.3-13.3	nr	9.2-10	32-34.8	0.1-1
ivosidenib (Tibsovo) newly diagnosed AML	43	61	11	14	36	nr	25	21	54	nr
ivosidenib (Tibsovo) relapsed/refractory AML	32	34	16	26	31	nr	18	28	60	nr
ixazomib (Ninlaro) n=720	25 (18)	42 (36)	nr	19 (11)	26 (21)	nr	nr	nr	nr	nr

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Adverse Effects (continued)

Drug	Fluid Retention/ Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
lenalidomide/ dexamethasone (Revlimid) (dexamethasone/placebo) in multiple myeloma	26 (21)	39 (27)	nr	21 (9)	26 (21)	nr	reported	nr	31 (24)	8 (6)
lenalidomide (myelodysplastic syndromes)	20	49	20	36	24	nr	9	nr	11	6
lenalidomide (MCL)	nr	31	reported	22	30	nr	reported	nr	31	nr
lenalidomide (FL or MZL)	13	31	15	22	reported	nr	4.5	5	16	nr
midostaurin (Rydapt) n=345, AML	nr	nr	46 (38)	nr	83 (70)	nr	33 (31)	66 (62)	nr	8 (nr)
midostaurin (Rydapt) n=142, ASM	40	54	26	14	82	14	35	nr	60	nr
nilotinib (Tasigna) n=438 CML resistant/intolerant to imatinib (Gleevec)	11	19-22	21-31	28-33	18-31	reported	14	reported	8-23	1-10
n=279 nilotinib (Tasigna) 300 mg twice daily CML-newly diagnosed (imatinib [Gleevec])	8 (37)	14 (37)	28 (16)	36 (16)	19 (38)	reported	14 (16)	reported	7 (all grades) (5) (grade 3/4)	1-10
panobinostat (Farydak) + bortezomib + dexamethasone (placebo + bortezomib + dexamethasone)	(19)	68 (42)	nr	reported	36 (21)	nr	nr	nr	62 (52)	reported
pomalidomide (Pomalyst) monotherapy in MM	23	34	reported	22	nr	reported	reported	nr	38	nr

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Adverse Effects (continued)

Drug	Fluid Retention/ Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
pomalidomide (Pomalyst) monotherapy in KS	29	32	nr	71	36	reported	nr	nr	54	nr
ponatinib (Iclusig) CML-any phase n=417 Ph+ALL n=32	19 22	26 13	39 25	54 34	32 22	11 9	22 6	23 9	55 34	71 53
ruxolitinib (Jakafi) n=155 myelofibrosis	nr	nr	14.8 (5.3)	nr	nr	nr	nr	nr	96.1 (86.8)	nr
ruxolitinib (Jakafi) n=110 polycythemia vera	nr	15	≥ 15	nr	6	nr	nr	nr	72	5
ruxolitinib (Jakafi) n=71 aGVHD	51	24	21	23	nr	49	nr	nr	75	20
selinexor (Xpovio) n=202 MM	nr	44	10	nr	72	reported	nr	nr	59	nr
selinexor (Xpovio) n=134 DLBCL	17	37	4.5	nr	57	10	15	nr	82	nr
thalidomide (Thalomid) plus dexamethasone (dexamethasone alone)	34 (25)	nr	nr	30 (18)	13 (12)	nr	17 (14)	nr	nr	nr
venetoclax (Venclexta) CLL/SLL	22	19-43	11	13-18	19-42	nr	29	13	3-33	nr
venetoclax (Venclexta) AML	31-46	38-54	nr	31-33	46-64	46-49	10-31	nr	15-61	12-15
vorinostat (Zolinza)	13	52	12	nr	41	nr	20	nr	14	nr
zanubrutinib (Brukinsa)	nr	23	4.2	36	nr	11	14	nr	14	12

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

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In clinical studies with patients with previously treated MCL, the most common adverse reactions reported in the acalabrutinib arm occurring in ≥ 20% of patients included anemia (46%), thrombocytopenia (44%), headache (39%), neutropenia (36%), diarrhea (31%), fatigue (28%), myalgia (21%), and bruising (21%). The most common grade 3 or greater non-hematological adverse reaction reported was diarrhea (3.2%). The most frequently occurring adverse reactions (incidence ≥ 30%) of any grade in patients with CLL who received acalabrutinib were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

The most common adverse reaction to chlorambucil is bone marrow suppression and GI toxicities, such as nausea, vomiting, diarrhea, and oral ulceration. Urticaria and severe dermatologic hypersensitivities, such as erythema multiforme, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome (SJS) have been reported. CNS side effects, including tremors, muscular twitching, myoclonus, confusion, agitation, ataxia, flaccid paresis, and hallucinations along with generalized seizures, have been rarely reported with chlorambucil.

In addition, pulmonary fibrosis, hepatotoxicity and jaundice, drug fever, peripheral neuropathy, interstitial pneumonia, sterile cystitis, infertility, and secondary malignancies, including leukemia, have been reported.

Nephrotic syndrome as well as thrombotic microangiopathy associated with dasatinib (Sprycel) has been identified as a postmarketing adverse event. Thrombotic microangiopathy associated with bosutinib (Busulfan), imatinib (Gleevec), nilotinib (Tasigna), and ponatinib (Iclusig) has also been identified as a postmarketing adverse event for these medications. Arterial (including aortic) aneurysms, dissections, and rupture; impaired wound healing; and GI perforation/fistula have also been reported as a postmarketing experience adverse reaction for ponatinib. Hypothyroidism has been reported as a clinically significant adverse event occurring in 3% of ponatinib patients in the phase 2 study; hyperthyroidism has also been reported as a postmarketing adverse event with ponatinib.

The most common adverse reactions occurring in ≥ 20% of patients treated with duvelisib in the clinical trials evaluating the B-cell malignancies CLL/SLL and FL not listed above were neutropenia, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia.

The most common adverse reactions or laboratory abnormalities reported with enasidenib in clinical trials not listed above were elevated bilirubin (81%), decreased calcium (74%), decreased potassium (41%), decreased appetite (34%), vomiting (34%), decreased phosphorus (27%), differentiation syndrome (14%), dysgeusia (12%), noninfectious leukocytosis (12%), and tumor lysis syndrome (6%). Other adverse effects reported in ≤ 10% of patients included pulmonary edema and acute respiratory distress syndrome.

The most common adverse reactions (incidence ≥ 10%) reported with fedratinib not listed above were vomiting, fatigue/asthenia, muscle spasms, increased serum creatinine, and extremity pain.

The most common adverse reactions, occurring in ≥ 10% of patients treated with gilteritinib in the clinical trial that were non-hematological in nature and not included above were increased transaminase, fatigue/malaise, fever, dyspnea, cough, constipation, eye disorders, dizziness, hypotension, vomiting, renal impairment, abdominal pain, neuropathy, insomnia, and dysgeusia. Other clinically important adverse events occurring in ≤ 10% of patients were ECG QT prolongation (9%), hypersensitivity reactions (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute

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febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

The most common adverse events, occurring in ≥ 20% of patients treated with glasdegib in combination with low-dose cytarabine not listed above were anemia, fatigue, hemorrhage, febrile neutropenia, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, and constipation.

The most common adverse events (≥ 20%) of any grade occurring with ivosidenib were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough, and constipation. The most common adverse reactions leading to dose interruption were QT prolongation (7%), differentiation syndrome (3%), leukocytosis (3%), and dyspnea (3%).

Hydroxyurea use may cause dermatological reactions, such as maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral and facial erythema. Pulmonary toxicity has been associated with hydroxyurea as a postmarketing adverse event.

The most frequent adverse reaction to hydroxyurea, mercaptopurine, and melphalan is myelosuppression.

Nausea, vomiting, diarrhea, oral ulceration, and liver dysfunction have been reported with melphalan. Other reported adverse reactions include pulmonary fibrosis (some with fatal outcomes), interstitial pneumonitis, and dermatologic issues, such as hypersensitivity rash.

Ventricular tachyarrhythmias occurred in 1% of patients treated with ibrutinib (Imbruvica) in clinical trials compared to 0.2% treated with control. Atrial arrhythmias occurred in 7% treated with ibrutinib compare to 1.5% treated with control. Additionally, ischemic cerebrovascular events (e.g., cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) occurred in 1% of ibrutinib-treated patients compared to 0.4% of control patients (≥ grade 3: 0.5% versus 0.2%, respectively). Various postmarketing experience adverse reactions have been reported with ibrutinib, including interstitial lung disease as well as skin and subcutaneous disorders (such as Stevens-Johnson Syndrome (SJS), onycholysis, panniculitis, neutrophilic dermatoses). Long-term safety data, including follow-up over 5 years of 1,178 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, and relapsed/refractory MCL n=370) demonstrated the cumulative rate of hypertension increased over time with prolonged use of ibrutinib; for ≥ grade 3 hypertension, the prevalence was 4% for year 0 to 1, 6% for year 1 to 2, 8% for year 2 to 3, 9% for year 3 to 4 and for year 4 to 5. The overall incidence for the 5-year treatment period was 11%.

Serious or fatal infections occurred in 21% of patients treated with idelalisib monotherapy and in 36% of patients treated with idelalisib combination therapy in clinical trials. The most common infections were pneumonia, sepsis, and febrile neutropenia. Serious of fatal *pneumocystis jirovecii* pneumonia (PJP) or cytomegalovirus (CMV) infections occurred in < 1% of idelalisib-treated patients.

Pseudoporphyria associated with imatinib has been identified as a postmarketing adverse effect.

Herpes zoster was reported in 4% of patient receiving ixazomib compared to 2% of patients receiving placebo in clinical trials. Patients who received antiviral prophylaxis while receiving ixazomib had a lower incidence (< 1%) of herpes zoster compared to patients who did not receive prophylaxis (6%).

Eye disorders were reported in 26% of patients who received ixazomib/lenalidomide/dexamethasone compared to 16% of patients who received placebo/lenalidomide /dexamethasone in clinical trials. The

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most commonly reported events were blurred vision, dry eye, and conjunctivitis. Progressive multifocal leukoencephalopathy (PML), angioedema, aGVHD, and solid organ transplant rejection have been reported with lenalidomide in the postmarketing setting.

In clinical studies with patients with AML, the most commonly reported adverse reactions that occurred in ≥ 10% of patients and ≥ 2% more frequently in the midostaurin arm than in the placebo arm included febrile neutropenia (83%), nausea (83%), mucositis (66%), vomiting (61%), headache (46%), petechiae (36%), musculoskeletal pain (33%), epistaxis (28%), device-related infection (24%), hyperglycemia (20%), upper respiratory tract infection (20%), hemorrhoids (15%), arthralgia (14%), hyperhidrosis (14%), activated partial thromboplastin time prolonged (13%), renal insufficiency (12%), and insomnia (12%). The most frequent serious adverse reaction in the AML study population was febrile neutropenia (16%), which was equal to the incidence of febrile neutropenia in the placebo arm (16%). The most frequent adverse reaction leading to midostaurin discontinuation on the AML study was renal insufficiency (1%).

In clinical studies with patients with ASM, SM-AHN, or MCL, the most commonly reported adverse reactions that occurred in ≥ 10% of patients and ≥ 2% more frequently in the midostaurin arm than in the placebo arm included nausea (82%), vomiting (68%), diarrhea (54%), edema (40%), musculoskeletal pain (35%), abdominal pain (34%), fatigue (34%), upper respiratory tract infection (30%), constipation (29%), pyrexia (27%), headache (26%), dyspnea (23%), arthralgia (19%), cough (18%), urinary tract infection (16%), GI hemorrhage (14%), rash (14%), dizziness (13%), pleural effusion (13%), epistaxis (12%), insomnia (11%), QT prolongation (11%), renal insufficiency (11%), herpesvirus infection (10%), and pneumonia (10%). Adverse reactions led to dose modifications in 56% of patients. The most common adverse events that led to midostaurin dose modifications in the ASM trial were GI symptoms, QT prolongation, neutropenia, pyrexia, thrombocytopenia, GI hemorrhage, lipase increase and fatigue. Treatment discontinuation due to adverse reactions occurred in 21% of patients, these adverse events included infection, nausea or vomiting, QT prolongation, and GI hemorrhage.

Other frequent serious adverse effects reported with panobinostat included pneumonia (18%), thrombocytopenia (11%), fatigue (6%), and sepsis (6%). Adverse reactions led to discontinuation of panobinostat in 36% of patients treated in the clinical trial. The most common adverse reactions resulting in treatment discontinuation were diarrhea, fatigue, and pneumonia.

Postmarketing adverse effects identified for pomalidomide include severe cutaneous reactions and elevated liver enzymes. Additional postmarketing adverse reactions for pomalidomide include hypothyroidism, hyperthyroidism, anaphylaxis, solid organ transplant rejection, and others.

SJS has also been reported as a postmarketing adverse effect of ponatinib.

Ruxolitinib is associated with thrombocytopenia (all grades) 69.7% of ruxolitinib (Jakafi) patients versus 30.5% of placebo. Neutropenia (all grades) occurred in 18.7% of ruxolitinib (Jakafi) patients versus 4% of placebo. Weight gain was reported in 7.1% of ruxolitinib (Jakafi) versus 1.3% of placebo patients (all grades).

The most common adverse effects, occurring in ≥ 20% of MM patients treated with selinexor in combination with dexamethasone, not listed above, were thrombocytopenia, fatigue, decreased appetite, decreased weight, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection. Other adverse reactions, occurring in ≥ 10% of MM patients treated with selinexor in combination with dexamethasone were cough, mental status changes,

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pyrexia, hyperglycemia, dizziness, insomnia, lymphopenia, dehydration, hypercreatininemia, pneumonia, epistaxis, hypokalemia, dysgeusia, and blurred vision. In patients with DLBCL, the most common adverse reactions occurring in ≥ 20% of patients and not listed in the table above were fatigue, appetite decrease, weight decrease, constipation, vomiting, and pyrexia; grade 3 to 4 laboratory abnormalities occurring in ≥ 15% of patients were thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia.

Vorinostat is commonly associated with taste disorders.

SJS, DRESS, pulmonary hypertension, and viral infections associated with thalidomide have all been reported in postmarketing experience.

Serious adverse reactions were reported in 44% of patients who received venetoclax in clinical trials. Those serious adverse reactions occurring in 2% or greater were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia, anemia, and tumor lysis syndrome.

The most common adverse reactions to tretinoin include headache, fever, skin/mucous membrane dryness, bone pain, nausea/vomiting, rash, mucositis, pruritus, increased sweating, visual disturbances, ocular disorders, alopecia, skin changes, changed visual acuity, weakness, and fatigue. There is a risk of evolving leukocytosis as well as RA-APL syndrome, which is characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, hepatic, renal, and multi-organ failure. The syndrome usually occurs during the first month of treatment with some cases reported following the first dose of tretinoin.

The most common adverse effects (≥ 20%) reported with zanubrutinib in clinical trials were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (23%), diarrhea (20%), and cough (20%). Other common adverse effects occurring in > 10% of patients included musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

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Pediatrics

Safe and effective use of the following agents in patients < 18 years of age has not been established: acalabrutinib (Calquence), bosutinib (Bosulif), chlorambucil (Leukeran), duvelisib (Copiktra), enasidenib (Idhifa), fedratinib (Inrebic), gilteritinib (Xospata), glasdegib (Daurismo), hydroxyurea, ibrutinib (Imbruvica), idelalisib (Zydelig), ivosidenib (Tibsovo), ixazomib (Ninlaro), lenalidomide (Revlimid), melphalan, midostaurin (Rydapt), panobinostat (Farydak), pomalidomide (Pomalyst), ponatinib (Iclusig), selinexor (Xpovio), venetoclax (Venclexta), vorinostat (Zolinza), and zanubrutinib (Brukinsa).

Safety and effectiveness of thalidomide have not been established in children < 12 years old.

Imatinib (Gleevec) is FDA-approved in newly diagnosed pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph +CML) in chronic phase, as well as pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphocytic leukemia (Ph+ALL) at a dose of 340 mg/m^2/day (not to exceed 600 mg). There are no data in children under 1 year of age. Growth retardation in children and pre-adolescents receiving imatinib has been reported. Therefore,

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

Mercaptopurine is an essential part of the maintenance treatment of pediatric ALL; maintenance doses vary from patient to patient and sometimes between protocols. The usual daily maintenance dose of mercaptopurine is 1.5 to 2.5 mg/kg/day as a single dose given in conjunction with other agents (most frequently methotrexate) for remission maintenance. Cases of symptomatic hypoglycemia have been reported in children with ALL receiving mercaptopurine. Reported cases were in children under the age of 6 or with a low body mass index.

Dasatinib (Sprycel) is FDA-approved in pediatric patients with chronic phase Ph+ CML and Ph+ ALL with the starting dose based on body weight (40 mg to 100 mg) given once daily. The dose should be recalculated every 3 months based on body weight changes or as needed. For pediatric patients with CML, additional dose escalation recommendations up to the maximum dose of 120 mg per day are provided in the prescribing information. For Ph+ ALL, begin therapy on or before day 15 of induction chemotherapy once diagnosis is confirmed and continue for 2 years. The safety profile in pediatric patients was comparable to adults. Pediatric patients should be monitored for bone growth and development. Five (5.2%) of the pediatric patients experienced adverse effects on bone growth, including delayed fusion of epiphyses, osteopenia, growth retardation, and gynecomastia.

Nilotinib (Tasigna) is FDA-approved in pediatric patients ≥ 1 year of age for new diagnosed Ph+ CML-CP and in Ph+ CML-CP with resistance or intolerance to tyrosine-kinase inhibitor therapy. The clinical trials included patients ≥ 2 years of age. Inclusion of patients to ≥ 1 year of age was based on efficacy in the 2 to 6 year old pediatric patients. All pediatric patients were treated with nilotinib at a dose of 230 mg/m^2 twice daily (maximum, 400 mg). The safety profile was similar to adverse reactions observed in adult patients with the exceptions of increased hyperbilirubinemia (grade 2 to 4: 13%) and transaminase elevation (AST grade 3 to 4: 1%; ALT grade 3 to 4: 9%). In pediatric patients, growth retardation has occurred in patients with Ph+ CML-CP receiving nilotinib.

Safety and effectiveness of ruxolitinib (Jakafi) for acute GVHD have been established in pediatric patients ≥ 12 years of age based extrapolated evidence in adults as well as pharmacokinetic studies.

There are limited clinical data on the pediatric use of tretinoin and safety and effectiveness in pediatric patients below the age of 1 year have not been established. Increased caution is recommended in the treatment of pediatric patients and dose reduction may be considered for pediatric patients experiencing serious or intolerable toxicity; however, the efficacy and safety of tretinoin at doses lower than 45 mg/m^2/day have not been established.

Pregnancy

The labels for thalidomide (Thalomid), lenalidomide (Revlimid), and pomalidomide (Pomalyst) have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and contain a contraindication, boxed warning, and REMS program due to the risk of embryo-fetal toxicity.

Thalidomide, lenalidomide, pomalidomide: Lenalidomide and pomalidomide are thalidomide analogues. Thalidomide is a human teratogen inducing a high frequency of severe and life-threatening birth defects such as phocomelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bines, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent

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external auditory canals), facial palsy, eye abnormalities (enophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants. Sexually active females of reproductive potential should use 2 methods of reliable birth control simultaneously: 1 highly effective form of contraception-tubal ligation, intrauterine device (IUD), hormonal or partner's vasectomy, and 1 additional effective contraceptive method – male condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with thalidomide and must be continued for 4 weeks following discontinuation of thalidomide. Males receiving thalidomide must always use a condom during any sexual contact with females of reproductive potential while taking thalidomide and for up to 28 days after discontinuing thalidomide even if they have undergone a successful vasectomy.

Busulfan (Myleran), chlorambucil (Leukeran), dasatinib (Sprycel), hydroxyurea, imatinib (Gleevec), melphalan, ponatinib (Iclusig), procarbazine (Matulane), thioguanine (Tabloid), and tretinoin may cause fetal harm when administered to pregnant women and are classified as Pregnancy Category D. Women should be advised not to become pregnant while on therapy with any of these agents. Mercaptopurine (Purixan), previously classified as Pregnancy Category D, has had its labeling updated to comply with the PLLR; it states mercaptopurine may cause fetal harm if administered during pregnancy and increases the risk for miscarriage and stillbirth. Females of reproductive potential should use effective contraception during therapy with mercaptopurine and for 6 months following the final dose, and males with female partners of reproductive potential should use effective contraception during therapy and for 3 months following the final dose.

Acalabrutinib (Calquence), bosutinib (Bosulif), duvelisib (Copiktra), enasidenib (Idhifa), gilteritinib (Xospata), glasdegib (Daurismo), ibrutinib (Imbruvica), ivosidenib (Tibsovo), nilotinib (Tasigna), selinexor (Xpovio), vorinostat (Zolinza), and zanubrutinib (Brukinsa) also may cause fetal harm when administered to a pregnant woman; however, their labeling includes descriptive text rather than an assigned Pregnancy Category due to the Pregnancy and Lactation Labeling Rule (PLLR). Idelalisib's labeling was updated in compliance with the PLLR and now states idelalisib may cause fetal harm when administered to a pregnant woman based on results of animal studies (there are no available data in humans). Ruxolitinib (Jakafi) labeling was also updated for compliance with PLLR and contains summary data of adverse developmental outcomes in animals. There are no studies with use of ruxolitinib in pregnant women to determine risk. Likewise, there are no available data on the use of fedratinib (Inrebic) in pregnant women to inform of any drug-associated risks to the mother or fetus.

Female patients of reproductive potential should use effective contraception during treatment with acalabrutinib and for a minimum of 1 week following the last dose due to the potential for embryo-fetal harm and dystocia when administered to pregnant women. Females of reproductive potential being treated with venetoclax, dasatinib, or glasdegib should use effective contraception measures during treatment and for at least 30 days after the final dose. Likewise, females of reproductive potential being treated with duvelisib or ibrutinib should avoid pregnancy (e.g., use effective contraception) during treatment and for up to 1 month after ending treatment. Females of reproductive potential being treated with enasidenib should avoid pregnancy during treatment and for at least 2 months after ending treatment. Men should avoid fathering a child (e.g., use effective contraception) while receiving duvelisib or ibrutinib and for 1 month following the last dose of treatment. Men should avoid fathering a child while receiving enasidenib and for at least 2 months following the last dose of treatment. Females of reproductive potential should use effective

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contraception during treatment and for at least 2 weeks after the last dose of bosutinib. Females of reproductive potential being treated with ponatinib should use effective contraception during treatment and for 3 weeks after the last dose. Imatinib can cause fetal harm when administered to a pregnant woman based on human and animal data. There have been postmarketing reports of spontaneous abortions and congenital anomalies from women who have been exposed to imatinib during pregnancy. Females of reproductive receiving imatinib should use effective contraception during treatment and for 14 days after stopping imatinib treatment. Females of reproductive potential should utilize effective contraception during treatment with gilteritinib and for a minimum of 6 months following the final dose; likewise, males of reproductive potential should use effective contraception during treatment with gilteritinib and for a minimum of 4 months following the final dose. Males with female partners of reproductive potential should utilize effective contraception during treatment with glasdegib and for a minimum of 30 days after the final dose. Females of reproductive potential as well as male patients with a female partner of reproductive potential should use effective contraception while taking selinexor and for 1 week following the last dose. Females of reproductive potential should utilize effective contraception while taking vorinostat and for a minimum of 6 months following the final dose; males with female partners of reproductive potential should use contraception during therapy and for a minimum of 3 months following the final dose. Similar to selinexor, females of reproductive potential and males with female partners of reproductive potential should use effective contraception while receiving zanubrutinib and for at least 1 week after the last dose.

Ixazomib (Ninlaro) may cause fetal harm when administered to a pregnant woman. There are no human data available; ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Females of reproductive potential must use effective contraception during treatment with ixazomib and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception.

Panobinostat (Farydak) can cause fetal harm when administered to pregnant women. Panobinostat has been found to be teratogenic in rats and rabbits. Females of reproductive potential being treated with panobinostat should use effective contraception while taking panobinostat and for at least 3 months after the last dose of panobinostat. Sexually active men receiving panobinostat should use condoms while on treatment and for at least 6 months after their last dose of panobinostat.

Venetoclax (Venclexta) may cause fetal harm although there are no available human data; in animal studies venetoclax was associated with increased post-implantation loss and decreased fetal body weight at exposures approximately 1.2 times the human exposure at the recommended dose. No teratogenicity was observed in the animals exposed to venetoclax. Based on animal findings, male fertility may be compromised by treatment with venetoclax.

There are no available data on midostaurin (Rydapt) use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage; however, midostaurin may cause fetal harm when administered to a pregnant woman based on mechanism of action and findings in animal reproduction studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with midostaurin and for 4 months after the last dose. Males with female sexual partners of reproductive potential should use effective contraception during midostaurin treatment and for at least 4 months after stopping treatment. Based on findings in animals, midostaurin may impair fertility in females and males. It is not

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known whether these effects on fertility are reversible. Females exposed to midostaurin during pregnancy directly or through male partner taking midostaurin should contact the manufacturer.

Renal Impairment

No clinical studies were conducted with acalabrutinib (Calquence), dasatinib (Sprycel), melphalan, nilotinib (Tasigna), ponatinib (Iclusig), thalidomide, chlorambucil (Leukeran), or vorinostat (Zolinza) in patients with decreased renal function. Renal impairment is not expected to influence drug exposure, and no dosage adjustment of these products is recommended in patients with renal impairment.

Duvelisib (Copiktra) exposure was not found to be significantly altered in patients with a creatinine clearance (CrCl) between 23 to 80 mL/min; no dose adjustments are recommended for renal impairment.

The dose of fedratinib (Inrebic) should be decreased in patients with severe renal impairment (CrCl, 15 to 29 mL/min. No dose adjustment is required in those with mild to moderate renal impairment; however, those with moderate renal impairment require more intense safety monitoring.

Gilteritinib (Xospata) pharmacokinetics were not found to be significantly altered in patients with a CrCl between 30 to 80 mL/min; the impact of a CrCl ≤ 29 mL/min has not been evaluated.

Ibrutinib (Imbruvica) exposure is not altered in patients with CrCl greater than 25 mL/min. There are no data in patients with severe renal impairment (CrCl, < 25 mL/min) or in patients undergoing dialysis.

Ivosidenib (Tibsovo) has not been evaluated in patients with severe renal impairment; the risks and benefits should be assessed prior to initiating therapy in these patients. No modification is needed for those with mild to moderate renal impairment (eGFR > 30 mL/min/1.73 m^2).

Selinexor (Xpovio) pharmacokinetics were not found to be significantly altered in patients with a CrCl between 15 to 89 mL/min; the impact of end-stage renal disease (CrCl <15 mL/min) or hemodialysis has not been evaluated.

No dose adjustment of venetoclax (Venclexta) is needed for patients with mild or moderate renal impairment (CrCl, ≥ 30 mL/min). A recommended dose has not been determined for patients with severe renal impairment or patients on dialysis.

No dose adjustment of idelalisib (Zydelig) is necessary for patients with CrCl ≥ 15 mL/min.

The plasma exposure of panobinostat (Farydak) was not impacted in patients with mild to severe renal impairment (CrCl, < 30 mL/min). However, panobinostat (Farydak) has not been studied in patients with end stage renal disease (ESRD) or patients receiving dialysis.

Agents with Specified Renal Dose Modifications

For imatinib (Gleevec), patients with renal impairment (CrCl, 20 to 39 mL/min) should receive a 50% decrease in the recommended starting dose. Doses may be increased as tolerated with a maximum recommended dose of 400 mg daily. Doses exceeding 600 mg are not recommended for patients with a CrCl 40 to 59 mL/min. Imatinib should be used with caution in patients with severe renal impairment; a dose of 100 mg per day was tolerated by 2 patients with severe renal impairment.

The dose of bosutinib (Bosulif) should be reduced to 400 mg daily in patients with a CrCl of 30 to 50 mL/min and to 300 mg in patients with CrCl less than 30 mL/min at baseline.

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The dose of fedratinib (Inrebic) should be decreased to 200 mg once daily in patients with severe renal impairment (CrCl, 15 to 29 mL/min).

The exposure of ruxolitinib and its active metabolites increases in moderate and renal impairment and in ESRD. Dose adjustments are recommended. Reduce ruxolitinib (Jakafi) starting dose to 10 mg twice daily for the treatment of myelofibrosis in patients with moderate (CrCl, 30 to 59 mL/min) or severe renal impairment (CrCl, 15 to 29 mL/min) and a platelet count between 100 x 10^9/L and 150 x 10^9/L. The starting dose for the treatment of myelofibrosis should be reduced to 5 mg daily in patients with moderate (CrCl, 30 to 59 mL/min) or severe renal impairment (CrCl, 15 to 29 mL/min) and a platelet count between 50 x 10^9/L to 100 x 10^9/L. Avoid ruxolitinib use in patients with myelofibrosis not requiring dialysis with moderate or severe renal impairment and a platelet count < 50 x 10^9/L. The recommended starting dose for myelofibrosis patients with ESRD on dialysis is 15 mg once after a dialysis session for patients with a platelet count between 100 x 10^9/L and 200 x 10^9/L or 20 mg for patients with a platelet count greater than 100 x 10^9/L.

The dose of ruxolitinib for the treatment of polycythemia vera in patients with moderate (CrCl, 30 to 59 mL/min) or severe renal impairment (CrCl, 15 to 29 mL/min) should be reduced to 5 mg twice daily. The recommended starting dose for ruxolitinib in the treatment of polycythemia vera patients with ESRD on dialysis is 10 mg daily.

Reduce the starting dose of ixazomib (Ninlaro) in patients with severe renal impairment or ESRD requiring dialysis. Ixazomib is not dialyzable and, therefore, can be administered without regard to the timing of dialysis.

The recommended starting dose of pomalidomide is 3 mg daily for MM patients with severe renal impairment undergoing dialysis. For KS patients with severe renal impairment who are receiving dialysis, the dosage should be decreased to 4 mg daily. Pomalidomide should be taken after the completion of the dialysis procedure on hemodialysis days.

The starting dose of lenalidomide in patients with moderate renal impairment (CrCl, 30 to 60 mL/min) should be reduced to 10 mg daily for the treatment of mantle cell lymphoma (MCL), multiple myeloma (MM), follicular lymphoma (FL), and marginal zone lymphoma (MZL), and to 5 mg daily for the treatment of myelodysplastic syndrome (MDS) or maintenance following auto-HSCT. For FL or MZL patients with a CrCl 30 to 60 mL/min, following 2 cycles, the dose can be increased to 15 mg based on patient tolerability. In patients with severe renal impairment (CrCl, < 30 mL/min) not receiving dialysis, the dose of lenalidomide should be reduced to 15 mg every 48 hours for the treatment of MCL or MM, 5 mg once daily for FL or MZL, and to 2.5 mg once day for the treatment of MDS or maintenance following auto-HSCT. Patients receiving dialysis should be given lenalidomide 5 mg once daily for the treatment of MCL, MM, FL, or MZL; the dose should be administered after dialysis on the days the patient is being dialyzed, and 2.5 mg once daily in the same fashion for the treatment of MDS or maintenance therapy following auto-HSCT in patients receiving dialysis.

Agents Used with Caution but without Specific Renal Dosing Recommendations

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment.

Glasdegib (Daurismo) pharmacokinetics were not found to be significantly altered in patients with an estimated glomerular filtration rate (eGFR) between 15 to 89 mL/min; therefore, no dosage adjustment is required for these patients. However, patients with severe renal impairment (eGFR, 15

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to 29 mL/min) should be monitored for an increased potential for adverse reactions (e.g., QTc prolongation) due to increased drug levels.

Dose adjustments of zanubrutinib (Brukinsa) are not required in mild to moderate renal impairment (CrCl, ≥ 30 mL/min); however, patients with severe renal impairment (CrCl, < 30 mL/min) or on dialysis should be monitored for adverse effects.

Hepatic Impairment

Agents with Specific Hepatic Dosing Adjustment Recommendations

Reduce dose of bosutinib (Bosulif) to 200 mg daily for mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment.

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

The exposure of ruxolitinib and its active metabolites increases in any severity of hepatic impairment. Dose adjustments are recommended. Reduce ruxolitinib (Jakafi) starting dose for the treatment of myelofibrosis to 10 mg twice daily for patients with any degree of hepatic impairment (Child-Pugh A, B, or C) and a platelet count between 100 x 10^9/L and 150 x 10^9/L and to 5 mg daily in these same patients who have a platelet count of 50 x 10^9/L to < 100 x 10^9/L. Avoid ruxolitinib in patients with hepatic impairment with platelet counts < 50 x 10^9/L. Monitor blood counts more closely and consider 5 mg once daily for those using ruxolitinib for stage 3 or 4 liver GVHD. The dose of ruxolitinib for the treatment of polycythemia vera should be reduced to 5 mg twice daily in patients with any degree of hepatic impairment (Child-Pugh A, B, or C).

Vorinostat (Zolinza) starting dose should be reduced to 300 mg once daily with food in patients with mild to moderate hepatic impairment (bilirubin 1 to 3 times the upper limit of normal [ULN] or AST > ULN). There is insufficient evidence to recommend a starting dose for patients with severe hepatic impairment (bilirubin > 3 times the ULN).

The starting dose of ponatinib (Iclusig) is 30 mg once daily in patients with any degree of hepatic impairment (Child-Pugh A, B, or C).

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

Patients with mild or moderate hepatic impairment (bilirubin greater than 1 to 1.5 times the ULN) had an increased AUC of panobinostat (Farydak) of 43% and 105%, respectively. The starting dose of panobinostat should be reduced in patients with mild to moderate hepatic impairment. The use of panobinostat should be avoided in patients with severe hepatic impairment.

Patients with mild hepatic impairment (Child-Pugh A) receiving ibrutinib (Imbruvica) should be dose reduced to 140 mg once daily. Patients with moderate hepatic impairment (Child-Pugh B) receiving ibrutinib should be dose reduced to 70 mg once daily. The use of ibrutinib in patients with severe hepatic impairment (Child-Pugh class C) should be avoided.

For patients with mild to moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose of pomalidomide is 3 mg daily. For patients with severe hepatic impairment (Child-Pugh

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class C), the recommended dose is 2 mg daily. For KS patients with any degree of hepatic impairment (Child-Pugh A, B, or C), the recommended dosage should be decreased to 3 mg daily.

Dose adjustments of zanubrutinib are not required in mild to moderate hepatic impairment. Safety has not been assessed in patients with severe hepatic impairment; the recommended dose in patients with severe hepatic impairment is 80 mg orally twice daily. All patients with hepatic impairment should be closely monitored for adverse effects.

Agents to Be Used with Caution in Some Stages of Hepatic Dysfunction

Consideration should be given to reducing the dosage of mercaptopurine in patients with impaired hepatic function.

Patients with baseline hepatic impairment should be monitored for signs of idelalisib (Zydelig) toxicity and dose modifications for adverse reactions may be necessary.

Avoid the use of pomalidomide in patients with serum bilirubin greater than 2 mg/dL and AST/ALT greater than 3 times the ULN.

Reduce the starting dose of ixazomib (Ninlaro) in patients with moderate or severe hepatic impairment.

Although no dose adjustment is recommended in patients with mild or moderate hepatic impairment based on the results of the population pharmacokinetic analysis, a trend for increased adverse events was observed in patients receiving venetoclax (Venclexta) with moderate hepatic impairment; these patients should be monitored more closely for signs of toxicity during the initiation and ramp-up phase of dosing with venetoclax (Venclexta). The once daily dose of venetoclax should be decreased by 50% in patients with severe hepatic impairment (Child-Pugh class C); monitor carefully for toxicity.

Agents Lacking Study Data to Support Use in Various Stages of Hepatic Dysfunction

Acalabrutinib (Calquence) has not been evaluated in patients with moderate or severe hepatic impairment, and administration should be avoided in patients with severe hepatic impairment.

Safety and effectiveness of melphalan, thalidomide, chlorambucil, and lenalidomide have not been determined in hepatic impairment.

Fedratinib (Inrebic) has not been studied in patients with severe hepatic impairment; its use is not recommended in this population.

Gilteritinib (Xospata) pharmacokinetics were not found to be significantly altered in patients with mild or moderate hepatic impairment (Child-Pugh class A or B); the impact of severe hepatic impairment (Child-Pugh class C) has not been evaluated.

Glasdegib (Daurismo) pharmacokinetics were not found to be significantly altered in patients with mild hepatic impairment; the impact of moderate to severe hepatic dysfunction has not been evaluated.

No dose adjustments are necessary in patients with mild to moderate hepatic impairment taking hydroxyurea, as it has not been studied in patients with severe hepatic impairment.

Ivosidenib (Tibsovo) has not been evaluated in patients with severe hepatic impairment; the risks and benefits should be assessed prior to initiating therapy in these patients. No modification is needed in patients with mild to moderate hepatic impairment (Child Pugh classes A and B).

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Selinexor (Xpovio) pharmacokinetics were not found to be significantly altered in patients with mild hepatic impairment; the impact of moderate and severe hepatic dysfunction has not been evaluated.

Agents with No Dosage Adjustments Required in Hepatic Dysfunction

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

Duvelisib (Copiktra) exposure was not found to be significantly altered in patients with hepatic impairment (Child-Pugh class A, B, and C); no dose adjustments are recommended for patients with hepatic impairment at baseline.

Geriatrics

Patients treated with acalabrutinib (Calquence) in clinical studies of CLL or MCL who were ≥ 65 years of age exhibited a higher likelihood of ≥ grade 3 adverse reactions (59% versus 45%, respectively) and serious adverse reactions (39% versus 25%, respectively) compared with patients < 65 years; no differences in efficacy were seen between elderly patients and younger patients.

No difference in efficacy or safety between older and younger patients was observed with chlorambucil (Leukeran), duvelisib (Copiktra), enasidenib (Idhifa), fedratinib (Inrebic), gilteritinib (Xospata), ivosidenib (Tibsovo), ixazomib (Ninlaro), melphalan, midostaurin (Rydapt; for the treatment of advanced systemic mastocytosis [ASM]), nilotinib (Tasigna), ruxolitinib (Jakafi), tretinoin, venetoclax (Venclexta), vorinostat (Zolinza), or zanubrutinib (Brukinsa).

Elderly patients receiving hydroxyurea, and melphalan should be carefully monitored for adverse effects.

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

Subgroup analysis of the German CML-Study IV indicated that patients aged 65 and older who were randomized to 800 mg/day of imatinib for newly diagnosed CML-CP achieved major molecular remission as fast as younger patients in contrast to older patients who were randomized to imatinib 400 mg/day who achieved remissions much later than younger patients.[265]

No overall differences in effectiveness were seen in patients 65 years or older treated with ibrutinib (Imbruvica); however, cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis), and GI events (diarrhea and dehydration) occurred more frequently among elderly patients. Grade 3 or higher adverse events also occurred more frequently among elderly patients.

No major differences in effectiveness were observed in patients aged 65 and older who received idelalisib (Zydelig). Older patients did have a higher incidence of discontinuation due to an adverse reaction, higher incidence of serious adverse reactions, and a higher incidence of death compared to younger patients.

The use of ponatinib (Iclusig) in patients with CP-CML ≥ 65 years of age yielded a lower major cytogenetic response rate (38%) as compared with patients < 65 years of age (64%). In patients with AP-CML, BP-CML and Ph+ALL, patients of age ≥ 65 years had a higher major hematologic response rate

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(47%) as compared to patients < 65 years of age (40%). Patients of age ≥ 65 years may be more likely to experience adverse reactions including reduced platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Patients ≥ 65 receiving thalidomide had higher incidences of atrial fibrillation, constipation, fatigue, nausea, hypokalemia, DVT, hyperglycemia, PE, and asthenia compared to patients < 65 years old.

Multiple myeloma patients > 65 years receiving lenalidomide were more likely to experience DVT, PE, atrial fibrillation, and renal failure compared to patients ≤ 65 years of age. Adverse effects with lenalidomide generally were higher in patients treated for FL or MZL.

There were no major differences in effectiveness observed between patients ≥ 65 years who were treated with pomalidomide compared to younger patients but the older cohort of patients did experience pneumonia more frequently than younger patients. No dosage adjustment is required for pomalidomide based on age.

No major differences in effectiveness were observed in patients ≥ 65 years of age who received selinexor (Xpovio) compared to younger patients; however, patients ≥75 years of age had a greater likelihood of discontinuing therapy due to an adverse event and experienced a higher rate of serious adverse events as well as a higher rate of fatal adverse events.

Midostaurin (Rydapt) clinical studies in AML did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently to midostaurin compared to younger subjects.

The majority of patients evaluated in clinical studies assessing glasdegib (Daurismo) in combination with low-dose cytarabine were ≥ 65 years of age; there was not an adequate number of younger patients to determine if differences in the safety profile existed.

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DOSAGES[266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293]

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
acalabrutinib (Calquence)	--	--	Monotherapy or in combination with obinutuzumab: 100 mg every 12 hours until disease progression or unacceptable toxicity	--	--	MCL: 100 mg every 12 hours until disease progression or unacceptable toxicity	Swallow capsules whole with water; do not open, break, or chew capsules In combination with obinutuzumab: start at cycle 1 of 28-day cycle with obinutuzumab starting at cycle 2 for total of 6 cycles; administer before obinutuzumab when given on the same day	100 mg capsules
bosutinib (Bosulif)	Newly diagnosed CP Ph+ CML: 400 mg once daily Resistant or intolerant CP, AP, BP Ph+ CML: 500 mg once daily May be increased to 600 mg daily if CHR is not reached by week 8 or a CcyR by week 12	--	--	--	--	--	Swallow tablets whole; do not crush or cut; take with food	100 mg, 400 mg, 500 mg tablets
busulfan (Myleran)	Remission induction: 60 mcg/kg or 1.8 mg/m^2: usual dose between 4 mg and 8 mg orally daily	--	--	--	--	--	--	2 mg tablets
chlorambucil (Leukeran)	--	--	0.1 to 0.2 mg/kg once daily for 3 to 6 weeks	--	--	HD: 0.1 to 0.2 mg/kg once daily for 3 to 6 weeks	Take entire daily dose at 1 time	2 mg tablets

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
dasatinib (Sprycel)	CP CML: 100 mg to 140 mg daily AP CML: 140 mg to 180 mg daily BP CML: 140 mg daily Pediatric patients with CP Ph+ CML: weight based, starting dose not to exceed 100 mg, may increase up to 120 mg daily	Ph+ ALL: 140 mg to 180 mg daily Pediatric patients with Ph+ ALL: weight based, not to exceed 100 mg	--	--	--	--	Swallow tablets whole; do not crush or cut; take with or without food either in the morning or in the evening	20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg tablets
duvelisib (Copiktra)	--	--	25 mg twice daily	--	--	FL: 25 mg twice daily	Swallow capsules whole; do not open, break, or chew; take with or without food	15 mg, 25 mg capsule
enasidenib (Idhifa)	--	--	--	--	--	AML: 100 mg once daily	Swallow tablets whole; do not crush or split; take with or without food at the same time each day	50 mg, 100 mg tablets

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
fedratinib (Inrebic)	--	--	--	--	--	Myelofibrosis: 400 mg once daily in patients with baseline platelet counts ≥ 50 x 10^9/L	Can be administered with or without food; a high-fat meal may reduce GI toxicity	100 mg capsule
gilteritinib (Xospata)	--	--	--	--	--	AML: 120 mg once daily Treat for a minimum of 6 months for clinical response	Swallow tablets whole; do not break or crush; take with or without food at the same time each day	40 mg tablet
glasdegib (Daurismo)	--	--	--	--	--	AML: 100 mg once daily of a 28-day cycle with cytarabine 20 mg SC twice daily on days 1 through 10 of each cycle Treat for a minimum of 6 cycles to allow for clinical response	Do not split or crush; take with or without food at the same time each day	25 mg, 100 mg tablet
hydroxyurea (Hydrea)	Individualize dose based on patient risk factors, response to treatment and current clinical practice standards; base all dosing on body weight, either actual or ideal weight, whichever is less (see prescribing information for details)	--	--	--	--	Solid tumors: Individualize dose based on patient risk factors, response to treatment and current clinical practice standards; base all dosing on body weight, either actual or ideal weight, whichever is less (see prescribing information for details)	Prophylactic administration of folic acid is recommended; hydroxyurea capsules should not be opened	500 mg capsules
ibrutinib (Imbruvica)	--	--	420 mg once daily	MCL: 560 mg once daily MZL: 560 mg once daily	--	WM: 420 mg once daily cGVHD: 420 mg once daily	Swallow capsules whole with water; do not open, break, or chew capsules	70 mg, 140 mg capsules 140 mg, 280 mg, 420 mg, 560 mg tablets

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
idelalisib (Zydelig)	--	--	150 mg twice daily	FL: 150 mg twice daily	--	--	Take with or without food; tablets should be swallowed whole	100 mg, 150 mg tablets
imatinib (Gleevec)	CP CML: 400 mg to 600 mg daily AP CML: 600 mg to 800 mg daily BP CML: 600 mg to 800 mg daily Pediatric patients with Ph+ CML CP: 340 mg/m^2/day (not to exceed 600 mg/day)	Ph+ ALL in adults: 600 mg daily Ph+ ALL in children: 340 mg/m^2/day (not to exceed 600 mg/day)	--	--	--	MDS/MPD: 400 mg daily ASM: 100 mg to 400 mg daily HES/CEL: 100 mg to 400 mg daily DFSP: 800 mg daily GIST: 400 to 800 mg daily	Take with a meal and a large glass of water; Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice daily; in children, imatinib (Gleevec) can be given as a once-daily dose in CML and Ph+ ALL, alternatively in children with CML, the daily dose may be split into 2 doses; For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice; administer suspension immediately after disintegration of tablet(s)	100 mg, 400 mg tablets
ivosidenib (Tibsovo)	--	--	--	--	--	IDH1 mutated AML: 500 mg once daily; treat for a minimum of 6 months to allow time for clinical response	May be taken with or without food but should not be administered with a high-fat meal; do not crush or split tablets	250 mg tablets

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
ixazomib (Ninlaro)	--	--	--	--	4 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle	--	Take at least 1 hour before or at least 2 hours after food; capsule should be swallowed whole with water; do not crush, chew or open capsule; ixazomib is used as part of a regimen that also includes lenalidomide and dexamethasone; consider antiviral prophylaxis to decrease the risk of herpes zoster reactivation	2.3 mg, 3 mg, 4 mg capsules
lenalidomide (Revlimid)	--	--	--	FL and MZL: 20 mg once daily on days 1-21 of a 28-day cycle for up to 12 cycles	MM: 25 mg once daily on days 1-21 of repeated 28-day cycles MM Maintenance Therapy following Auto-HSCT: 10 mg once daily continuously (Days 1-28 of repeated 28 day cycles); after 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated	MCL: 25 mg/day on days 1-21 of repeated 28-day cycles MDS: 10 mg daily	MM: Administer with dexamethasone per recommended dosing schedule; concomitant dexamethasone is not administered with lenalidomide for maintenance therapy following Auto-HSCT	2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg capsules
melphalan (Alkeran)	--	--	--	--	6 mg (3 tablets) daily	Ovarian CA: 0.2 mg/kg daily x 5 days	--	2 mg tablet

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
mercaptopurine (generic tablet, Purixan)	--	--	--	--	--	Maintenance dose in ALL: 1.5 to 2.5 mg/kg/day (50 to 75 $mg/m^2/day$) as a single dose; doses are adjusted based on patient response and toxicity	Procedures for proper handling and disposal of anticancer drugs should be considered; shake suspension vigorously for at least 30 seconds before administration	50 mg tablets (generic only), 20 mg/mL oral suspension (Purixan; brand only) dispensed with 2 oral dispensing syringes (1 each 1 mL and 5 mL oral syringes)
midostaurin (Rydapt)	--	--	--	--	--	FLT3 mutation positive AML: 50 mg orally twice daily on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with high-dose cytarabine ASM, SM-AHN, MCL-100 mg twice daily with food continued until disease progression or unacceptable toxicity	Doses should be taken twice daily with food at approximately 12 hour intervals; do not open or crush midostaurin capsules	25 mg capsules

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
nilotinib (Tasigna)	Newly diagnosed CP-CML: 300 mg twice daily Resistant or Intolerant: CML-CP: 400 mg twice daily Pediatric patients with CP Ph+ CML: 230 mg/m^2 twice daily; (round to nearest 50 mg and do not exceed single dose of 400 mg) CML-AP: 400 mg twice daily	--	--	--	--	--	Take on an empty stomach; no food for at least 2 hours before or at least 1 hour after dose; swallow capsules whole with water For patients unable to swallow capsules, the contents of each capsule may be dispersed in 1 teaspoon of applesauce and the mixture should be taken immediately	50 mg, 150 mg, 200 mg capsules
panobinostat (Farydak)	--	--	--	--	20 mg every other day for 3 doses per week in weeks 1 and 2 of each 21-day cycle for up to 8 cycles; the total duration of treatment may be extended to 16 weeks in appropriate patients	--	Take with or without food; capsules should be swallowed whole with a cup of water; do not open, crush, or chew capsules; panobinostat is administered in combination with bortezomib and dexamethasone	10 mg, 15 mg, 20 mg capsules

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Dosages (continued)

Drug	Diagnosis						Administration Comments	Dosage Forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
pomalidomide (Pomalyst)	--	--	--	--	4 mg once daily on days 1-21 of repeated 28-day cycles	KS: 5 mg once daily on days 1 to 21 of each 28-day cycle	Do not break, chew or open capsules; may be taken with or without food (at least 2 hours before or 2 hours after a meal) MM: give in combination with dexamethasone, until disease progression KS: until disease progression or unacceptable toxicity; continue HAART as HIV treatment in patients with AIDS-related KS	1 mg, 2 mg, 3 mg, 4 mg capsules
ponatinib (Iclusig)	Start dosing with 45 mg once daily; consider reducing the dose for CP-CML and AP-CML patients who have achieved a major cytogenetic response; consider discontinuing if response has not occurred by 3 months	Ph+ ALL: Start dosing with 45 mg once daily	--	--	--	--	May be taken with or without food; tablets should be swallowed whole, do not crush or dissolve tablets	15 mg, 45 mg tablets
procarbazine (Matulane)	--	--	--	--	--	HD: as part of a combination chemotherapy regimen (MOPP): 100 mg/m^2 daily for 14 days; all dosages are based on actual weight or lean body mass if patient is obese	--	50 mg capsules

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Dosages (continued)

Drug	Diagnosis						Administration comments	Dosage forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
ruxolitinib (Jakafi)	--	--	--	--	--	Myelofibrosis: Initial dosing varies from 5 mg twice daily to 20 mg twice daily based on initial platelet count Polycythemia Vera: 10 mg twice daily aGVHD: 5 mg twice daily, increase to 10 mg twice daily after at least 3 days depending on platelets and ANC; consider tapering after 6 months of treatment for certain patients	There are extemporaneous compounding instructions for administration through a nasogastric tube	5 mg, 10 mg, 15 mg, 20 mg, 25 mg tablets
selinexor (Xpovio)	--	--	--	DLBCL: 60 mg on days 1 and 3 weekly	80 mg on days 1 and 3 each week with dexamethasone 20 mg	--	Swallow tablets whole with water; do not break, chew, crush, or divide tablets; take at the same time of day; continue until disease progression or unacceptable toxicity	20 mg tablet (blister packs of weekly doses: 80 mg twice weekly or 60 mg, 80 mg, or 100 mg once weekly)
thalidomide (Thalomid)	--	--	--	--	200 mg once daily	ENL: 100 mg to 300 mg once daily; up to 400 mg/day for severe cutaneous ENL	MM: take in combination with dexamethasone in 28-day treatment cycles Take with water, preferably at bedtime and at least 1 hour after the evening meal	50 mg, 100 mg, 150 mg, 200 mg capsules

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Dosages (continued)

Drug	Diagnosis						Administration comments	Dosage forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
thioguanine (Tabloid)	--	--	--	--	--	Acute nonlymphocytic leukemias: Doses varies according to the stage and regimen being utilized; dose should be drive by chosen protocol	--	40 mg tablets
tretinoin	--	--	--	--	--	APL: 45 mg/m^2/day divided into 2 doses	--	10 mg capsule

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Dosages (continued)

Drug	Diagnosis						Administration comments	Dosage forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
venetoclax (Venclexta)	--	--	Ramp-Up phase dosing: 20 mg/day week 1; 50 mg/day week 2; 100 mg/day week 3; 200 mg/day week 4, and then 400 mg/day week 5 and thereafter Monotherapy: 400 mg once daily following completion of the ramp-up schedule In combination with obinutuzumab: use 5-week ramp-up schedule; after completing on cycle 2 day 28, patients should continue venetoclax 400 mg once daily from cycle 3 day 1 until the last day of cycle 12 In combination with rituximab: use 5-week ramp-up schedule; after completing continue 400 mg once daily for 24 months following rituximab initiation See product labeling for dosing of combination treatment agents	--	--	AML: Ramp-up phase dosing 100 mg day 1; 200 mg day 2; 400 mg day 3; 400 mg or 600 mg on day 4 and beyond depending on combination agent Continue until disease progression or unacceptable toxicity See product labeling for dosing of combination treatment agents	Take with a meal and water; tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing	10 mg, 50 mg, 100 mg tablets; starter pack (42 tablets: 14 x 10 mg, 7 x 50 mg, 21 x 100 mg)
vorinostat (Zolinza)	--	--	--	--	--	CTCL: 400 mg once daily	Take with food; capsules should not be opened or crushed	100 mg capsule

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Dosages (continued)

Drug	Diagnosis						Administration comments	Dosage forms
	CML	Ph+ ALL	CLL/SLL	NHL	MM	Other		
zanubrutinib (Brukinsa)	--	--	--	--	--	MCL: 160 mg twice daily or 320 mg once daily continued until disease progression or unacceptable toxicity	Swallowed whole with water, with or without food; capsules should not be opened, broken, or chewed	80 mg capsule

aGVHD = acute graft versus host disease; ALL = acute lymphoblastic leukemia; AP = accelerated phase; APL = acute promyelocytic leukemia; ASM = aggressive systemic mastocytosis; BC = blast crisis; BP = blast phase; CCyR = complete cytogenetic response; cGVHD = chronic graft versus host disease; CHR = complete hematological response; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CP = chronic phase; CTLC = cutaneous T-cell lymphoma; DFSP = dermatofibrosarcoma protuberans; ENL = erythema nodosum leprosum; FL = follicular lymphoma; GIST = gastrointestinal stromal tumor; HD = Hodgkin's disease; HES/CEL = hypereosinophilic syndrome/chronic eosinophilic leukemia; MCL= mantle cell lymphoma; MDS/MDD = myelodysplastic/myeloproliferative disease; MM = multiple myeloma; MZL = marginal zone lymphoma; NHL = non-Hodgkin's lymphoma; Ph+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia; Ph+ CML = Philadelphia chromosome-positive chronic myelogenous (myeloid) leukemia; SLL = small cell lymphocytic leukemia

Recommendations for consideration of discontinuation of treatment with nilotinib (Tasigna) are now included in the product's labeling. Patients who meet criteria outlined in the package insert and who have achieved a sustained molecular response (MR4.5) for a minimum of 1 year may be considered for possible nilotinib discontinuation. Furthermore, recommendations for reinitiation of nilotinib therapy in patients who lose their molecular response after discontinuation of therapy with nilotinib are outlined in the package insert

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CLINICAL TRIALS

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

Due to a paucity of data in the literature, clinical trials that are open-label, not placebo-controlled, and have dropout rates in excess of 20% have been included in this therapeutic class review. In addition, where published phase 3 data for the FDA-approved indications is lacking, phase 1/2 studies cited in the package insert are included in this therapeutic class review.

Clinical trials involving busulfan (Myleran), procarbazine (Matulane), hydroxyurea (Hydrea), melphalan (Alkeran), and thioguanine (Tabloid) will not be included in this review due to lack of routine use of these agents in modern day oral chemotherapy regimens. Additionally, discussion of chlorambucil will be limited in scope to the treatment of CLL, where this agent continues to have some role in contemporary management of the disease state.

Aggressive Systemic Mastocytosis (ASM)

imatinib (Gleevec)

An open-label, multicenter, phase 2 trial was conducted with imatinib in patients diagnosed with life-threatening diseases associated with Abl, Kit, or platelet derived growth factor receptor (PDGFR) protein tyrosine kinases.[294] Five of these patients were diagnosed with ASM and were treated with 100 mg to 400 mg of imatinib daily. In addition to these 5 patients, 10 published case reports and case series describe the use of imatinib in 23 additional patients with ASM. Cytogenetic abnormalities were detected in 14 of the 20 patients tested. Twenty nine percent of imatinib-treated patients achieved a complete hematologic response (CHR) and 32% a partial hematologic response. Patients that harbor the D816V mutation of c-Kit are not sensitive to imatinib.

midostaurin (Rydapt)

The efficacy of midostaurin as a single agent in ASM, systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mantle-cell lymphoma (MCL) (collectively referred to as advanced SM) was evaluated in a phase-2, single-arm, open-label, multicenter trial.[295] The study enrolled 116 adult patients with relapse or progression to ≤ 2 prior regimens for systemic mastocytosis (SM). Patients received midostaurin 100 mg orally twice daily in 28-day cycles until protocol-defined disease progression, death, the development of unacceptable toxic effects, or withdrawal of consent. Of the 116 patients treated, a study steering committee identified 89 patients with measurable clinical findings that were related to organ damage from infiltrating mast cells (C-findings) and were evaluable

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for response. Of those 89 patients, there was an overall response rate (ORR) of 60% (95% confidence interval [CI], 49 to 70; p<0.001), with 19 (21%) achieving incomplete remission by 6 cycles of midostaurin based on modified Valent criteria for ASM and SM-AHN. The median overall survival (OS) was 28.7 months (95% CI, 18.1 to not estimated) in the primary efficacy population, including the median OS of 20.7 months (95% CI, 16 to 44.4) among patients with SM-AHN, and 9.4 months (95% CI, 7.5 to not estimated) among patients with MCL. Among patients with ASM, the median survival was not reached. The median progression-free survival (PFS) was 14.1 months in the primary efficacy population but was longer among patients with ASM (28.7 months) than among patients with SM-AHN (11 months) and patients with MCL (11.3 months).

In an open-label, phase 2 trial 26 patients with advanced systemic mastocytosis received midostaurin 100 mg twice daily as 28-day cycles.[296] During the first 12 cycles, the ORR was 69% with 50% having a major response. With ongoing therapy, 2 patients achieved a CR. Median OS for the entire cohort was 40 months. The most frequent grade 3 or higher adverse events were hyperlipasemia (15%) and anemia (12%). With a median follow up of 10 years no unexpected toxicities were noted.

Acute Graft-Versus-Host disease (aGVHD)

ruxolitinib (Jakafi)

REACH1: Ruxolitinib was studied in a phase 2, single-arm, open-label trial involving 49 patients with aGVHD occurring after allogeneic hematopoietic stem cell transplantation (HSCT) who were refractory to corticosteroids alone.[297] Patients received ruxolitinib 5 mg twice daily, and the dose could be increased to 10 mg twice daily after day 3 if patients were not experiencing toxicity. The median age was 57 years (range, 18 to 72 years). The primary endpoint was ORR at day 28. At baseline, 27% of patients had grade 2 aGVHD, 55% had grade 3, and 18% had grade 4 aGVHD. The ORR at day 28 was 57.1% (95% CI, 42.2 to 71.2). Of those patients with grade 2 disease, 100% had a response, while 40.7% and 44.4% of patients with grade 3 and 4 disease, respectively, experienced a response. Complete response (CR) occurred in 30.6% of patients, while 4.1% and 22.4% had very good partial or partial response (PR), respectively. For patients who responded, the median time from the day 28 response to either death or need for new therapy for aGVHD was 173 days (95% CI, 66 to not estimable).

Chronic Graft- Versus- Host Disease (cGVHD)

ibrutinib (Imbruvica)

A multicenter, open-label, single-arm study established the safety and efficacy of ibrutinib for the treatment of patients with cGVHD after failure of first-line corticosteroid therapy and requiring additional therapy (n=42).[298,299] ALL, AML, and CLL were the most common underlying malignancies leading to transplantation and the median time since cGVHD diagnosis was 14 months in the included patients (median number of prior treatments, 2; range, 1 to 3 treatments). Ibrutinib was administered as 420 mg once daily orally and the primary endpoint was cGVHD response based on 2005 National Institutes of Health criteria. ORR occurred in 67% of patients (95% CI, 51 to 80). CR occurred in 21% while PR occurred in 45%. Forty-eight percent of patients also had a sustained response rate (CR or PR for at least 20 weeks.

Dermatofibrosarcoma Protuberans (DFSP)

imatinib (Gleevec) monotherapy

An open-label, multicenter, phase 2 study was conducted testing imatinib monotherapy in a diverse

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population of patients with life-threatening diseases associated with Abl, Kit, or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with imatinib 800 mg daily. A further 6 DFSP patients treated with imatinib are reported in 5 published case reports. An ORR of 83% was seen in the total of 18 patients.[300]

Erythema Nodosum Leprosum (ENL)

thalidomide – acute treatment of cutaneous manifestations of ENL

Two randomized, double blind controlled trials reported the dermatologic response to a 7-day course of thalidomide 100 mg four times daily versus control in patients with cutaneous manifestations of moderate to severe ENL.[301] In the first trial of 92 patients there was a 75% response rate and in the second trial of 52 patients, there was a 66% response rate.

thalidomide – prevention and suppression of recurrence of cutaneous manifestations of ENL

A retrospective evaluation of 102 patients treated by the US Public Health Service.[302] A subset of patients with ENL who were controlled on thalidomide demonstrated repeated relapse upon drug withdrawal but achieved remission with reinstitution of therapy.

Gastrointestinal Stromal Tumor (GIST)

imatinib (Gleevec) and placebo – adjuvant post-operative therapy

A randomized, double-blind, placebo-controlled, multicenter, 1-year, phase 3 trial compared adjuvant imatinib 400 mg (n=359) to placebo (n=354) in patients with fully resected GIST at least 3 cm in size and positive for the KIT protein by immunohistochemistry.[303] Patients assigned to placebo were eligible to crossover to imatinib treatment in the event of tumor recurrence. The primary endpoint was recurrence-free survival, and analysis was by intention-to-treat. Accrual was stopped early because the trial results crossed the interim analysis efficacy boundary for recurrence-free survival. At median follow-up of 19.7 months, 8% of patients in the imatinib group and 20% in the placebo group had tumor recurrence or had died. Imatinib significantly improved recurrence-free survival compared with placebo (98% [95% CI, 96 to 100] versus 83% [95% CI, 78 to 88] at 1 year; hazard ratio [HR], 0.35 [95% CI, 0.22 to 0.53]; 1-sided p<0.0001). Adjuvant imatinib was well tolerated. The most common serious events were dermatitis (3% versus 0), abdominal pain (3% versus 1%), and diarrhea (2% versus 1%) in the imatinib group and hyperglycemia (1% versus 2%) in the placebo group. Adjuvant imatinib has also been studied in a randomized, open-label, phase 3 study in patients who have a high estimated risk for GIST recurrence after surgery.[304] Patients assigned to 3 years of imatinib had longer recurrence-free survival (RFS) compared with those assigned to 1 year (HR, 0.6; 95% CI, 0.44 to 0.81; p<0.001; 5-year RFS, 71.1% versus 52.3%, respectively) and longer OS (HR, 0.6; 95% CI, 0.37 to 0.97; p=0.024; 5-year survival, 92% versus 85.3%).[305]

imatinib (Gleevec) versus placebo in patients with metastatic resistant or unresectable resistant disease

Patients (n=41) with metastatic or unresectable GIST who had previously benefitted from first-line imatinib (initial response or stable disease for ≥ 6 months) and had progressed on at least imatinib and sunitinib (Sutent®) were prospectively randomized to imatinib 400 mg daily or placebo.[306] The primary endpoint was PFS. After a median follow-up of 5.2 months, median PFS was 1.8 months (95% CI, 1.7 to 3.6) with imatinib compared to 0.9 months (95% CI, 0.9 to 1.7) with placebo (HR for progression or death, 0.46; 95% CI, 0.27 to 0.78; p=0.005). Patients assigned to placebo were allowed to crossover to

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imatinib after progression. The most common grade 3 or higher adverse events were anemia, fatigue, and hyperbilirubinemia. The authors concluded that in patients with TKI-refractory GIST, the disease continues to harbor many clones that are sensitive to TKIs and continued kinase suppression might slow, although not halt, disease progression.

Kaposi Sarcoma

Kaposi Sarcoma – adults

pomalidomide (Pomalyst) – HIV-positive and HIV-negative patients

An open-label, single center, single-arm clinical study (12-C-0047, NCT01495598) was used to assess the efficacy and safety of pomalidomide in patients with (n=18) and without HIV (n=10). Patients received pomalidomide 5 mg orally once daily on days 1 through 21 of each 28-day cycle until disease progression or unacceptable toxicity; patients also were given aspirin 81 mg once daily as thromboprophylaxis. Patients who were HIV-positive continued to receive highly active antiretroviral therapy (HAART). Patients with symptomatic pulmonary or visceral KS, history of venous or arterial thromboembolism, or procoagulant disorders were excluded. The primary efficacy endpoint was ORR as evaluated by the investigator based on the AIDS Clinical Trial Group (ACTG) Oncology Committee response criteria for KS. Across all 28 patients, the ORR was 71% (95% CI, 51 to 87) with 14% of patients experiencing a complete response (CR) and 57% experiencing a partial response (PR). The overall patient population had a median duration of response (DOR) of 12.1 months (95% CI, 7.6 to 16.8) with 50% of patients exhibiting a response duration > 12 months and 20% exhibiting a response duration > 24 months. For the 18 patients who were HIV-positive, the ORR was 67% (95% CI, 41 to 87) with 17% (3 patients) having a CR and 50% (9 patients) a PR; the median DOR was 12.5 months (95% CI, 6.5 to 24.9). For the 10 HIV-negative patients, the ORR was 80% (95% CI, 44 to 98) with 1 patient (10%) experiencing a CR and 7 patients (70%) experiencing a PR; the median DOR was 10.5 months (95% CI, 3.9 to 24.2).

Leukemias

Acute Lymphoblastic Leukemia-Philadelphia Chromosome Positive (Ph+ ALL) – adults

dasatinib (Sprycel) – resistance or intolerance to prior therapy

START-L was a phase 2, open-label, single-arm, multicenter trial in 36 adult patients with imatinib (Gleevec)-resistant or intolerant Ph+ ALL. This trial was designed to evaluate the effectiveness and tolerability of dasatinib 140 mg daily in this patient population. With a minimum follow-up of 8 months, treatment with dasatinib produced major hematologic responses in 42% of patients and 67% of those patients remained progression-free at time of reported data. Most adverse events were mild with febrile neutropenia being the most frequent severe adverse event. [307]

A phase 3, randomized trial evaluated the efficacy and safety of dasatinib 140 mg once daily versus 70 mg twice daily in patients with advanced phase CML or Ph+ALL (n=84) resistant or intolerant to imatinib.[308] The rate of confirmed major hematologic response was 38% with once daily dosing and was 32% with twice daily dosing. The rate of major cytogenetic response with once daily dosing was 70% and was 52% with twice daily dosing. The once daily dosing had longer PFS (3 months versus 4 months) and shorter OS (median, 9.1 months versus 6.5 months). Safety profiles were similar between the 2 groups although pleural effusion was less common with once daily dosing (all grades, 18% versus 32%). None of the differences between the 2 schedules were statistically significant.

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ponatinib (Iclusig) – relapsed/refractory Ph+ ALL with and without T315I mutation

A phase 3 trial (PACE) included a subgroup of 32 patients with Ph+ ALL.[309] These patients were heavily pre-treated and were resistant or intolerant to previous TKI therapies. Major hematologic response to ponatinib among the Ph+ ALL patients was 41%. The estimated PFS at 12 months was 7% with a median PFS of 3 months and the OS rate at 12 months was 40%. Of the 32 patients, 22 of those patients were found to have a T315I mutation. In this cohort, MHR was reached in 36%, and there were no significant differences in DOR or OS outcomes compared to the other 10 patients who did not demonstrate a T315I mutation.

imatinib (Gleevec) – relapsed/refractory Ph+ ALL

Numerous phase 2 studies have evaluated the efficacy of imatinib as either monotherapy or combined with chemotherapy in adults with Ph+ ALL.[310] A phase 2, open-label, nonrandomized, multicenter study of 48 adult patients with relapsed or refractory Ph+ ALL treated patients with either 400 mg imatinib daily or 600 mg imatinib daily for an initial 24 weeks but the drug could be continued indefinitely in cases where the investigator judged that further treatment was of clinical benefit.[311] A CHR was achieved in 9 (19%) patients, a marrow-complete response or partial marrow response was observed in 5 patients (10%) and 15 patients (31%), respectively. Hematologic responses lasting at least 4 weeks were reported for 13 patients (27%), including 3 CHRs (6%). Complete cytogenetic response (CCyR) was reported for 8 (17%) patients. The estimated median time to progression was 2.2 months (95% CI, 1.8 to 2.8) and the estimated 6 month PFS was 12% (95% CI, 2 to 22). Median survival was 9.2 months for patients who had a CHR/marrow-complete response and 7.1 months for patients with a partial response (PR), all of the nonresponders had died and their median survival was 3.6 months ($p<0.001$). The most frequently reported adverse events were nausea, vomiting, and edema. None of the patients discontinued imatinib because of treatment-related nonhematologic adverse events.

Acute Lymphoblastic Leukemia-Philadelphia Chromosome Positive (Ph+ ALL) – pediatrics

dasatinib (Sprycel)

The effectiveness of dasatinib was assessed in a multicenter study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL.[312] One cohort (n=78) received dasatinib at 60 mg/m^2 for up to 24 months in combination with chemotherapy. The median age was 10.4 years (range, 2.6 years to 17.9 years) and 22% had extramedullary disease. The 3-year, event-free survival, defined as the time from treatment initiation to lack of CR, relapse, secondary malignancy, or death was 64.1% (95% CI, 52.4 to 74.7).

imatinib (Gleevec)

A multicenter study by the Children's Oncology Group cooperative examined the outcome of 92 patients ranging in age from 1 year old to 21 years old with Ph+ ALL who were treated with imatinib 340 mg/m^2/day in combination with chemotherapy.[313] Eligible patients were enrolled after completion of 4 weeks of induction therapy. The study design called for integration of imatinib into successive blocks of therapy across 5 cohorts to ensure therapy would be tolerated. Cohort 5 patients had continuous imatinib dosing and accrued a total of 44 patients who had a total of 280 days of imatinib exposure. Patients in cohort 5 had a 3-year event-free survival (EFS) of 80% ± 11% (95% CI, 64 to 90). This was more than twice the historical controls 3-year EFS (35% ± 4%, $p<0.0001$). There were no significant toxicities associated with adding imatinib to intensive chemotherapy.

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Acute Lymphoblastic Leukemia (ALL)

mercaptopurine

The utilization of mercaptopurine in the treatment of ALL dates back more than 50 years.[314] Many current ALL protocols utilize mercaptopurine during the maintenance therapy portion of the treatment protocol.

Acute Myeloid Leukemia (AML)

enasidenib (Idhifa) – IDH2 mutation-positive

A phase 1/2 multicenter, open-label, single-arm, 2-cohort study (Study AG221-C-001) assessed the efficacy of enasidenib for the treatment of AML in 199 adults with refractory or relapsed AML and an IDH2 mutation (as determined by a genetic assay).[315,316] In both cohorts, patients received enasidenib 100 mg daily orally until disease progression or unacceptable toxicity (dose reductions were allowed for toxicities). The median follow up was 6.6 months (range, 0.4 to 27.7) and the mean age at baseline was 68 years (range, 19 to 100 years), 52% were male, 77% were Caucasian, 85% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 52% had refractory disease, 13% had a prior stem cell transplant, and 55% had ≥ 2 prior treatment regimens. The rate of CR/CR with partial hematological recovery (CRh), duration of CR/CRh, and rate of conversion from transfusion dependence to independence was used to establish efficacy. CR/CRh occurred in 23% of patients (95% CI, 18 to 30; median DOR, 8.2 months [95% CI, 4.3 to 19.4]). During follow up, CR occurred in 19% of patients (95% CI, 13 to 25; median DOR, 8.2 months [95% CI, 4.7 to 19.4]). CRh, defined as 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts, occurred in 4% of patients (95% CI, 2 to 8; median DOR, 9.6 months [95% CI, 0.7 to not available]). Of the 157 patients who were dependent on transfusions (red blood cell [RBC] and/or platelet) at baseline, 34% became transfusion-independent during the 56-day post baseline period. Additionally, 72% (32/42) of those who were transfusion-independent at baseline maintained this status.

glasdegib (Daurismo) – newly diagnosed adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy

BRIGHT AML 1003 was a randomized, multicenter, open-label trial that enrolled 115 patients who were ≥ 55 years of age and had newly diagnosed AML.[317,318] All patients enrolled in the trial had to meet ≥ 1 of the following criteria: age ≥ 75 years of age, severe cardiac disease, baseline ECOG performance status of 2, or baseline serum creatinine > 1.3 mg/dL. All patients received cytarabine 20 mg subcutaneously (SC) twice daily on days 1 through 10 of a 28-day cycle, and patients were randomized 2:1 to the addition of glasdegib 100 mg orally daily to the cytarabine regimen or cytarabine alone. The majority of patients in each arm were ≥ 75 years old. The CR rate was 18.2% in the glasdegib arm and 2.6% in the cytarabine alone control arm. OS, with a median follow up of 20 months was significantly improved in the glasdegib arm, 8.3 months compared to the cytarabine alone control arm at 4.3 months (HR, 0.46; 95% CI, 0.3, 0.71; p=0.0002).

gilteritinib (Xospata) – relapsed/refractory FLT3-mutated

ADMIRAL: A phase 3, open-label, randomized trial evaluated the efficacy of gilteritinib in 138 adults with relapsed or refractory AML with a FLT3 mutation; 121 patients had FLT3-ITD alone, 12 had FLT3-TKD alone, and 5 had both mutations.[319] The median age was 60 years. Gilteritinib was given orally at a starting dose of 120 mg once daily until unacceptable toxicity or lack of clinical benefit. Dose reductions were made to manage adverse events, and dose increases were allowed to increase clinical

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benefit. The primary endpoint was a composite of CR and CRh. CR was defined as an absolute neutrophil count (ANC) ≥ 1 x 10^9/L, platelets ≥ 100 x 10^9/L, normal marrow differential with < 5% blasts, RBC, and platelet transfusion independent, and no evidence of extramedullary leukemia. CRh was defined as marrow blasts < 5%, partial hematologic recovery ANC ≥ 0.5 x 10^9/L and platelets ≥ 50 x 10^9/L, no evidence of extramedullary leukemia, and patient was not classified as achieving CR. The median follow-up was 4.6 months. At the first interim analysis, a total of 21% of patients treated with gilteritinib achieved CR or CRh (CR in 11.6% and CRh in 9.4%). The CR/CRh rate was 23% (29/126) in patients with FLT3-ITD or FLT3-ITD/TKD, and 0% (0/12) in patients with FLT3-TKD only. Overall, for patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The median DOR in patients with CR/CRh was 4.6 months (8.6 months [range, 1 to 13.8] for patients in CR; 2.9 months [range, 0.1 to 15.8] for patients in CRh). The final analysis of ADMIRAL assessed 371 patients who were randomized 2:1 to gilteritinib 120 mg once daily versus a prespecified chemotherapy regimen. The median follow-up was 17.8 months (range, 14.9 to 19.1). In the final analysis, OS was achieved in 69.2% (171/247) of those treated with gilteritinib compared to 72.6% (90/124) treated with chemotherapy, but the median survival in those treated with gilteritinib was 9.3 months (range, 7.7 to 10.7) versus 5.6 months (range, 4.7 to 7.3) with chemotherapy (HR, 0.64; 95% CI, 0.49 to 0.83; p=0.0004). CR was achieved in 14.2% (95% CI, 10.1 to 19.2) of those treated with gilteritinib versus 10.5% (95% CI, 5.7 to 17.3) with chemotherapy (median DOR of 14.8 months [range, 0.6 to 23.1+] and 1.8 months [range, < 0.1+ to 1.8], respectively).

ivosidenib (Tibsovo) – IDH1 mutation-positive

Ivosidenib was studied in a phase 1, multicenter, open-label trial that consisted of both a dose-escalation phase and a dose-expansion study.[320,321] Patients ≥ 18 years old with documented IDH1-mutated hematologic malignancies were eligible. The dose escalation portion of the study established dose limiting toxicities of oral ivosidenib given continuously in 28-day cycles. The dose expansion phase involved 4 groups with different eligibility criteria. Three of the 4 groups involved patients with IDH1-mutated AML, including patients with relapsed and/or refractory (R/R) AML in 2nd or greater relapse, relapse after HSCT, refractory to induction or reinduction or relapse within 1 year (n=126), untreated patients with AML who were not eligible to receive standard of care treatment (n=25) and finally, other R/R AML patients who did not fit the criteria for group 1 (n=18). Clinical activity of ivosidenib was assessed in R/R AML patients who received a dose of 500 mg once daily in either the dose-escalation or dose-expansion phases. Efficacy was assessed by the rates of CR plus rates of CRh. CR was defined as < 5% blasts in the bone marrow, no evidence of disease and full recovery of peripheral blood counts (platelets > 100,000/microliter and ANC > 1,000/microliter) while CRh was defined as < 5% blasts in bone marrow, no evidence of disease and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC >500/microliter). With a median follow-up of 8.3 months and a median treatment duration of 4.1 months, 43/174 patients (24.7%) achieved a CR (median DOR, 10.1 months [95% CI, 6.5 to 22.2] and 14/174 patients (8%) had achieved a CRh (median DOR, 8.2 months [95% CI, 5.6 to 12]. The median time to achieve CR or CRh was 2 months (range, 0.9 to 5.6 months). The median OS of the R/R AML patients treated with ivosidenib 500 mg daily was 8.8 months (95% CI, 6.7 to 10.2). A total of 37/179 (20.7%) patients assessed who received ivosidenib at a starting dose of 500 mg daily experienced at least 1 grade 3 or higher toxicity. Of special concern, 14/179 (7.8%) of patients experienced grade ≥ 3 QT prolongation on ECG and 7/179 (3.9%) experienced ≥ grade 3 IDH differentiation syndrome. Treatment for IDH differentiation syndrome, which consisted of glucocorticoids and other measures, led to the resolution of the syndrome in 17/19 patients. None of the cases of IDH differentiation syndrome were fatal. QT prolongation led to dose interruptions in 7.3%

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and dose reductions in 1.1%, but there were no fatalities related to QT prolongation toxicity.

The efficacy of ivosidenib was evaluated in an open-label, single-arm, multicenter clinical trial of adult patients with newly diagnosed AML with a susceptible IDH1 mutation who were ≥ 75 years of age or who had comorbidities that precluded the use of intensive induction chemotherapy.[322] Included comorbidities that would preclude use of intensive induction chemotherapy were ≥ 1 of the following: baseline ECOG performance status of ≥ 2, hepatic impairment with bilirubin > 1.5 x ULN, severe cardiac or pulmonary disease, or CrCl < 45 mL/min. Ivosidenib was administered as 500 mg orally daily until disease progression, unacceptable toxicity, or until the patient underwent a hematopoietic stem cell transplantation, the latter of which occurred in 2 of the 28 patients. CR occurred in 28.6% (95% CI, 13.2 to 48.7; median DOR, not estimable [95% CI, 4.2 months to not estimable]). CRh occurred in 14.3% (95% CI, 4 to 32.7). The median time to CR or CRh was 2.8 months (range, 1.9. to 12.9).

midostaurin (Rydapt) versus placebo – FLT3 mutation-positive

Midostaurin in combination with chemotherapy was investigated in a global, phase 3, randomized, double-blind, placebo-controlled trial of 717 patients with newly-diagnosed FLT3-mutated AML.[323] The objective of this trial was to determine if the addition of midostaurin to combination daunorubicin/cytarabine induction, high-dose cytarabine consolidation therapy followed by 1 year of maintenance therapy would improve OS compared to standard chemotherapy in younger adults (aged 18 to 59 years) with activating FLT3 mutations. Patients were randomized (1:1) to receive either midostaurin 50 mg twice daily (n=360) or placebo (n=357) with food on days 8 to 21 in combination with daunorubicin (60 mg/m^2 daily on days 1 to 3) plus cytarabine (200 mg/m^2 daily on days 1 to 7) for up to 2 cycles of induction and high-dose cytarabine (3 g/m^2 every 12 hours on days 1, 3 and 5) for up to 4 cycles of consolidation, followed by continuous midostaurin or placebo treatment, according to initial assignment, for up to 12 additional 28-day cycles. Patients who proceeded to HSCT stopped receiving study treatment. The 2 treatment groups were generally balanced with respect to the baseline demographics and disease characteristics (including FT3-ITD allelic ratio and FLT3-TKD mutations), except that the placebo arm had a higher percentage of females (59%) than in the midostaurin arm (52%). The final analysis was to occur after 509 deaths, but the trial was amended to change the timing of the OS analysis and promote event-free survival (EFS). EFS was defined as the earliest of death, relapse, or no CR within 61 days of the start of induction, as a key secondary endpoint due to the slow rate of deaths that occurred. Midostaurin plus standard chemotherapy was superior to placebo plus standard chemotherapy with a median OS of 26 months (95% CI, 18.5 to 46.5) in the placebo arm versus 74.7 months (95% CI, 31.5 to not obtained; 1 sided p=0.007) in the midostaurin arm. The median EFS of 3 months (95% CI, 1.9 to 5.8) in the placebo arm and 8 months (95% CI, 5.3 to 10.6; 1 sided p=0.0044) in the midostaurin arm. The overall rate of HSCT (induction failure, first CR, or salvage after relapse) was 59% (214/360) for patients in the midostaurin arm versus 55% (197/357) in the placebo arm. Toxicities between the 2 groups were similar. There were higher incidences of grades 3 to 5 anemia and rash in the midostaurin group compared to placebo (92.7% versus 87.8% and 14.1% versus 7.6%, respectively). Among patients who achieved a CR, the median time to recovery of the ANC was 26 days in both groups, and the median time to recovery of the platelet count was 21 days in both groups. [324]

venetoclax (Venclexta) – newly diagnosed AML in patients ≥ 75 years of age or with comorbidities precluding use of intensive induction chemotherapy

Two open-label, non-randomized trials were utilized to establish the efficacy of venetoclax in patients with newly diagnosed AML who were either ≥ 75 years of age or had comorbidities that precluded the

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use of intensive induction chemotherapy (≥ 1 of the following: baseline ECOG 2 to 3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CrCl < 45 mL/min, or other comorbidity).[325,326] In the first trial, following ramp-up dosing, 115 patients received 400 mg venetoclax once daily and either azacitidine or decitabine. The median follow-up was 7.9 months (range, 0.4 to 36) with azacitidine and 5.5 months (range, 0.4 to 30) with decitabine. CR and CRh was achieved in 37% (95% CI, 26 to 50) and 24% (95% CI, 14 to 36), respectively, of those who received venetoclax and azacitidine and 54% (95% CI, 25 to 81) and 1% (95% CI, 0.2 to 36), respectively, of those who received venetoclax and decitabine. In the second trial, venetoclax was assessed in combination with low-dose, SC cytarabine (n=82). Following ramp-up dosing, patients received 600 mg venetoclax once daily. The median follow-up was 6.5 months (range, 0.3 to 34). CR and CRh were achieved in 21% (95% CI, 12 to 34) and 21% (95% CI, 12 to 34), respectively.

Acute Promyelocytic Leukemia (APL)

all-trans-retinoic acid/tretinoin

A phase 3 trial randomized 346 patients with previously untreated APL to either all-trans-retinoic acid (tretinoin) or daunorubicin plus cytarabine as induction treatment.[327] Patients who achieved a CR were given 1 cycle of consolidation therapy identical to their induction regimen followed by high-dose cytarabine plus daunorubicin. Patients who were still in complete remission after 2 cycles of consolidation were then randomly assigned to maintenance treatment with all-trans-retinoic acid (tretinoin) or observation. In the chemotherapy arm, 69% of patients attained a CR while 72% of patients who received all-trans-retinoic-acid (tretinoin) reached a CR (p=0.56). APL is known to be associated with a high risk for early death; there was no difference in mortality during induction between the 2 groups. There were less serious infections in the all-trans-retinoic acid (tretinoin) group, but that group also had more serious pulmonary toxic effects. Other toxicities seen in the all-trans-retinoic acid (tretinoin) group were pseudotumor cerebri, hyperleukocytosis, and retinoic acid syndrome. By intention-to-treat analysis, the rates of OS at years 1, 2, and 3 were 75%, 57%, and 50%, respectively, for the chemotherapy group and were 82%, 72%, and 67%, respectively, for the all-trans-retinoic acid (tretinoin) group (p=0.003). The authors concluded that while all-trans-retinoic acid (tretinoin) did not improve the rate of CR or decrease early mortality, it was associated with a reduced risk of relapse.

Although the FDA-approved indication for tretinoin is for remission induction in APL patients who are refractory to, have relapsed from or have a contraindication to anthracycline chemotherapy, contemporary protocols for the treatment of APL utilize tretinoin in the upfront, first-line setting for off-label treatment induction in conjunction with either arsenic trioxide or an anthracycline.[328]

Chronic Myeloid Leukemia (CML)

bosutinib (Bosulif) – versus imatinib in newly diagnosed Chronic Phase (CP) CML

BFORE was a phase 3, open-label, randomized trial of bosutinib versus imatinib in adult patients who were newly diagnosed with CP-CML.329 [330]A total of 536 patients were randomized to either bosutinib 400 mg once daily or imatinib 400 mg once daily and the study has a planned follow up of 5 years. The major efficacy variable was MMR at 12 months. In addition, efficacy was measured by the rate of CCyR by 12 months. At 12-month follow-up, 47.2% (95% CI, 40.9 to 53.4) of the patients receiving bosutinib experienced a MMR compared to 36.9% (95% CI, 30.8 to 43) of patients receiving imatinib (p=0.02). Similarly, the rate of CCyR was 77.2% (95% CI, 72 to 82.5) for bosutinib treated patients compared to 66.4% (95% CI, 60.4 to 72.4) of imatinib-treated patients (p=0.0075). Diarrhea grade 3 or higher (7.8%

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vs 0.8%) and increased ALT (19% vs 1.5%) and AST levels (9.7% vs 1.9%) were more common with bosutinib than imatinib

bosutinib (Bosulif) – second- or third-line therapy

The safety and effectiveness of bosutinib was evaluated in a single-arm, open-label, multi-cohort, phase 1/2 study with 546 adults with chronic, accelerated or blast phase CML.[331] All patients had disease that progressed after treatment with imatinib (Gleevec) or imatinib followed by another TKI (dasatinib [Sprycel] and/or nilotinib [Tasigna]), or who could not tolerate the adverse effects of prior therapy. In patients with CP CML, efficacy was determined by the number of patients who experienced a major cytogenetic response (MCyR) within the first 24 weeks of treatment. Results showed 33.8% of patients previously treated with imatinib achieved MCyR after 24 weeks (95% CI, 28.2 to 39.9). With a minimum follow-up of 48 months, 59% of patients achieved a MCyR.[332] Of patients who achieved MCyR, 52.8% had a MCyR lasting at least 18 months. The 2 year OS rate was 91%. In patients previously treated with imatinib followed by dasatinib and/or nilotinib, 26.9% achieved MCyR within the first 24 weeks of treatment (95% CI, 18.8 to 36.2). With a minimum follow-up of 28.5 months, 32% of patients achieved a MCyR and a CCyR was attained by 24%, including in 1 patient who had been treated with 3 prior TKIs. Only 5 patients progressed to accelerated or blast-phase disease while on the drug. At 2 years, Kaplan-Meier-estimated PFS was 73% and estimated OS was 83%.[333] In patients with AP-CML previously treated with at least imatinib, 30.4% had complete hematologic response and 55.1% achieved overall hematologic responses within the first 48 weeks of treatment. A total of 15% and 28.3% of patients with blast phase CML achieved complete hematologic response and overall hematologic response, respectively. Grade 3 to 4 adverse effects included thrombocytopenia (26% of patients), neutropenia (11%), diarrhea (9%), anemia (9%), and rash (8%). At 4 years, the cumulative incidence of disease progression (transformation to AP-CML or BP-CML, increasing white blood cell count or loss of confirmed CHR or unconfirmed MCyR) was 22% for patients resistant to imatinib and 10% for those intolerant to imatinib. In a separate study, higher risk patients (all patients were either in AP or BC or being treated for ALL) who had experienced treatment failure in either imatinib or another TKI were treated with bosutinib.[334] In AP or BC patients, 40% and 37%, respectively, attained a MCyR. Responses were most durable in AP patients where approximately 50% of responders continued to have a response. The most common serious adverse effects were pneumonia and pyrexia. Two treatment-related deaths occurred in the trial.

dasatinib (Sprycel) versus imatinib (Gleevec) – first-line therapy

Dasatinib versus imatinib study in treatment-naïve chronic phase CML patients (DASISION) was a randomized, open-label, multicenter, phase 3 study of 519 patients with newly diagnosed CP CML randomly assigned to dasatinib 100 mg once daily or imatinib 400 mg once daily.[335] The primary endpoint was CCyR by 12 months, confirmed on 2 consecutive assessments a minimum of 28 days apart. After at least 12 months follow-up, the rate of confirmed complete cytogenetic response was higher in the dasatinib group at 77% compared with the imatinib at 66% (p=0.007). Median time to confirmed CCyR was 3.1 months in dasatinib responders (199 patients) and 5.6 months in imatinib responders (177 patients). The rate of complete cytogenetic response observed on at least 1 assessment was also higher with dasatinib (83% versus 72%, p=0.001). For secondary endpoint, the rate of major molecular response was higher with dasatinib at 46% compared with imatinib at 28% (p<0.0001), and in the dasatinib group responses were achieved in a shorter time (p<0.0001). In the dasatinib group, 5 patients (1.9%) had progression to accelerated or blast phase of CML compared with 9 patients (3.5%) receiving imatinib, this was not statistically significant. The safety of the 2 groups was comparable. There is published 36- to 48-month follow-up data from the DASISION study showing

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superior cytogenetic and molecular response rates at certain time points with dasatinib and lower rates of progression to accelerated or blast phase compared to imatinib.[336] The final 5-year follow up continued to demonstrate an overall faster time to cytogenetic and molecular response for dasatinib compared to imatinib, as well as sustained higher cumulative rates of response and a lower rate of transformation for dasatinib. However, the 5-year rates of PFS (85% for dasatinib, 86% for imatinib) and OS (91% for dasatinib, 90% for imatinib) were equal in both arms.[337]

dasatinib (Sprycel) – second-line therapy

The FDA approval for the use of dasatinib in patients who are resistant or intolerant to prior therapy was based on several phase 2 trials; therefore, these trials are included in this review. These phase 2, single-arm studies (START-A, START-B, START-C, START-R,) examined the safety and efficacy of dasatinib (Sprycel) in patients with Ph+ CML who were resistant or intolerant to imatinib. The START-A trial evaluated the safety and efficacy of dasatinib (Sprycel) in patients with AP CML resistant or intolerant to imatinib. At 1 year, PFS and OS were 66% and 82% respectively.[338] The efficacy of dasatinib in imatinib -resistant or intolerant patients with CML in myeloid blast crisis was evaluated in START-B. Median PFS and OS were 6.7 months and 11.8 months for patients in START-B.[339,340,341] The START-C trial evaluated dasatinib in CP CML patients who were resistant or intolerant to imatinib. After a median follow-up of 15.2 months, a complete hematologic response was attained or maintained in 91% of patients and a MCyR was attained or maintained by 59% (52% imatinib resistant and 80% imatinib intolerant). Fifteen month PFS was 90% and OS was 96%.[342]START-R compared dasatinib to high-dose imatinib (800 mg/day) in patients with CP- CML resistant to imatinib.[343] At a minimum follow-up of 2 years, dasatinib demonstrated higher rates CHR (93% versus 82%), MCyR (53% versus 33%), and CCyR (44% versus 18%). In addition, PFS also favored dasatinib. All of these studies dosed dasatinib as 70 mg twice daily.

A randomized, 2-arm, multicenter, open-label phase 3 trial evaluated dasatinib as either a 140 mg once daily or a 70 mg twice daily dosing schedule in 317 patients with AP-CML who were resistant or intolerant to imatinib.[344] The primary objective was to evaluate the efficacy of the 2 dosing schedules in terms of best-confirmed major hematologic response. Other secondary endpoints included evaluation of overall hematologic response, MCyR, time to and duration of responses, PFS, OS, and safety. Patients in both groups had comparable hematologic and cytogenetic response rates. Hematologic response rates were achieved in 66% of patients in the once-daily dose group (95% confidence interval [CI], 59 to 74) and 68% of patients in the twice daily group (95% CI, 60 to 75). The MCyR rate was 39% (95% CI, 31 to 47) in the once daily group and 43% (95% CI, 35 to 51) in the twice-daily group. Compared with 70 mg twice daily, 140 mg once daily was associated with a lower incidence of all-grade fluid-retention events, specifically fewer pleural effusions (all grades, 20% versus 39%, $p<0.001$) were seen in the once daily dose group. A similar proportion of patients in both groups had sustained a durable response at 24 months.

CA180-34: A phase 3 dose-optimization study in adults with CP-CML who were resistant to or intolerant of imatinib randomized 670 patients to dasatinib 100 mg once daily, 50 mg twice daily, 140 mg once daily, or 70 mg twice daily. Long-term follow-up results indicated the 6-year rate of survival without transformation to AP or BP on study treatment was 76% overall (100 mg once daily = 76%; 50 mg twice daily = 80%; 140 mg once daily = 83%; and 70 mg twice daily = 74%).[345] A final analysis at 7 years of follow up demonstrated that MMR, PFS, and OS were all similar across the different dosage groups. The incidence of drug-related pleural effusion was higher in the 100 mg arm at 28% compared to 35% with the other 3 dose groups. Arterial ischemic events occurred in ≤ 4% of patients across all dose groups.[346]

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dasatinib (Sprycel) – pediatric patients with CP-CML

A total of 97 pediatric patients with a diagnosis of CP-CML were treated with dasatinib across 2 trials. The median age of study participants was 13.5 years (range, 2 to 20 years). The first trial was a non-randomized, dose-finding trial and the second trial was an open-label, non-randomized, single-arm trial. Of the 97 patients, 91 were treated at a dose of dasatinib 60 mg/m^2 once daily (maximum dose, 100 mg daily) until disease progression or unacceptable toxicity. Of the 97 patients, 51 were newly diagnosed CP-CML patients and 46 were patients with a history of resistance or intolerance to previous treatment with imatinib. The median time to MMR was 8.3 months (95% CI, 5 to 11.8) across the entire cohort of patients. With a median follow up of 5.2 years, the median durations of CCyR and MMR could not be estimated because less than half of the patients with an initial response had eventually progressed. The range of DOR was 2.4 to 86.9+ months for CCyR and 2.6 to 73.6+ months for MMR.

imatinib (Gleevec) – chronic phase (CP), accelerated phase (AP), or blastic phase (BP) CML after failure of interferon-alfa therapy

Three trials established the role of imatinib after failure of interferon-alfa in either CP, AP, or BP CML.[347] For CP-CML, 532 patients were treated after failure of interferon therapy and there was a 95% complete hematologic response. For AP-CML, 235 patients were treated after failure of interferon therapy, there was a 71% complete hematologic response. Finally, for BP-CML, 260 patients were treated after failure of interferon therapy, there was a 31% complete hematologic response in this group.

imatinib (Gleevec) versus interferon-alfa/low-dose cytarabine

The IRIS (International Randomized Study of Interferon and STI571) trial was a phase 3, randomized, open-label trial that compared imatinib with interferon-alfa and low-dose cytarabine in 1,106 newly diagnosed CP-CML patients.[348] Crossover to the alternate group was allowed for cases of treatment failure or intolerance. The primary endpoint was disease progression defined as death from any cause during treatment, development of AP-CML or BP-CML, loss of complete hematologic response, loss of major cytogenetic response, or a rapidly increasing white cell count. Secondary endpoints were the rate of complete hematologic response, the rate of major cytogenetic response, safety, and tolerability. After a median follow-up of 19 months, the estimated rate of a major cytogenetic response at 18 months was 87.1% (95% CI, 84.1 to 90) versus 34.7% (95% CI, 29.3 to 40) and the estimated rates of complete cytogenetic response were 76.2% (95% CI, 72.5 to 79.9) and 14.5% (95% CI, 10.5 to 18.5) for imatinib and interferon/cytarabine, respectively (both $p<0.001$). The estimated rate of freedom from progression to AP-CML or BP-CML was 96.7% versus 91.5% favoring imatinib ($p<0.001$). At 12 months, the disease had not progressed in 96.6% of patients in the imatinib group compared to 79.9% in the interferon/cytarabine group ($p<0.001$). Imatinib was better tolerated than interferon/cytarabine. At a median follow-up of 10.9 years, the estimated OS of the group randomized to imatinib was 83.3% and serious adverse events considered to be related to imatinib were uncommon and occurred most frequently during the first year of treatment.[349] The authors concluded that efficacy of imatinib persisted over time and that long-term administration of imatinib was not associated with unacceptable cumulative or late toxic effects.

imatinib (Gleevec) – CP-CML pediatrics

An open-label, multicenter, single-arm phase 2 trial examined 51 pediatric patients with newly diagnosed and untreated CP-CML.[350] There was a 78% incidence of complete hematologic response after 8 weeks of therapy and the CCyR was 65%, comparable to results observed in adults.

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A phase 3 trial evaluated 146 children and adolescents (age range 1.3 to 18 years) with newly diagnosed CML-CP.[351] The trial also included 3 patients with CML-AP and 7 with CML-BP. Patients with CML-CP received imatinib 300 mg/m^2. With a median follow up time of 25 months, the event-free survival rate at 18 months for patients with CML-CP was 97% (95% CI 94.2-99.9)

nilotinib (Tasigna) versus imatinib (Gleevec) – first-line therapy

Evaluating Nilotinib Efficacy and Safety in Clinical Trials in Newly Diagnosed Patients (ENESTnd) was a randomized, open-label, multicenter, phase 3 study which randomized 846 patients with Ph+ chronic phase CML to nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, or imatinib 400 mg once daily.[352] At 12 months, the rates of major molecular response (primary endpoint) for nilotinib were 44 and 43% respectively (for the 300 mg and 400 mg doses) versus 22% for imatinib (p<0.001 for both comparisons). The rates of complete cytogenetic response by 12 months were significantly higher for nilotinib (80% for the 300 mg dose and 78% for the 400 mg dose) compared with imatinib (65%) (p<0.001 for both comparisons). Patients receiving either nilotinib dose had a significant improvement in the time to progression to accelerated phase (AP) or blast crisis (BC), compared with patients on imatinib (p=0.01 and p=0.004, respectively). None of the patients who progressed to the accelerated phase or blast phase had a major molecular response. Adverse events which occurred more frequently with imatinib were GI effects and fluid-retention. Dermatologic adverse events and headache were more frequent with nilotinib. Discontinuations due to increased aminotransferase and bilirubin levels were low in all 3 treatment arms. At 5-year follow up, significantly more patients in the nilotinib arms achieved MMR (77% for both nilotinib arms versus 60% for imatinib; p<0.0001). Fewer patients progressed to AP or BC in the nilotinib arms (10 patients in the 300 mg nilotinib twice daily arm, 6 patients in the nilotinib 400 mg twice daily arm, and 21 patients in the imatinib arm.) The rates of early molecular response were significantly higher for nilotinib across all risk groups. The estimated 5-year PFS and OS rates were 92% and 93.7%, 96% and 96%, and 91% and 913% respectively for nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib, respectively.[353]

nilotinib (Tasigna) – subsequent-line therapy

A phase 2 open-label trial evaluated the safety and efficacy of nilotinib 400 mg twice daily in patients with CP-CML (n=280) and AP-CML (n=119) resistant or intolerant to imatinib.[354,355] The efficacy endpoint for CP-CML was MCyR and the endpoint for AP-CML was major hematologic response (MHR). The overall MCyR at 2-year follow up for patients in the CP-CML arm was 59% and 77% of patients maintained MCyR at 24 months. In patients with AP-CML, confirmed hematologic response was seen in 55% of patients with at least 24-month follow-up. The estimated PFS and OS rates were 70% and 30%, respectively, for patients who entered the study with AP-CML.

nilotinib (Tasigna) – pediatrics with newly diagnosed CP-CML or resistant/intolerant CP-CML

Nilotinib was evaluated in 2 pediatric trials which resulted in pooled data for 69 children (from ages 2 to < 18 years old).[356] This pool included both newly diagnosed CP-CML pediatric patients (n=25) and imatinib/dasatinib resistant or intolerant CP-CML pediatric patients (n=44). Patients were dosed at 230 mg/m^2 twice daily, rounded to the nearest 50 mg with a maximum single dose of 400 mg). The cumulative MMR rate at 12 cycles for pediatric patients with newly diagnosed CP-CML was 64% and the cumulative MMR rate at 12 cycles for pediatric patients with resistant or intolerant CP-CML was 47.7%.

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nilotinib (Tasigna) – treatment discontinuation

ENESTop is an open-label, multicenter, single-arm study with 163 adult patients with CP-CML who have received TKIs for ≥ 3 years and who have achieved a sustained molecular response (MR4.5) on nilotinib following prior imatinib therapy.[357,358] Patients were required to have received imatinib for > 4 weeks without documented sustained molecular response on imatinib at the time of switching to nilotinib and then continued on nilotinib for at least 2 years and had achieved a MR4.5 on nilotinib. Of the 163 patients, 126 patients entered the treatment free remission (TFR) phase. At the 96-week data analysis cut-off, 61 patients (48.4%) had discontinued the TFR phase, 58 patients due to loss of MMR. Among those 58 patients, 56 patients restarted nilotinib and 52 patients (92.9%) regained a sustained molecular response. There were 4 patients (7.1%) who did not regain a sustained molecular response by the time of data cutoff.

ponatinib (Iclusig)

The PACE trial enrolled 449 adult patients onto a phase 2, single-arm, open-label trial of ponatinib 45 mg given once daily.[359] Patients had CP-CML, AP-CML, BP-CML or Ph+ALL. The patients were divided into 6 cohorts depending on their disease state, history of resistance or intolerance to a prior TKI, and their T315I mutation status. Primary endpoint for patients with CP-CML was MCyR and the primary endpoint for AP-CML, BP-CML, and Ph+ALL patients was major hematologic response (MHR). Secondary endpoints for all diagnoses included time to the response, duration of the response, PFS, OS, and safety. The trial included 37% of patients who had received 2 previous TKIs (imatinib, dasatinib, nilotinib, or bosutinib) and 55% had received 3 or more TKIs. Of the CP-CML patients who achieved a MCyR (56 %), the average time to reach MCyR was 2.8 months (range, 1.6 to 11.3). Among CP-CML patients who achieved MCyR, responses were durable in 91% at 12 months. The estimated PFS and OS at 12 months were 80% and 94%, respectively.[360] For AP-CML, BP-CML, and Ph+ALL, which included the resistant or intolerant cohort, as well as the T315I mutation cohort, the rates of MHR were 55%, 31%, and 41%, respectively. The time to reach MHR was 3 weeks (range, 2 to 25), 4.1 weeks (range, 1.7 to 16.1), and 2.9 weeks (range, 1.6 to 24), respectively. The median DOR was 12 months, 5 months, and 3 months, respectively. Response rates were high among all patients in any stage with a T315I mutation, which is resistant to all other targeted therapies. Hematologic adverse events included thrombocytopenia (37% of patients), neutropenia (19% of patients), and anemia (13% of patients). Nonhematologic serious adverse events occurring in more than 1% of patients included pancreatitis (5%), abdominal pain (2%), and increased lipase levels (2%). Serious-grade arterial thrombotic events (including cardiovascular, cerebrovascular, and peripheral vascular events) were seen in 8.9% of patients in the trial. Data on an additional 13 months of exposure in patients who continued in the trial showed the cumulative incidence of serious arterial thrombotic events was 11.8%; the incidence of all arterial thrombotic events, serious or not, was 17.1%. Of the 270 patients on the trial who had CP-CML, the 5-year results indicated that 60% of patients achieved a MCyR and 40% achieved a MMR.[361] Estimated 5-year survival was 73% for patients with CP-CML. The most common adverse events were rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), dry skin (42%), and constipation (41%).

Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia (HES/CEL)

imatinib (Gleevec)

An open-label, multicenter, phase 2 trial was conducted with imatinib in patients diagnosed with life-threatening diseases associated with Abl, Kit, or platelet derived growth factor receptor (PDGFR) protein tyrosine kinases.[362] Fourteen of these patients were diagnosed with HES/CEL. HES patients

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were treated with 100 mg to 1,000 mg of imatinib daily. A further 162 patients with HES/CEL were reported in 35 published case reports and case series. These patients received imatinib at doses of 75 mg to 800 mg daily. Overall, 61% of patients had a complete hematologic response and 13% had a partial hematologic response.

Multiple Myeloma

ixazomib (Ninlaro)/lenalidomide/dexamethasone versus placebo/lenalidomide/dexamethasone

TOURMALINE-MM1: The efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone were evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients with relapsed and/or refractory multiple myeloma who had received at least 1 prior line of therapy.[363] A total of 722 patients were randomized in a 1:1 ratio to receive either the combination of ixazomib, lenalidomide, and dexamethasone (n=360) or placebo, lenalidomide, and dexamethasone (n=362) until disease progression or unacceptable toxicity. Patients received ixazomib 4 mg or placebo on days 1, 8, and 15 plus lenalidomide (25 mg) on days 1 through 21 and dexamethasone (40 mg) on days 1, 8, 15, and 22 of a 28-day cycle. Response was assessed every 4 weeks until disease progression. At a median follow up of 14.7 months, PFS of the ixazomib regimen was 20.6 months compared to 14.7 months for the placebo regimen (HR, 0.74; p=0.01). A planned interim OS analysis was conducted with 35% of the required number of deaths for final OS analysis; there were 81 deaths in the ixazomib group and 90 deaths in the control group. An OS benefit was not demonstrated but follow-up is ongoing. The rates of serious adverse events were similar between the 2 regimens (47% for ixazomib (Ninlaro) group and 49% in placebo group). Grade 3 or 4 thrombocytopenia occurred more frequently in ixazomib-treated patients (12% and 7% versus 5% and 4%, respectively). Patients reported similar quality of life scores in the 2 groups. A preplanned subanalysis assessed the safety and efficacy of the 2 groups according to individual patient cytogenetic risks.[364] High-risk cytogenetic abnormalities included del(17p), t(4;14), and/or t(4;16). Of the 722 randomized patients, 522 had available cytogenetic results and 137 (25%) were identified as having 1 of the high-risk cytogenetic abnormalities. Median PFS of 20.6 months versus 15.6 months was seen in the ixazomib arm compared to the placebo arm with HR equal to 0.64 (95% CI, 0.462 to 0.888; p=0.007).

lenalidomide /dexamethasone versus melphalan/prednisone/thalidomide (MPT) – first-line therapy

The FIRST (Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide) trial was a phase 3, open-label, randomized trial enrolling 1,623 previously untreated, symptomatic, stem cell transplant-ineligible patients to 1 of 3 arms.[365] These arms included lenalidomide and dexamethasone in 28-day cycles for either 72 weeks (n=541) or until disease progression (n=535) or the standard therapy arm (n=547) with melphalan/prednisone/thalidomide (MPT). The primary endpoint was PFS. At a median of 37 months of follow-up, PFS was 25.5 months with continuous dosing of lenalidomide/dexamethasone, 20.7 months for the 72 week arm of lenalidomide/dexamethasone therapy, and 21.2 months for the standard therapy (MPT) arm (HR, 0.72 for continuous lenalidomide-dexamethasone versus MPT; p<0.001). Continuous lenalidomide-dexamethasone was also superior to MPT for OS at 4 years (59% versus 51%). Patients in the continuous lenalidomide/dexamethasone arm had fewer hematologic and neurologic toxicities but a higher incidence of infections compared to the MPT arm.

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lenalidomide – multiple myeloma maintenance therapy after auto-HSCT

Two randomized, double blind, placebo controlled studies evaluated the efficacy and safety of lenalidomide maintenance therapy in multiple myeloma patients after auto-HSCT.[366] Study 1 enrolled 460 patients who underwent induction therapy followed by auto-HSCT; within 90 to 100 days after auto-HSCT patients with at least a stable disease response were randomized to either lenalidomide or placebo maintenance. Study 2 enrolled 614 patients with multiple myeloma who were randomized within 6 months after induction therapy and auto-HSCT to either lenalidomide or placebo. In both studies, lenalidomide was dosed at 10 mg once day on days 1 to28 of repeated 28-day cycles. Dose reductions or increases were allowed per protocol-defined parameters. The major efficacy endpoint of both studies was PFS. At the preplanned interim analyses of both studies, the respective data monitoring committees recommended unblinding the trials due to data favoring lenalidomide over placebo. At the time of unblinding, the PFS in Study 1 was a median of 33.9 months for the lenalidomide maintenance arm versus 19.0 months in the placebo arm (HR, 0.38; 95% CI, 0.27 to 0.54) and in Study 2, the PFS was a median of 41.2 months in the lenalidomide arm and 23.0 months in the placebo arm (HR, 0.5; 95% CI, 0.39-0.54). OS updated at a subsequent analysis demonstrated a median OS of 111 months versus 84.2 months and 105.9 months versus 88.1 months for lenalidomide and placebo in Studies 1 and 2, respectively.

melphalan/prednisone/thalidomide (MPT) versus melphalan/prednisone/lenalidomide (MPL)

E1A06: A phase 3, randomized, multicenter trial compared MPT with MPL as primary treatment in newly diagnosed elderly patients (n=306) with multiple myeloma who were not transplant eligible.[367] The median age of the patients enrolled was 75.7 years. At a median follow up of 41 months, there was no statistically significant difference in terms of efficacy. PFS was 21 months on the MPT arm and 18.7 months on the MPL arm (HR, 0.84; 95% CI, 0.64 to 1.09). OS was 52.6 months for MPT patients and 47.7 months for MPL patients (p=0.476). The toxicity profile differed between the 2 regimens with grade 3 or higher nonhematologic toxicity rates of 59.9% for MPT-treated patients and 40% for MPL-treated patients. Quality of life analysis favored MPL over MPT at the end of induction (p=0.007).

panobinostat (Farydak)/bortezomib/dexamethasone versus placebo/bortezomib/dexamethasone

PANORAMA1: The efficacy and safety of panobinostat in combination with bortezomib (Velcade®) and dexamethasone was evaluated in a randomized, double-blind, placebo-controlled, phase 3, multicenter study in patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy. Treatment was administered for a maximum of 16 cycles (48 weeks).[368] A total of 768 patients were randomized in a 1:1 ratio to receive either the combination of panobinostat, bortezomib, dexamethasone (n=387) or placebo, bortezomib, dexamethasone (n=381), stratified by prior use of bortezomib and the number of prior lines of anti-myeloma therapy. Demographics and baseline disease characteristics were balanced between arms. The median number of prior therapies was 1; 48% of patients received 2 or 3 prior lines of therapy. More than half (57%) of the patients had prior stem cell transplantation. The most common prior antineoplastic therapies were, in order of prevalence: corticosteroids, melphalan, thalidomide, cyclophosphamide, bortezomib, and lenalidomide. The median duration of follow-up was 29 months in both arms. The primary endpoint was PFS, using modified European Bone Marrow Transplant Group (EBMT) criteria, as assessed by the investigators. In the overall trial population, the median PFS was 12 months (95% CI, 10.3 to 12.9) in the panobinostat, bortezomib, dexamethasone arm and 8.1 months (95% CI, 7.6 to 9.2) in the placebo, bortezomib, dexamethasone arm, (HR, 0.63; 95% CI, 0.52 to 0.76). At the time of interim analysis, OS was not statistically different between arms. The ORR did not differ between the 2 groups; however,

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there was a higher complete or near complete response rate in the panobinostat group (107 versus 60 in the placebo group, p=0.00006).The most common grade 3 to 4 serious adverse events were thrombocytopenia (67% in the panobinostat group versus 31% in the placebo group), lymphopenia (53% versus 40%), diarrhea (26% versus 8%), fatigue (24% versus 12%), and peripheral neuropathy (18% versus 15%) for panobinostat group compared to placebo, respectively.

The approval of panobinostat was based upon the efficacy and safety in a pre-specified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of 2 prior therapies as the benefit to risk ratio appeared to be greater in this more heavily pretreated population than in the overall trial population. Of these 193 patients, 76% of them had received ≥ 2 prior lines of therapy. The median PFS was 10.6 months (95% CI, 7.6 to 13.8) in the panobinostat, bortezomib, and dexamethasone arm and 5.8 months (95% CI, 4.4 to 7.1) in the placebo, bortezomib, and dexamethasone arm (HR, 0.52; 95% CI, 0.36 to 0.76).

pomalidomide (Pomalyst) plus low-dose dexamethasone versus high-dose dexamethasone alone

MM-003: A randomized, open-label, international multicenter, phase 3 trial was conducted in patients with refractory or relapsed refractory multiple myeloma who had failed at least 2 previous treatments including bortezomib and lenalidomide.[369] The 302 patients were randomized 2:1 to receive either pomalidomide 4 mg/day on days 1 through 21 plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22) or high-dose dexamethasone (40 mg/day on days 1 through 4, 9 through 12, and 17 through 20). Pomalidomide plus low-dose dexamethasone was chosen as the control arm based on a previous study which had shown superior ORR for pomalidomide plus low-dose dexamethasone compared to single agent pomalidomide (ORR, 33% versus 8%, respectively).[370] Therapy for the pomalidomide plus low-dose dexamethasone versus pomalidomide plus high-dose dexamethasone was continued until disease progression or unacceptable toxicity. The primary endpoint was PFS. After a median follow-up of 10 months, the median PFS was 4 months (95% CI, 3.6 to 4.7) for the pomalidomide-low dose dexamethasone arm versus 1.9 months (95% CI, 1.9 to 2.2) with high-dose dexamethasone (HR, 0.48 [95% CI, 0.39 to 0.6; p<0.001]). The incidence of grade 3 to 4 neutropenia (48% versus 16%) was higher in the combination arm but the incidences of anemia (33% versus 37%) and thrombocytopenia (22% versus 26%) were higher in the high-dose dexamethasone arm. Nonhematologic grade 3 to 4 adverse events occurring more commonly in the pomalidomide combination arm were pneumonia (13% versus 8%) and bone pain (7% versus 5%).

selinexor (Xpovio) plus dexamethasone – relapsed/refractory to ≥ 4 prior therapies, including ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody

STORM: A phase 2b, multinational, single-arm, open-label study assessed the safety and effectiveness of selinexor in 202 adult patients with relapsed or refractory multiple myeloma.[371,372] The 2-part study assessed the role of selinexor in patients with (1) quad-refractory (bortezomib, carfilzomib, lenalidomide, and pomalidomide) and penta-refractory (also refractory to anti-CD38 antibody) multiple myeloma (MM) and (2) penta-refractory MM only. Included patients were required to have a diagnosis of MM based on modified International Myeloma Working Group (IMWG) guidelines, and those with smoldering or active CNS MM, plasma cell leukemia, or systemic amyloid light chain amyloidosis were excluded. All patients received twice weekly oral selinexor 80 mg and dexamethasone 20 mg on days 1 and 3 of each week until disease progression, death, or unacceptable toxicity. The primary endpoint was ORR, as assessed by an Independent Review Committee (IRC) based on the IMWG Uniform Response Criteria for Multiple Myeloma. The approval of selinexor is based on a prespecified subgroup analysis of patients' refractory to bortezomib, carfilzomib (≥ 2 proteasome inhibitors), lenalidomide,

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pomalidomide (≥ 2 immunomodulators), and daratumumab (anti-CD38 monoclonal antibody). This subgroup of more heavily treated patients (83 of the 122 participants in Part 2) was defined as most likely to have the greatest benefit to risk ratio compared to the overall trial population. The median age of this group was 65 years (range, 40 to 86 years), and the majority were male (61%) and Caucasian (70%). The median number of years since diagnosis was 7 (range, 1 to 23), the median number of prior treatment regimens was 8 (range, 4 to 18), and 81% had a previous stem cell transplant. The ORR in this subgroup was 25.3% (95% CI, 16.4 to 36). Stringent CR, CR, very good PR, and PR occurred in 1, 0, 4, and 16 patients, respectively. The median time to first response and DOR were 4 weeks (range, 1 to 10) and 3.8 months (95% CI, 2.3 to not estimable), respectively.

thalidomide (Thalomid)/dexamethasone versus dexamethasone alone

A randomized, open-label, phase 3 trial compared thalidomide plus dexamethasone (n=103) to dexamethasone alone (n=104) in newly diagnosed multiple myeloma patients.[373] Thalidomide was dosed at 200 mg daily for 4 weeks. Dexamethasone was dosed at 40 mg orally on days 1 through 4, days 9 to 12, and days 17 through 20. Each cycle was repeated every 4 weeks. The primary endpoints were best response within 4 cycles of treatment and toxicity during this same time frame. The best response within 4 cycles of therapy was significantly higher with thalidomide/dexamethasone compared with dexamethasone alone; 63% versus 41%, respectively (p=0.0017). Grade 3 or higher nonhematologic toxicities were seen with 67% of patients within 4 cycles with the combination and 43% of dexamethasone monotherapy arm (p<0.001). These grade 3 or higher toxicities seen more frequently in the combination arm included deep vein thrombosis (DVT) (17% versus 3%), skin rash (4% versus zero), bradycardia (1% versus zero), and peripheral neuropathy (7% versus 4%). On the basis of these results, routine DVT prophylaxis is recommended in all patients being treated with thalidomide/dexamethasone.

Myelofibrosis (MF)

fedratinib (Inrebic) and placebo

JACARTA:[374,375] A phase 3, multinational, randomized, double-blind, placebo-controlled trial assessed safety and effectiveness of fedratinib for the treatment of patients with intermediate-2 or high-risk primary or secondary MF (post-polycythemia vera MF or post-essential thrombocythemia MF with splenomegaly; n=289). Included patients were randomized to fedratinib 500 mg, fedratinib 400 mg, or placebo once daily for ≥ 6 cycles. At baseline, 64% had primary MF, 26% had post-polycythemia vera MF, and 10% had post-essential thrombocytopenia MF, of which 52% had intermediate-2 risk and 48% had high-risk disease. The median age was 65 years (range, 27 to 86) and 59% were male. The primary outcome was spleen response, defined as the proportion of patients achieving ≥ 35% reduction from baseline in spleen volume at the end of cycle 6 (as measured by magnetic resonance imaging [MRI] or computerized tomography [CT] scan) and confirmed with a follow-up scan 4 weeks later. This was achieved in 36% (95% CI, 27 to 46) of fedratinib 400 mg-treated patients and 40% (95% CI, 30 to 50) of fedratinib 500 mg-treated patients compared to 1% (95% CI, 0 to 3) of placebo-treated patients (p<0.0001). Per Kaplan-Meier estimates, the median DOR was 18.2 months in the fedratinib 400 mg treatment group. In addition, 36% (95% CI, 26 to 46) of fedratinib 400 mg-treated patients and 34% (95% CI, 24 to 44) of fedratinib 500 mg-treated patients achieved ≥ 50% reduction in total symptom score at the end of cycle 6 on the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary compared to 7% (95% CI, 2 to 13) of placebo-treated patients. The MFSAF assesses 6 of the core symptoms of MF (p<0.0001). The most common adverse effects were anemia, GI toxicity, and increased liver enzymes, serum creatinine, and pancreatic enzymes; however, 4 cases of

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encephalopathy occurred in the fedratinib 500 mg/day treatment group. Fedratinib is not approved for use as 500 mg/day.

ruxolitinib (Jakafi) and placebo

COMFORT-I:[376,377,378] This randomized, double-blind, placebo-controlled, phase 3, study, compared ruxolitinib to placebo in 309 MF patients who were refractory to or were not candidates for available therapy. The primary efficacy endpoint (proportion of patients achieving ≥ 35% reduction from baseline in spleen volume at week 24 as measured by MRI or CT) was reached in 41.9% of ruxolitinib patients compared with 0.7% of placebo (p<0.0001). A reduction in spleen volume was maintained in patients who received ruxolitinib; 67% of the patients with a response had the response for 48 weeks or more. There was an improvement of ≥ 50% in the total symptom score at 24 weeks in 45.9% of patients who received ruxolitinib versus 5.3% of patients who received placebo (p<0.0001). Patients treated with ruxolitinib demonstrated clinically meaningful improvements in quality of life scoring while those receiving placebo had diminished scores on standardized quality of life assessment tools. Thirteen deaths occurred in the ruxolitinib group versus 24 deaths in the placebo arm (HR, 0.5; 95% CI, 0.25 to 0.98; p=0.04). The rate of discontinuation due to adverse events was 11% in the ruxolitinib group and 10.6% in placebo. Published 2-year follow-up to COMFORT-I demonstrated that 100 of the 155 patients randomized to ruxolitinib were still receiving treatment.[379] Mean spleen volume reductions in the ruxolitinib group were 34.9% at week 96; improvements in quality of life measures were also maintained. Improved survival was observed for ruxolitinib (27 deaths) versus placebo (41 deaths) (HR, 0.58; 95% CI, 0.36 to 0.95; p=0.03). At the final 5-year trial results, a total of 27.7% of patients initially randomized to ruxolitinib were still receiving treatment compared to no patients who were initially randomized to placebo while 25.2% of patients who crossed over to ruxolitinib were still receiving treatment.[380] The median DOR to reduced spleen volume was 168.3 weeks for patients randomized to ruxolitinib and that same group demonstrated prolonged OS compared to patients initially randomized to placebo despite the crossover to ruxolitinib (OS not reached in ruxolitinib arm versus 200 weeks in the placebo initial randomization arm; HR, 0.69 [95% CI 0.5 to 0.96; p=0.025]). No new safety signals were seen in this long-term analysis compared to those already previously reported.

COMFORT-II: [381,382] A randomized, open-label study in 219 MF patients compared (2:1) ruxolitinib to best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. Medications received by over 10% of patients were hydroxyurea (47%) and glucocorticoids (16%). A total of 28% of ruxolitinib patients had at least a 35% reduction in spleen volume at week 48 (primary endpoint), versus 0% in the group receiving the best available therapy (p<0.0001); the corresponding percentages at week 24, were 32% and 0% (p<001). At 48 weeks, the mean palpable spleen length had decreased by 56% with ruxolitinib but had increased by 4% with the best available therapy. The median DOR was not reached with ruxolitinib, with 80% of patients still having a response at a median follow-up of 12 months. A secondary endpoint was the proportion of patients achieving a ≥ 35% reduction of spleen volume was shown in 31.9% of ruxolitinib patients versus 0% with best available therapy at week 24 (p<0.0001). The most common hematologic abnormalities (≥ grade 3) in either group were thrombocytopenia and anemia. A published 3-year follow-up of the COMFORT-II study demonstrated that 45% of patients initially randomized to ruxolitinib remained on treatment.[383] Patients with spleen volume reductions ≥ 35% by MRI (equivalent to approximately 50% reduction by palpation) had a sustained response for at least 144 weeks. Anemia and thrombocytopenia were the main toxicities at the 3-year follow-up but these were generally manageable, improved over time, and led to treatment discontinuation in only 3.6% of patients. Finally, patients randomized to ruxolitinib showed longer OS than those randomized to best available therapy (HR, 0.48; 95% CI, 0.28 to 0.85;

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p=0.009).

A pooled analysis of OS in both the COMFORT I and the COMFORT II trials was conducted.[384] Overall, 301 patients received ruxolitinib (155 in COMFORT I and 146 in COMFORT II) compared to 154 patients who received placebo (COMFORT I) and 73 patients who received best available therapy (COMFORT II). OS at week 144 was 78% for patients who received ruxolitinib compared to 61% in the 2 control groups (HR, 0.65; 95% CI, 0.46 to 0.9; p=0.01).

Non-Hodgkin's Lymphomas

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

acalabrutinib (Calquence) monotherapy versus acalabrutinib plus obinutuzumab (Gazyva) versus obinutuzumab plus chlorambucil – previously untreated

A phase 3, randomized, global, multicenter, open-label, controlled trial evaluated acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab in 535 treatment-naïve CLL patients (ELEVATE TN, NCT02475681).[385,386] Patients in the acalabrutinib treatment arm (n=179) received 100 mg twice a day until progressive disease or unacceptable toxic effects occurred. For patients receiving acalabrutinib and obinutuzumab (n=179), acalabrutinib, at the dosing regimen listed above, was administered for 1 cycle prior to obinutuzumab administration to decrease the likelihood for infusion-related reactions with IV obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1,000 mg), and 15 (1,000 mg) of cycle 2 and on day 1 (1,000 mg) of cycles 3 through 7. For patients in the chlorambucil plus obinutuzumab group (n=177), oral chlorambucil was given at a dose of 0.5 mg/kg on days 1 and 15 of each cycle, for 6 cycles, and IV obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1,000 mg), and 15 (1,000 mg) of cycle 1 and on day 1 (1,000 mg) of cycles 2 through 6. The primary endpoint was PFS for the 2 combination groups as assessed by an IRC; crossover to acalabrutinib was allowed in patients who progressed on obinutuzumab plus chlorambucil. After a median follow-up time of 28.3 months, the median PFS was longer with acalabrutinib plus obinutuzumab and acalabrutinib monotherapy, than with obinutuzumab plus chlorambucil (not reached [NR] with acalabrutinib + obinutuzumab versus 22.6 months with obinutuzumab + chlorambucil, hazard ratio [HR] 0.1; 95% CI, 0.06 to 0.17; p<0.0001; and NR with acalabrutinib monotherapy versus 22.6 months with obinutuzumab + chlorambucil, HR 0.2; 95% CI, 0.13 to 0.3; p<0.0001). Overall, estimated PFS at 24 months was 93% with acalabrutinib + obinutuzumab (95% CI, 87 to 96), 87% with acalabrutinib monotherapy (95% CI, 81 to 92), and 47% with obinutuzumab + chlorambucil (95% CI, 39 to 55). Acalabrutinib alone as monotherapy or in combination with obinutuzumab resulted in a statistically significant improvement in PFS compared to obinutuzumab + chlorambucil in treatment-naive CLL patients.

acalabrutinib versus investigator's choice of idelalisib (Zydelig) plus rituximab (Rituxan) or bendamustine plus rituximab – relapsed or refractory CLL after at least 1 prior systemic therapy

A multicenter, randomized, open-label trial evaluated acalabrutinib as monotherapy in 310 relapsed or refractory CLL patients (ASCEND, NCT02970318).[387] Patients had disease progression following at least 1 prior systemic therapy; patients with transformed disease, prolymphocytic leukemia, or prior treatment with venetoclax, a BTK inhibitor, or a phosphoinositide-3 kinase inhibitor were excluded. Patients were randomized 1:1 to acalabrutinib 100 mg approximately every 12 hours until disease progression or unacceptable toxicity (n=155) or investigator's choice (n=155) of either: (A) idelalisib 150 mg orally approximately every 12 hours, in combination with 8 infusions of rituximab dosed at 375 mg/m^2 IV on day 1 of cycle 1, followed by 500 mg/m^2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses with a 28-day cycle length; or (B) bendamustine 70 mg/m^2 IV on day 1 and 2 of each

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28-day cycle in combination with rituximab dosed as 375 mg/m^2 IV on day 1 of cycle 1, then 500 mg/m^2 on day 1 of subsequent cycles for up to 6 cycles. The primary efficacy endpoints was PFS as determined by IRC. At a median follow-up of 16.1 months, the median PFS was not estimable in the acalabrutinib monotherapy arm compared to 16.4 months (95% CI, 14 to 17.1) in the investigator's choice arm corresponding with an HR of 0.31 (95% CI, 0.2 to 0.49; p<0.0001).

chlorambucil versus chlorambucil plus rituximab (Rituxan) or chlorambucil plus obinutuzumab (Gazyva) – previously untreated

A phase 3, randomized trial evaluated chlorambucil as monotherapy compared to chlorambucil in combination with a CD20 antibody (either rituximab or obinutuzumab).[388] A total of 781 patients with previously untreated CLL and an estimated CrCl of 30 to 69 mL/min or a cumulative illness rating score (CIRS) greater than 6 (range, 0 to 56; higher numbers indicating a higher degree of illness) were randomized in a 1:2:2 fashion. Patients received 6 cycles of treatment (28-day cycles). The primary endpoint was PFS as assessed by the site investigators; secondary endpoints included event-free survival, the time to new treatment, adverse events, and OS. The chlorambucil combination arms (rituximab or obinutuzumab) both had significantly improved median PFS compared to the chlorambucil alone arm. For the obinutuzumab combination, the median PFS was 26.7 months compared to 11.1 months for chlorambucil alone (HR, 0.18; 95% CI, 0.13 to 0.24; p<0.001) and for the rituximab combination, the PFS was 16.3 months (HR, 0.44; 95% CI, 0.34 to 0.57; p<0.001). This benefit was seen in all analyzed subgroups, except in patients with del (17p). When the 2 combination arms were compared, there was a significant improvement in PFS for obinutuzumab-chlorambucil compared to rituximab-chlorambucil (26.7 months versus 15.2 months; HR, 0.39; 95% CI, 0.31 to 0.49; p<0.001). There were more adverse events noted in the chlorambucil-obinutuzumab arm with myelosuppression and infusion related reactions occurring more frequently than in the other 2 arms of the study. However, the percentage of patients who died because of an adverse event was lower in the obinutuzumab-chlorambucil group (4%) compared to either the rituximab-chlorambucil group (6%) or the chlorambucil alone group (9%). At the time of study publication, OS was significantly better in the obinutuzumab-chlorambucil arm compared to chlorambucil alone (HR, 0.41; 95% CI, 0.23 to 0.74; p=0.002). There was no statistically significant difference in OS with rituximab-chlorambucil versus chlorambucil alone or obinutuzumab-chlorambucil compared to rituximab-chlorambucil.

duvelisib (Copiktra) – relapsed or refractory patients

DUO: A multicenter, phase 3, randomized, open-label study compared duvelisib to ofatumumab in 319 patients with CLL/SLL, after ≥ 1 previous therapy. Patients were randomized 1:1 to receive either duvelisib 25 mg twice daily or intravenously administered ofatumumab.[389,390] The study met the primary endpoint, with significant improvement in PFS compared to ofatumumab for all patients (median, 13.3 months versus 9.9 months, respectively; HR, 0.52; p<0.0001) as assessed by the IRC. ORR was higher with duvelisib than ofatumumab (74% versus 45%, respectively; p<0.0001). Adverse events that were identified as grade 3 or higher occurred in 87% of duvelisib patients and 48% of ofatumumab patients. Pneumonia was the most frequently reported serious adverse events reported in both treatment groups (duvelisib 15%; ofatumumab 3%). In the ofatumumab arm, 7 patients had fatal adverse events; however, none were attributed to the study drug.

ibrutinib (Imbruvica) versus chlorambucil (Leukeran) – previously untreated CLL without 17p deletion

RESONATE-2 was a randomized, international, open-label, phase 3 trial which examined the use of ibrutinib compared to chlorambucil for patients (n=269) with previously untreated CLL who were 65 years or older and who did not have a chromosome 17p13.1 deletion.[391] Patients assigned to the

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ibrutinib arm continued therapy until disease progression or unacceptable toxicity. Patients assigned to chlorambucil were treated for up to 12 cycles or until disease progression, determination of lack of a response, or unacceptable toxicity, whichever occurred first. The primary endpoint was PFS as assessed by an IRC according to the iwCLL criteria, with modification to account for the known treatment-related lymphocytosis with ibrutinib, which, in the absence of other indicators does not qualify as progressive disease. At a median follow-up of 18.4 months, ibrutinib significantly prolonged PFS compared to chlorambucil (median not reached versus 18.9 months, respectively). The relative risk of disease progression or death was 84% lower with ibrutinib therapy compared to chlorambucil therapy (HR, 0.16; 95% CI, 0.09 to 0.28; p<0.001). The median OS had not been reached in either group but the OS rate at 24 months was 98% with ibrutinib versus 85% with chlorambucil (HR, 0.16, 95% CI, 0.05 to 0.56; p=0.001). The most common adverse effect in ibrutinib-treated patients was diarrhea (42% with grade 3 diarrhea in 4% of patients). Other adverse effects that occurred in 20% or more of ibrutinib-treated patients were fatigue, nausea, and cough. Adverse events that occurred in 20% or more of chlorambucil-treated patients included fatigue, neutropenia, nausea, anemia, and vomiting. More patients discontinued chlorambucil (23%) due to adverse effects compared to ibrutinib (9%). At 24 month follow up, the rate of PFS in ibrutinib-treated patients was 89% and ORR was 92%.[392] With a median follow up of 60 months, PFS and OS continued to favor ibrutinib over chlorambucil. For ibrutinib versus chlorambucil, respectively, PFS was 70% versus 12 % (HR, 0.146; 95% CI, 0.098 to 0.218) and OS was 83% versus 68% (HR, 0.45; 95% CI 0.266 to 0.761).[393]

ibrutinib (Imbruvica) plus rituximab (Rituxan) versus chemoimmunotherapy (fludarabine/cyclophosphamide/rituximab (Rituxan) – previously untreated CLL

A phase 3, multicenter, open-label trial randomized 529 patients who were 70 years of age or younger and had previously untreated CLL to ibrutinib 420 mg/day plus rituximab or chemoimmunotherapy consisting of fludarabine, cyclophosphamide and rituximab.[394] Both regimens were 28-day cycles and administered for 6 cycles; in the ibrutinib/rituximab arm, ibrutinib monotherapy was continued until disease progression. Patients were stratified according to age, ECOG performance status, Rai stage, and the presence or absence of chromosome 11q22.3 deletion. The primary endpoint was PFS while OS was a secondary endpoint. There were interim analyses planned at 24 to 27 months after full enrollment and then annually until data maturity. At a median follow-up of 33.6 months, PFS favored ibrutinib/rituximab over chemoimmunotherapy, 89.4% versus 72.9% at 3 years (HR, 0.35; 95% CI, 0.22 to 0.56; p<0.001). OS also favored ibrutinib/rituximab over chemoimmunotherapy; 90.7% versus 62.5% at 3 years (HR, 0.17; 95% CI, 0.05 to 0.54; p<0.001). In the subgroup of patients without IGHV mutation, ibrutinib/rituximab showed superior PFS at 3 years (90.7% versus 62.5%; HR, 0.26; 95% CI, 0.14 to 0.5; however, in the subgroup with IGHV mutation, the PFS was 87.7% for ibrutinib/rituximab and 88% in the chemoimmunotherapy group (HR, 0.44; 95% CI, 0.14 to 1.36). When examining the grade 3 or higher adverse events, there was a lower incidence of neutropenia in the ibrutinib/rituximab group compared to the chemoimmunotherapy group (25.6% versus 44.9%) as well as a lower incidence of infectious complications including neutropenic fever (10.5% versus 20.3%). Grade 3 or higher hypertension (18.8% versus 8.2%) and hemorrhagic events (1.1% versus 0%) occurred in the ibrutinib/rituximab arm compared to the chemoimmunotherapy arm. Atrial fibrillation of any grade occurred in 7.4% of ibrutinib/rituximab patients compared to 3.2% of chemoimmunotherapy patients.

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ibrutinib (Imbruvica) versus ibrutinib (Imbruvica) plus rituximab (Rituxan) versus chemoimmunotherapy (bendamustine [Treanda]) plus rituximab (Rituxan) – previously untreated CLL

A phase 3, randomized trial was conducted in patients ≥ 65 years of age who had previously untreated CLL.[395] Patients were randomly assigned to receive either bendamustine plus rituximab, ibrutinib monotherapy, or ibrutinib plus rituximab. Patients were stratified by risk category according to Rai stage, del17p or del11q status, and ZAP70 methylation status. Each treatment arm utilized 28-day treatment cycles. Bendamustine/rituximab and the rituximab/ ibrutinib were administered for 6 cycles while both ibrutinib-containing arms continued receiving ibrutinib until unacceptable toxic effects or disease progression. The estimated percentage of patients with PFS at 2 years was 74% (95% CI, 66 to 80) with bendamustine/rituximab, 87% (95% CI, 81 to 92) with ibrutinib, and 88% (95% CI, 81 to 92) with ibrutinib plus rituximab. The hazard ratios for disease progression or death were 0.39 (95% CI, 0.26 to 0.58) for the comparison of ibrutinib versus bendamustine/rituximab (p<0.001) and 0.38 (95% CI, 0.25 to 0.59) for the comparison of ibrutinib/rituximab versus bendamustine/rituximab (p<0.001). There was no significant difference between the ibrutinib plus rituximab group compared to the ibrutinib monotherapy group regarding PFS (HR, 1; 95% CI, 0.62 to 1.62; p=0.49). With a median follow-up of 38 months there was no significant difference among the 3 groups with regard to OS. The rates of serious hematologic adverse events were higher with bendamustine/rituximab while the rates of serious non-hematologic adverse events were higher with the ibrutinib-containing regimens.

ibrutinib (Imbruvica) plus bendamustine and rituximab versus placebo plus bendamustine and rituximab – previously treated without 17p deletion

HELIOS was a phase 3, placebo-controlled trial comparing ibrutinib added to bendamustine/rituximab with placebo added to bendamustine/rituximab in previously treated CLL patients without 17p deletion.[396] A total of 578 patients were randomized 1:1 to either ibrutinib (420 mg daily) or placebo, in combination with 6 cycles of bendamustine/rituximab, followed by either ibrutinib or placebo alone. PFS at 36 months was 68% for the ibrutinib-containing arm and 13.9% for the placebo-containing arm. Median OS was not reached in either arm. MRD-negative responses were 26.3% for the ibrutinib arm and 6.2% for the placebo arm (p<0.001).

ibrutinib (Imbruvica) – previously treated CLL with 17p deletion

RESONATE-17 was a phase 2, open-label, multicenter study involving 144 previously treated del 17p deletion CLL or SLL patients.[397] Enrolled patients had received a median of 2 previous treatments. Ibrutinib 420 mg was given orally once daily until progressive disease or unacceptable toxicity. The primary endpoint was ORR, but there were preplanned exploratory analyses for both PFS and OS. With a median follow up of 11.5 months, the ORR was 64% (95% CI, 56 to 71) according to an IRC and 83% (95% CI, 76 to 88) according to investigator assessment. The PFS and OS at 24 months were 63% (95% CI, 54 to 70) and 75% (95% CI, 67 to 81), respectively. Serious toxicities observed included major bleeding (9%) and grade 3 or higher infections (30%), including pneumonia (13%).

ibrutinib (Imbruvica) plus rituximab (Rituxan) versus fludarabine, cyclophosphamide, and rituximab

E1912 was a multicenter, open-label, randomized, phase 3 assessing the efficacy and safety of treatment with ibrutinib in combination with 6 cycles of rituximab (n=354) compared to chemoimmunotherapy with fludarabine plus cyclophosphamide plus rituximab (FCR, n=175).[398,399] Patients enrolled were previously untreated patients with CLL who were ≤ 70 years of age; patients with 17p deletion were excluded. The primary endpoint was PFS, and OS was assessed as a secondary

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endpoint. Ibrutinib was given at 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was dosed at 25 mg/m^2, and cyclophosphamide was dosed at 250 mg/m^2, both administered on days 1, 2, and 3 of cycles 1 through 6. Rituximab was started during cycle 2 for the ibrutinib arm and in cycle 1 for the FCR arm at a dose of 50 mg/m^2 on day 1 of the first cycle, 325 mg/m^2 on day 2 of the first cycle, and 500 mg/m^2 on day 1 of the 5 subsequent cycles, for a total of six 28-day cycles. At a median follow-up of 33.6 months, PFS was significantly greater for patients in the ibrutinib–rituximab group over chemoimmunotherapy (89.4% versus 72.9%, respectively, at 3 years; HR, 0.35 [95% CI, 0.22 to 0.56; p<0.001]). OS was also significantly improved with ibrutinib–rituximab compared to chemoimmunotherapy (98.8% versus 91.5%, respectively, at 3 years; HR, 0.17 [95% CI, 0.05 to 0.54; p<0.001]).

idelalisib (Zydelig) plus rituximab (Rituxan) versus rituximab (Rituxan) plus placebo

A multicenter, randomized, double-blind, placebo-controlled phase 3 trial assessed the efficacy and safety of idelalisib in combination with rituximab versus rituximab plus placebo in 220 patients with CLL.[400] Patients enrolled in the trial were required to have had progressive disease within 24 months after their last treatment. Additionally, patients were not eligible to receive cytotoxic agents due to severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies, had an estimated CrCl of < 60 mL/min, or had significant co-existing illnesses. Previous treatment must have included either a CD20 antibody-based regimen or at least 2 previous cytotoxic regimens. All patients received rituximab for a total of 8 infusions and were randomly assigned to either idelalisib 150 mg twice daily or placebo. The primary endpoint was PFS. Secondary endpoints were CHR, ORR, lymph-node response, and OS. At 24 weeks, the rate of PFS was 93% in the idelalisib group, as compared with 46% in the placebo group. The median PFS was 5.5 months in the placebo group and was not yet reached in the idelalisib group (HR for progression or death in the idelalisib group, 0.15; 95% CI, 0.08 to 0.28; p<0.001). The overall response was 81% in patients receiving idelalisib compared to 13% in patients receiving rituximab plus placebo (odds ratio, 29.92; p<0.001) and OS at 12 months favored idelalisib (92% versus 80%; HR for death, 0.28; p=0.02). At the first prespecified interim analysis, the study was stopped early by the data monitoring and safety board due to improved efficacy with idelalisib. The 5 most common adverse events in the idelalisib group were pyrexia, fatigue, nausea, chills, and diarrhea. In the placebo group, the most common adverse events were infusion-related reactions, fatigue, cough, nausea, and dyspnea. The most frequent serious adverse events in the two groups were pneumonia, pyrexia, and febrile neutropenia.

idelalisib (Zydelig) – relapsed small lymphocytic lymphoma after failure of ≥ 2 previous therapies

A single-arm, open-label trial evaluated idelalisib (150 mg orally twice daily until evidence of disease progression or unacceptable toxicity) in 26 patients with small lymphocytic lymphoma who had relapsed within 6 months following rituximab and an alkylating agent and had received at least 2 prior therapies.[401] The primary endpoint was ORR as assessed by an independent review committee. The ORR

venetoclax (Venclexta) plus ibrutinib – first-line CLL

A phase 2, open-label trial (n=80) examined the combination of ibrutinib and venetoclax in previously untreated high-risk (defined as ≥ 1 of the following features: chromosome 17p deletion, mutated TP53, chromosome 11q deletion, unmutated IGHV) or ≥ 65 years old patients with CLL.[402] Dosing consisted of ibrutinib 420 mg once daily for 3 cycles, followed by the addition of venetoclax with weekly dose escalation to 400 mg once daily. Combined therapy was administered for 24 cycles. Response was assessed according to the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria and

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minimal residual disease (MRD) was assessed by flow cytometry analysis. After 12 cycles of combined treatment, 88% of patients had CR or CR with incomplete count recovery, and 61% had remission with undetectable MRD. Responses were noted across all subgroups. Toxicities were consistent with the known adverse event profiles of venetoclax and ibrutinib including 3 patients who had laboratory evidence of tumor lysis syndrome.

venetoclax (Venclexta) plus rituximab (Rituxan) versus bendamustine (Treanda) – relapsed or refractory CLL or SLL

MURANO: A phase 3, open-label trial randomized 389 patients with relapsed or refractory CLL who had received 1 to 3 previous treatments to receive venetoclax (for up to 2 years) plus rituximab for the first 6 months or bendamustine plus rituximab for 6 months.[403] The primary endpoint was investigator-assessed PFS. The 2-year rates of PFS were 84.9% for the venetoclax/rituximab group and 36.3% for the bendamustine/rituximab group (HR, 0.17; 95% CI, 0.11 to 0.25; p<0.001). The benefit was demonstrated across all subgroups included those with 17p deletion. The rate of grade 3 or 4 neutropenia was higher in the venetoclax arm but the rates of grade 3 or higher febrile neutropenia and infections was higher in the bendamustine arm. The rate of grade 3 or 4 tumor lysis syndrome in the venetoclax arm was 3.1%.

venetoclax (Venclexta) plus obinutuzumab versus obinutuzumab plus chlorambucil – previously untreated CLL with coexisting medical conditions

CLL14: A phase 3, multicenter, randomized (1:1), multicenter, open-label, active-controlled trial evaluated the efficacy and safety of venetoclax in combination with obinutuzumab compared to obinutuzumab with chlorambucil in 432 patients with previously untreated CLL with coexisting medical conditions.[404] All patients received obinutuzumab at 1,000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of subsequent cycles for 6 cycles (each cycle 28 days). Included patients were randomized 1:1 to either the 5-week venetoclax ramp-up schedule on day 22 of cycle 1 and then 400 mg once daily from cycle 3 day 1 through cycle 12 or to oral chlorambucil on days 1 and 15 in all cycles (1 through 12). The median duration of follow-up was 28 months (range, 0 to 36). Disease progression or death occurred in 13% of venetoclax-treated patients compared to 37% of chlorambucil-treated patients (PFS HR, 0.33; 95% CI, 0.22 to 0.51; p<0.0001). ORR (CR and PR) occurred in 85% (95% CI, 79 to 89) of venetoclax-treated patients compared to 71% (95% CI, 65 to 77) of chlorambucil-treated patients.

venetoclax (Venclexta) – relapsed/refractory CLL with chromosome 17p deletion

The efficacy of venetoclax was studied in an open-label, single-arm, multicenter phase 3 clinical trial involving 106 patients with CLL with 17p deletion who had received at least 1 prior therapy.[405] The median number of prior therapies the patients in the study had received was 2.5 (range, 1 to 10). The dosing schedule involved a 4 week ramp-up which resulted in a 400 mg once daily dose beginning on week 5 of therapy. The primary efficacy endpoint was ORR as assessed by an IRC using the International Workshop for Chronic Lymphocytic Leukemia updated National Cancer Institute-sponsored Working Group guidelines. At the time of data evaluation, the median time on treatment was 12.1 months. An ORR of 80% was demonstrated. The median time to first response was 0.8 months (range: 0.1 to 8.1 months). The median DOR had not been reached at time of data evaluation. The DOR ranged from 2.9 months to over 19 months. An additional 51 patients were enrolled in the safety expansion cohort and the follow-up analysis of the 157 patients with a median time on venetoclax of 23.1 months (range, 0 to 44.2) was reported.[406] The investigator-assessed ORR was 77% with 20% having a complete remission and an estimated PFS at 24 months of 54% (95% CI, 45% to 62%).

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venetoclax (Venclexta) – relapsed/refractory CLL after ibrutinib (Imbruvica) or idelalisib (Zydelig)

A phase 2, open-label trial evaluated venetoclax in patients with relapsed or refractory CLL, including heavily pretreated patients or those with a 17p deletion.[407] Primary endpoints were ORR and safety. In the subgroup of 36 patients who had previously been treated with idelalisib, the ORR was 67% with 2 patients achieving a complete remission and 1 had complete remission with incomplete bone marrow recovery. The estimated 12-month PFS was 79%. Grade 3 or higher adverse events were primarily hematologic and no patients experienced tumor lysis syndrome.

venetoclax (Venclexta) - relapsed/refractory CLL after or ibrutinib (Imbruvica)

A phase 2, open-label trial evaluated venetoclax in 91 patients with relapsed or refractory CLL after previous treatment with ibrutinib.[408] The primary endpoint was ORR. The median follow up was 14 months and 65% (59 of 91) patients had an overall response. The most common grade 3 or higher adverse events were hematologic toxicity.

Diffuse large B-cell lymphoma (DLBCL)

selinexor (Xpovio) – relapsed or refractory DLBCL

The multicenter, multinational, single-arm, open-label, phase 2b SADAL study (NCT02227251) evaluated selinexor in adults with relapsed or refractory pathologically confirmed DLBCL, not otherwise specified (NOS), who had received 2 to 5 systemic regimens.[409,410] Patients enrolled were not eligible for autologous HSCT and had a minimum of 60 days since the prior systemic therapy. A total of 175 patients received selinexor 60 mg orally on days 1 and 3 of each week until disease progression or unacceptable toxicity. The primary efficacy endpoint was ORR and DOR as evaluated by an IRC using Lugano 2014 criteria. Although 48 patients were excluded as they were enrolled prior to version 6 of the protocol; 127 patients who received selinexor 60 mg were evaluated for the primary outcome. The ORR was 28% (95% CI, 20.7 to 37) with 15 patients (12%) reaching a complete response and 21 (17%) a partial response. No patient deaths were determined to be associated with selinexor. It was concluded monotherapy with selinexor provided durable responses and exhibited a manageable safety profile in these DLBCL patients.

Indolent NHLs – Follicular Lymphoma (FL)/Small Lymphocytic Lymphoma (SLL)

duvelisib (Copiktra) – relapsed or refractory FL patients

A single-arm, multicenter trial assessed the efficacy of duvelisib in 83 patients with FL who were refractory (defined as less than a partial remission or relapse within 6 months after last dose) to rituximab and to either chemotherapy or radioimmunotherapy.[411] Primary endpoint was ORR and DOR as assessed by an IRC. The ORR was 42% (95% CI, 31 to 54), with 41% of patients experiencing a PR and 1 patient having a CR. Of the 35 responding patients, 15 (43%) maintained responses for ≥ 6 months and 6 (17%) maintained responses for ≥ 12 months.

idelalisib (Zydelig) – relapsed or refractory patients

A single-arm, multicenter, open-label, phase 2 study examined 125 patients with indolent NHL who had either not had a response to rituximab (Rituxan) and an alkylating agent or who had a relapse within 6 months after receiving these therapies[412]. Patients received idelalisib 150 mg twice daily until disease progression or patient withdrawal from the study. Subtypes of indolent NHL included follicular lymphoma (n=72), small lymphocytic lymphoma (n=28), marginal-zone lymphoma (n=15), and lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia (n=10). Patients had

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received a median of 4 prior regimens (range, 2 to 12) and 14 patients had undergone autologous stem-cell transplantation. The primary endpoint was ORR. Secondary endpoints included DOR, PFS, and safety. The ORR was 57% (95% CI, 48 to 66), with 71 responses in 125 patients. Seven patients (6%) had a CR, 63 (50%) had a partial response (PR), and 1 patient had a minor response. The median time to response was 1.9 months (range, 1.6 to 8.3 months). The median DOR was 12.5 months (range, 0.03 to 14.8 months). The median PFS was 11 months (range, 0.03 to 16.6 months) with 47% of the patients remaining progression-free at 48 weeks. At the time of data cutoff, the median OS was 20.3 months (range, 0.7 to 22 months) and OS at 1 year was estimated to be 80%. The median follow-up time was 9.7 months. Adverse events that occurred in more than 20% of patients were diarrhea (43%), fatigue (30%), nausea (30%), cough (29%), and pyrexia (28%). Adverse events led to discontinuation of idelalisib (Zydelig) in 25 patients. These events included elevations in AST or ALT (4%), colitis (3%), pneumonia and pneumonitis (2%), diarrhea (2%), and neutropenia (2%).

lenalidomide (Revlimid) versus placebo – relapsed or refractory patients

AUGMENT was a randomized, double-blind trial with 358 patients who had relapsed or refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL) which compared lenalidomide plus rituximab to placebo plus rituximab (patients randomized 1:1).[413] All patients had previously received ≥ 1 prior systemic therapy. Randomization was stratified by FL versus MZL. Lenalidomide was administered as 20 mg once daily for days 1 to 21 of a 28-day cycle for up to 12 cycles or until unacceptable toxicity (doses adjusted for renal function and adverse effects), and the dose of rituximab was 375 mg/m^2 every week in cycle 1 and on day 1 of every 28-day cycle thereafter through cycle 5. Median PFS was 39.4 months (95% CI, 22.9 to not estimable) in the lenalidomide/rituximab arm and 14.1 months (95% CI, 11.4 to 16.7) in the placebo arm (HR, 0.46; 95% CI, 0.34 to 0.62; p<0.0001). The ORR (CR + PR) was 77.5% (95% CI, 70.7 to 83.4) in the lenalidomide-treated group compared to 53.3% (95% CI, 45.8 to 60.8) in the placebo group. In patients with FL, the objective response was 80% (95% CI, 73 to 86) with lenalidomide compared to 55% (95% CI, 47 to 64) with placebo.

MAGNIFY was an open-label trial with 232 patients who had relapsed or refractory follicular, marginal zone, or mantle cell lymphoma.[414] Lenalidomide was administered as 20 mg once daily for days 1 to 21 of a 28-day cycle for up to 12 cycles or until unacceptable toxicity (doses adjusted for renal function and adverse effects), and the dose of rituximab was 375 mg/m^2 every week in cycle 1 and on day 1 of every other 28-day cycle thereafter through cycle 12. In patients with FL, the objective response was 59% (95% CI, 51 to 66), and the median DOR was not reached at a median follow-up of 7.9 months (95% CI, 4.6 to 9.2).

Mantle Cell Lymphoma

acalabrutinib (Calquence) – relapsed or refractory patients

A phase 2, open-label trial in 124 patients with relapsed or refractory mantle cell lymphoma was conducted. Patients were given oral acalabrutinib 100 mg twice daily.[415] The primary endpoint was ORR according to Lugano classification in addition to a safety analysis. At a median follow-up of 15.2 months, 100 patients (81%) of patients achieved an overall response with 49 (40%) achieving a complete response. The 12 month rates for DOR, PFS, and OS were 72% (95% CI, 62 to 80), 67% (95% CI, 58 to 75), and 87% (95% CI, 79 to 92), respectively. The most common grade 1 or 2 adverse events were headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%). Neutropenia (10%), anemia (9%), and pneumonia (5%) were the most common grade 3 or higher adverse events. The median treatment duration was 13.8 months. Fifty-four patients discontinued treatment due to progressive disease (31%) and adverse events (6%).

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ibrutinib (Imbruvica) – relapsed or refractory patients

Ibrutinib (Imbruvica) was examined in a phase 2, open-label trial in 111 patients with relapsed or refractory mantle cell lymphoma.[416] Patients were stratified by the number of previous cycles of bortezomib therapy (≥ 2, < 2, or no treatment with bortezomib). Patients were treated with 560 mg orally of ibrutinib until disease progression or unacceptable toxicity. The primary endpoint was ORR. Secondary endpoints included response duration, PFS, OS, and safety. At a median follow-up of 15.3 months, the ORR for all patients was 68% with 47% of patients having a partial response (PR) and 21% of patients having a CR. The response to ibrutinib did not vary on the basis of stratified groups. For the patients who had a response (n=75), the estimated median DOR was 17.5 months (range, 0 to 19.6 months) and the median time to a response was 1.9 months (range, 1.4 to 13.7 months). The estimated median PFS among all treated patients was 13.9 months (range, 0.7 to 21.4 months). The median PFS for patients who had a PR was 17.5 months and the median PFS for those patients who had a CR had not been reached. Ibrutinib is known to potentially mobilize mantle cell lymphoma cells from tissues to the peripheral blood and 34% of patients in this trial had a transient increase in the absolute lymphocyte count during the course of ibrutinib treatment, with the peak count occurring at a median of 4 weeks after initiation of treatment. The most common nonhematologic adverse events occurring in more than 20% of patients were diarrhea (50%), fatigue (41%), nausea (31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper respiratory tract infection (23%), vomiting (23%), and decreased appetite (21%). The most common infections of grade 3 or higher were pneumonias. Grade 3 bleeding events occurred in 5 patients. Four patients had subdural hematomas; all were associated with falls, head trauma, or both, and all 4 patients were receiving either aspirin or warfarin within 2 days before or on the date of occurrence of the events. Subsequent studies of ibrutinib have excluded the use of warfarin but permitted the use of other anticoagulants.

lenalidomide (Revlimid) – relapsed or refractory patients

MCL-001 (EMERGE): A multicenter, single-arm, open-label phase 2 trial of single agent lenalidomide evaluated the safety and efficacy of lenalidomide in 134 patients with mantle cell lymphoma who had relapsed after or were refractory to bortezomib.[417] Patients were dosed at 25 mg once daily for 21 days every 28 days. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoints were ORR and DOR. Secondary endpoints were CR rate, PFS, OS, and safety. The ORR was 28% and a median DOR of 16.6 months (95% CI, 7.7 to 26.7 months). Median PFS was 4 months (95% CI, 3.6 to 5.6 months) and median OS was 19 months (95% CI, 12.5 to 23.9 months). The most common grade 3 to 4 adverse events were neutropenia (43 %), thrombocytopenia (28%), anemia (11%), pneumonia (8%), and fatigue (7%).

MCL-002 (SPRINT): A randomized, multicenter, phase 2 study examined 254 patients with mantle cell lymphoma who had received a median of 2 prior treatment regimens and were ineligible for intensive chemotherapy or stem-cell transplantation.[418] Patients were randomized to either lenalidomide 25 mg orally days 1 through 21 every 28 days (n=170) or single-agent investigator's choice of therapy (n=84). Patients who were randomized to investigator's choice were allowed to crossover to lenalidomide treatment at the time of disease progression. At a median follow up of 15.9 months, PFS was 8.7 months (95% CI, 5.5 to 12.1) for the lenalidomide group and 5.2 months (95% CI, 3.7 to 6.9) for patients who received investigator choice single agent therapy (HR, 0.61 [95% CI, 0.44 to 0.84; p=0.004]).

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zanubrutinib (Brukinsa) – relapsed or refractory patients

The accelerated approval of zanubrutinib for patients with MCL was primarily based on the findings from a phase 2, open-label, multicenter, single-arm study (BGB-3111-206) conducted in 86 patients in China with MCL who had previously received at least 1 therapy for MCL.[419,420] All patients received zanubrutinib at a dose of 160 mg orally twice daily with treatment continued until disease progression or unacceptable toxicity. The primary endpoint was ORR as determined by an IRC; secondary endpoints were PFS, DOR, ORR as determined by the investigator, and safety. Patients between the ages of 18 and 75 years with an ECOG performance status of 0 to 2 who had received previous regimens for MCL and had disease measurable by computed tomography/MRI (CT/MRI) were eligible for enrollment. Patients were also required to have evidence for morphological and cyclin D1 protein or translocation t(11;14), failure to achieve any response or progressive disease following the most recent treatment, and a life expectancy > 4 months. Patients with previous exposure to a BTK inhibitor, previous corticosteroid therapy as anti-neoplastic therapy, major surgery in past 4 weeks, or central nervous system (CNS) lymphoma were excluded. Patients had to have recovered from previous chemotherapy toxicity and not have active cardiovascular disease, uncontrolled systemic infections, human immunodeficiency virus (HIV), active hepatitis B or C, or a history of other malignancies within the past 2 years. Patients with life-threatening illnesses, prior allogeneic HSCT, or who were receiving strong CYP3A inhibitors or inducers were excluded. Women who were pregnant or lactating were also excluded. Patients were primarily male (78%) with a median age of 60.5 years (range, 34 to 75) and a median time since diagnosis of 30 months (range, 3 to 102 months). The median number of previous therapies was 2 (range, 1 to 4) with the most frequent previous regimen being either cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based (91%) or rituximab-based (74%). Most patients had extranodal involvement, and more than half had refractory disease. The majority of patients (58%) had a low risk mantle cell lymphoma international prognostic index (MIPI) score, followed by intermediate risk (29%), and high risk (13%). The primary endpoint of ORR assessment by IRC was 84% (95% CI, 74 to 91), with 59% of patients exhibiting a complete response and 24% achieving a partial response. The median DOR was 19.5 months (95% CI, 16.6 to not estimable). Regarding secondary endpoints, the median PFS was 16.7 months, and the investigator-assessed ORR was 84.7%.

A multicenter, phase 1/2, single-arm, dose-escalation study (BGB-3111-AU-003) evaluating 32 MCL patients who had previously received treatment for MCL provided additional support for the efficacy of zanubrutinib.[421,422] Patients received zanubrutinib 160 mg twice daily or 320 mg daily taken orally. The median age of patients enrolled with MCL was 70 years (range, 42 to 86) with the majority of patients being male (69%) and Caucasian (78%). Patients had intermediate risk MIPI scores (41%), followed by high risk (31%), and low risk (28%). The ORR by IRC was 84% (95% CI, 67 to 95) for the previously-treated MCL patients with 22% of patients achieving a complete response and 62% exhibiting a partial response. The median DOR was 18.5 months (95% CI, 12.6 to not estimable).

Marginal Zone Lymphoma (MZL)

ibrutinib (Imbruvica) – previously treated patients

A multicenter, open-label, single-arm, phase 2 study evaluated the safety and efficacy of ibrutinib in patients with previously treated MZL.[423] Of the 63 enrolled patients, all had received ≥ 1 prior therapy with an anti-CD20 antibody-containing regimen, and the median number of prior systemic therapies was 2 (range, 1 to 9). The primary endpoint was IRC-assessed ORR by 2007 IWG criteria. Patients received ibrutinib 560 mg once daily until disease progression or unacceptable toxicity. At a median

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follow up of 19.4 months, the IRC-assessed ORR was 48% (95% CI, 35 to 62), the DOR was not reached (95% CI, 16.7 to not estimable) and PFS was 14.2 months (95% CI, 8.3 to not estimable). Grade 3 or higher adverse events occurring in more than 5% of patients included anemia, pneumonia, and fatigue. Ten percent of patients required dose reductions due to adverse events and 17% discontinued ibrutinib due to adverse effects.

lenalidomide (Revlimid) versus placebo – relapsed or refractory patients

As described above, AUGMENT was a randomized, double-blind trial with 358 patients who had relapsed or refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL) which compared lenalidomide plus rituximab to placebo plus rituximab (patients randomized 1:1).[424] While the general results are described above, in patients with MZL, the objective response was 65% (95% CI, 45 to 81) with lenalidomide compared to 44% (95% CI, 26 to 62) with placebo.

MAGNIFY was an open-label trial with 232 patients who had relapsed or refractory relapsed or refractory follicular, marginal zone, or mantle cell lymphoma, as described above.[425] In patients with MZL, the objective response was 51% (95% CI, 36 to 66), and the median DOR was not reached at a median follow-up of 11.5 months (95% CI, 8 to 18.9).

Cutaneous T-cell Lymphomas

vorinostat (Zolinza)

In an open-label, single-arm, multicenter, non-randomized study, 74 patients with advanced CTCL were treated with vorinostat at a dose of 400 mg once daily. The primary endpoint was response rate to oral vorinostat in the treatment of skin disease in patients with advanced CTCL (Stage IIB and higher) who had progressive, persistent, or recurrent disease on or following 2 systemic therapies. Enrolled patients should have received, been intolerant to, or not a candidate for bexarotene. Extent of skin disease was quantitatively assessed by investigators using a modified Severity Weighted Assessment Tool (SWAT). The investigator measured the percentage total body surface area (%TBSA) involvement separately for patches, plaques, and tumors within 12 body regions using the patient's palm as a "ruler." The total % TBSA for each lesion type was multiplied by a severity weighting factor (1=patch, 2=plaque, and 4=tumor) and summed to derive the SWAT score. Efficacy was measured as either a Complete Clinical Response (CCR) defined as no evidence of disease, or PR defined as a ≥ 50% decrease in SWAT skin assessment. The ORR was 29.7% (22/74; 95% CI, 19.7 to 41.5) in all patients treated with vorinostat. One patient with Stage IIB CTCL achieved a CCR. Median time to response was 56 days. However, in rare cases it took up to 6 months for patients to achieve an objective response to vorinostat. Using a 25% increase in SWAT score from the nadir as criterion for tumor progression, the estimated median time-to-progression was 148 days for the overall population and 169 days in the 61 patients with Stage IIB and higher CTCL.[426]

Myelodysplastic/Myeloproliferative Disease (MDS/MPD)

imatinib (Gleevec)

An open-label, multicenter, phase 2 trial was conducted with imatinib 400 mg daily in patients diagnosed with life-threatening diseases associated with Abl, Kit or platelet derived growth factor receptor (PDGFR) protein tyrosine kinases. Seven of these patients were diagnosed with MDS/MPD. A further 24 patients with MDS/MPD have been reported in 12 published case reports and a clinical study. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a CHR and 12 (39%) had a MCyR, including 10 complete cytogenetic responses. All of the patients identified with a

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translocation involving chromosome 5q33 or 4q12 had a hematologic response. Only 1 out of 14 patients without a translocation associated with PDGFR gene-rearrangement achieved a CHR.[427]

lenalidomide 10 mg or lenalidomide 5 mg versus placebo

A randomized, double-blind, placebo-controlled, multicenter, phase 3 study (MDS-004) examined the efficacy and safety of lenalidomide in red blood cell (RBC) transfusion dependent patients with International Prognostic Scoring System (IPSS)-defined Low or Intermediate -1-risk MDS associated with an isolated del(5q) cytogenetic abnormality.[428] Patients received lenalidomide 10 mg/day (days 1 through 21) or 5 mg/day (days 1 through 28) on 28-day cycles or placebo. Crossover to lenalidomide or higher dose lenalidomide was allowed after 16 weeks. The primary endpoint was RBC-transfusion independence for ≥ 26 weeks. More patients in the lenalidomide 10 mg and 5 mg groups than in the placebo group achieved this primary outcome (56.1% and 42.6% versus 5.9%; respectively, both p<0.001).

Polycythemia Vera

ruxolitinib versus investigator's choice of therapy/standard therapy

RESPONSE: Ruxolitinib for the treatment of polycythemia vera was examined in a phase 3, randomized, open-label trial.[429]Adult patients who were phlebotomy dependent with splenomegaly (n=222) were randomized to ruxolitinib at a starting dose of 10 mg twice daily or standard therapy (investigator choice single-agent therapy). Patients were stratified according to previous response to hydroxyurea (inadequate response or unacceptable toxicity). The primary endpoint was the proportion of patients who had both hematocrit control and a reduction of 35% or more in spleen volume from baseline at week 32, as assessed by means of centrally reviewed MRI or CT studies. The primary endpoint was achieved in 21% of patients in the ruxolitinib group versus 1% of patients in the standard therapy group (p<0.001). Grade 3 or 4 anemia occurred in 2% of ruxolitinib patients compared to none of the standard treatment patients. Grade 3 or 4 thrombocytopenia occurred in 5% of the ruxolitinib patients versus 4% of the standard therapy patients. Herpes zoster infection was reported in 6% of patients in the ruxolitinib group and no patients in the standard therapy group. At a planned 80-week follow up and a median exposure of 111 weeks, no patients had continued on the investigator choice arm and 87.5% of those patients had crossed over to ruxolitinib, most at or shortly after the 32 week evaluation.[430] In the original ruxolitinib treated patients who had a response, the probability of maintaining hematocrit responses for ≥ 80 weeks was 89% and the spleen responses were maintained in 43 of the 44 responding patients at 80 weeks. New or worsening hematologic abnormalities in ruxolitinib-treated patients were primarily grade 1 or 2 decreases in hemoglobin, lymphocytes, and platelets. At the time of final analysis, 6 patients had progressed out of the 25 primary responders in the ruxolitinib study arm, and at 5 years, the probability of maintaining the primary composite response was 74% (95% CI, 51 to 88).431 Furthermore, the probability of maintaining a complete hematological remission was 55% (95% CI, 32 to 73), and the probability of 5 year survival in the intention-to-treat population (without adjustment for cross over) was 91.9% (95% CI, 84.4 to 95.9) for ruxolitinib group and 91% (95% CI, 82.8 to 95.4) with best available therapy. The most common adverse event in ruxolitinib-treated patients was anemia, with similar rates per 100 patient-years of exposure for ruxolitinib (8.9) compared to those who crossed over (8.8); most cases of anemia were mild to moderate in severity. Non-hematological adverse events and thromboembolic events were mostly lower with ruxolitinib therapy than with best available therapy. Overall, it was concluded that ruxolitinib is safe and effective as a long-term therapy in polycythemia vera patients with resistance or intolerance to hydroxyurea.

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RESPONSE-2: This randomized, open-label, phase 3 trial compared ruxolitinib to investigator-selected best available therapy in 149 patients with polycythemia vera who were inadequately controlled with hydroxyurea and but had no palpable splenomegaly.[432] Hematocrit control was achieved in 62% of the ruxolitinib-treated patients and 19% of the investigator choice- treated patients (OR, 7.28; 95% CI, 3.43 to 15.45; p<0.001). The most frequent adverse events were anemia and thrombocytopenia occurring in 14% versus 3% and 3% versus 8% of the ruxolitinib-treated patients and the investigator choice-treated patients, respectively. Among patients who achieved a hematocrit response at week 28, the probability of maintaining response up to week 80 was 78% in the ruxolitinib arm.[433] At week 80, durable complete hematologic remission was achieved in 24% of patients in the ruxolitinib arm versus 3% of patients initially randomized to the best available therapy arm. There were no new safety signals.

Waldenström's Macroglobulinemia (WG)

ibrutinib

Ibrutinib (Imbruvica) 420 mg daily was administered to 63 symptomatic patients with Waldenström's macroglobulinemia who had received at least 1 previous treatment.[434] Improvements were noted in the median serum IgM levels, median hemoglobin levels, and the amount of bone marrow involvement. The ORR was 90.5% with a median time to at least a minor response of 4 weeks. The most common adverse events of grade 2 or higher were neutropenia (22%) and thrombocytopenia (14%), which occurred more commonly in heavily pretreated patients.

A multicenter, open-label substudy examined 31 patients with WG who had disease refractory to rituximab, defined as either relapse within 12 months of the last dose of a rituximab-containing regimen or failure to achieve at least a minor response.[435] Patients were treated with ibrutinib 420 mg daily until disease progression or unacceptable toxicity. All analyses reported were descriptive, as the substudy was not powered for statistical comparisons. At a median follow up of 18 months, the estimated PFS and OS were 86% and 97%, respectively. Grade 3 or higher adverse events occurring in ≥ 5% or more patients included neutropenia (13%), hypertension (10%), anemia (6%), thrombocytopenia (6%), and diarrhea (6%). Five patients (16%) discontinued therapy, 3 due to progression and 2 due to adverse events.

A multicenter, randomized, phase 3 trial compared monotherapy with rituximab to ibrutinib plus rituximab in patients with Waldenström's macroglobulinemia.[436] The trial included both treatment naive patients and patients who had experienced a prior relapse. Those patients who had previously been treated with a rituximab-containing regimen had to have had a ≥ 12 month response to the prior regimen. Patients were excluded if they had resistance to prior rituximab-containing therapies or had received rituximab within 12 months prior to the beginning of the trial. Patients (n=150) were randomized 1:1 to either oral ibrutinib 420 mg daily or placebo, while all patients received rituximab dosed in accordance with current treatment guidelines. The primary endpoint was PFS as assessed by an IRC. Secondary endpoints included time until next treatment, OS, response rates, sustained hematologic improvement from baseline as measured by hemoglobin levels, quality of life, and safety. At 30 months, the primary endpoint of PFS was 82% with ibrutinib-rituximab compared to 28% with placebo-rituximab (HR, 0.2; p<0.001). Sustained increases in hemoglobin level occurred in more of the ibrutinib-rituximab treated patients compared to the placebo-rituximab group (73% versus 41%; p<0.001). The OS at 30 months was not significantly different between the 2 groups, but 30 patients in the placebo-rituximab group had crossed over to combination ibrutinib/rituximab after disease progression as confirmed by an IRC. Grade 3 or higher events occurring more frequently in the combination arm were atrial fibrillation (12% versus 1%) and hypertension (13% versus 4%).

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META-ANALYSIS

First-line treatment with next generation TKIs versus imatinib in CP-CML

A systematic review and meta-analysis of 8 randomized trials compared the effectiveness of newer TKIs (dasatinib, nilotinib, radotinib [not available in US], bosutinib, and ponatinib) in the first-line setting of CP-CML to imatinib.[437] The studies included only patients ≥ 18 years of age and those who were naïve to any TKI treatment prior to the study. Of the 8 included trials, 2 were of nilotinib, 3 were dasatinib, and there was 1 each for bosutinib, ponatinib, and radotinib. The goal of the meta-analysis was to compare the outcomes of newer generation TKIs versus imatinib in the first-line setting of CP-CML and to assess the effect of the risk scores on treatment response in this setting. The primary outcome measures were the CCyR and MMR rates at 12 months of TKI treatment. Secondary outcomes included PFS, OS, and progression to AP/BP. The pooled analysis demonstrated no difference in the CCyR (69.2% versus 60%; RR, 0.7 [95% CI, 0.7 to1.14]; p=0.15) but a significantly greater MMR (48% versus 24.5%; RR, 0.63 [95% CI, 0.46 to 0.87]; p=0.005) between the newer-generation TKIs versus imatinib, respectively. The degree of benefit on MMR was found to be independent of the patient's risk stratification (based on either the Sokal risk score or the Hasford risk score). The PFS and OS were not statistically significantly different between the 2 groups; however, the progression rate to AP/BP was significantly lower in patients treated with newer generation TKIs than those treated with imatinib (1% versus 3.2%; RR, 0.37 [95% CI, 0.2 to 0.67]; p=0.001) at 12 months of treatment. Although the newer generation TKIs showed no difference compared to imatinib in the first-line setting with regard to PFS or OS at 12 months, there was improved MMR and AP/BP progression. This finding supports the practice of utilizing nilotinib or dasatinib over imatinib in the first-line setting of CP-CML for patients with initial high risk scores.

Incidence of arterial events in TKI-treated CML patients

A meta-analysis involving 29 studies (n=15,706 patients) examined the incidence of arterial events in CML patients treated with TKIs.[438] The incidence rates of major arterial events were 0.8 per 100 patient-years for non-TKI treatments and 1.1 per 100 patient-years for dasatinib, 0.1 per 100 patient-years for imatinib, 0.4 per 100 patient-years for bosutinib, 2.8 per 100 patient-years for nilotinib, and 10.6 per 100 patient-years for ponatinib.

lenalidomide maintenance after HSCT for newly diagnosed multiple myeloma patients

While each of the randomized, controlled trials that compared lenalidomide maintenance to placebo in the post HSCT setting demonstrated significantly improved PFS for lenalidomide-treated patients, none of the individual trials were powered to use OS as a primary endpoint. A meta-analysis was conducted using data from 3 individual randomized, controlled trials involving a total of 1,208 patients (605 patients randomized to lenalidomide maintenance and 603 patients who received placebo or observation).[439] At a median follow-up of 79.5 months, OS was 86 months for the placebo or observation group and had not been reached for the lenalidomide group (HR, 0.75; 95% CI, 0.63 to 0.9; p=0.001). The authors concluded that lenalidomide maintenance therapy after HSCT demonstrated a significant OS benefit compared with placebo or observation.

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SUMMARY

Hematologic malignancies, usually involving aberrant bone marrow function, are a heterogeneous group of diseases including leukemias and lymphomas, as well as multiple myeloma, myelodysplastic syndrome, and other less common malignancies. The focus of oncology research in the era of next-generation sequencing is to identify genetic mutations specific for individual diseases and develop actionable therapeutic interventions capable of modifying the impact of these mutations and their associated disease processes. In contrast to older chemotherapy agents whose mechanism of action was minimally specific cytotoxicity, these newer targeted therapies are designed to dysregulate intracellular signaling pathways and inhibit abnormal growth factors and tumor angiogenesis.

Modulation of the immune system to fight cancer is another area of intense research. Thalidomide (Thalomid) and the thalidomide analogues, lenalidomide (Revlimid) and pomalidomide (Pomalyst), are all classified as immunomodulatory agents. The older cytotoxic agents included in this review, some of which may still be used in routine clinical practice, include busulfan, chlorambucil, hydroxyurea, mercaptopurine, procarbazine, and thioguanine.

Tretinoin, a vitamin A derivative, is classified as a differentiating agent as it induces leukemic cells to mature or differentiate from malignant promyelocytic cells into mature neutrophils.

The remaining agents included in this review, acalabrutinib (Calquence), bosutinib (Bosulif), dasatinib (Sprycel), duvelisib (Copiktra), enasidenib (Idhifa), fedratinib (Inrebic), gilteritinib (Xospata), ibrutinib (Imbruvica), idelalisib (Zydelig), imatinib (Gleevec), ivosidenib (Tibsovo), ixazomib (Ninlaro), midostaurin (Rydapt), nilotinib (Tasigna), panobinostat (Farydak), ponatinib (Iclusig), ruxolitinib (Jakafi), venetoclax (Venclexta), vorinostat (Zolinza), and zanubrutinib (Brukinsa) are small molecule inhibitors that target a broad spectrum of intracellular kinases. Glasdegib (Daurismo) is a hedgehog pathway inhibitor that inhibits transmembrane protein smoothened (SMO) and selinexor (Xpovio) is a nuclear export inhibitor. After the establishment of imatinib (Gleevec) as the new standard of care for chronic myeloid leukemia (CML) in the early 2000s, several second generation tyrosine kinase inhibitors (TKIs), including dasatinib (Sprycel), nilotinib (Tasigna), and bosutinib (Bosulif), were developed and are used in either the first-line setting instead of imatinib or in imatinib-refractory patients. Ponatinib (Iclusig), a third generation TKI for the treatment of CML, is reserved for patients with a particular mutation (T315I) or for whom no other TKI is indicated, due to its toxicity profile. Hydroxyurea is approved for resistant CML.

The use of the immunomodulatory agents thalidomide, lenalidomide (Revlimid), and pomalidomide (Pomalyst) have become part of the standard of care for transplant-eligible multiple myeloma patients, including as maintenance therapy after autologous hematopoietic stem cell transplant (lenalidomide [Revlimid]), while panobinostat (Farydak) and ixazomib (Ninlaro) are available for use in patients with refractory multiple myeloma. In May 2020, pomalidomide also received an Accelerated Approval for the additional indication of treating adults with acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART), as well as for the treatment of KS in adults who are human immunodeficiency virus (HIV)-negative. Selinexor (Xpovio) received initial Accelerated Approval for use in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma (RRMM) in patients who have received ≥ 4 prior therapies and whose disease is refractory to ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. In June 2020, selinexor received Accelerated Approval for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

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There are now several targeted agents approved for certain patients with AML. Midostaurin (Rydapt) and gilteritinib (Xospata) are available for AML patients with an identified FLT3 mutation, and enasidenib (Idhifa) and ivosidenib (Tibsovo) are approved agents for IDH2 and IDH1 mutated AML, respectively. Glasdegib (Daurismo) is approved in combination with low-dose cytarabine for the treatment of newly diagnosed AML in adult patients who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy. Venetoclax (Venclexta) is also approved for this specific population in combination with azacitidine, decitabine, or low-dose cytarabine.

Targeted agents for the treatment of a variety of non-Hodgkin's lymphomas have been approved as well. Duvelisib (Copiktra), ibrutinib (Imbruvica), idelalisib (Zydelig), and venetoclax (Venclexta) are indicated for the treatment of chronic lymphocytic leukemia (CLL). Ibrutinib (Imbruvica) is also FDA-approved for the treatment of chronic graft versus host disease (cGVHD), mantle cell lymphoma, and marginal zone lymphoma, while duvelisib (Copiktra) and idelalisib (Zydelig) are approved for the treatment of follicular lymphoma (FL). Acalabrutinib (Calquence) and zanubrutinib (Brukinsa) have been approved for the treatment of mantle cell lymphoma in patients who have undergone ≥ 1 prior therapy. Ruxolitinib (Jakafi) is now approved for corticosteroid refractory acute graft versus host disease (aGVHD).

CLL, in particular, has seen a huge paradigm shift in disease management with the introduction of these newer agents. In the past, chemotherapy played a large role in the management of CLL for many patients; however, now acalabrutinib (Calquence), ibrutinib (Imbruvica), and venetoclax (Venclexta) have consistently demonstrated much higher response rates than traditional chemotherapy or even chemoimmunotherapy combinations. The ongoing management of CLL is rapidly evolving due to the use of these newer agents.

The continued development of targeted agents provides many patients with hematologic malignancies the hope for expanded treatment options and prolonged survival.

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