Oncology Oral, Hematologic Cancers
Therapeutic Class Review (TCR)

August 1, 2016

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## FDA-APPROVED INDICATIONS

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<th>Drug</th>
<th>Manufacturer</th>
<th>FDA-Approved Indications</th>
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<tr>
<td>bosutinib (Bosulif®)</td>
<td>Pfizer</td>
<td>▪ Treatment of chronic, accelerated, or blast phase Ph+ chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy</td>
</tr>
<tr>
<td>busulfan (Myleran®)</td>
<td>Aspen Global</td>
<td>▪ Palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia</td>
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<tr>
<td>chlorambucil (Leukeran®)</td>
<td>Aspen Global</td>
<td>▪ 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</td>
</tr>
<tr>
<td>cladribine</td>
<td>generic</td>
<td>▪ Treatment of Hairy Cell Leukemia (HCL) as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms</td>
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<tr>
<td>dasatinib (Sprycel®)</td>
<td>Bristol-Meyers Squibb</td>
<td>▪ Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib (Gleevec)</td>
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<td></td>
<td></td>
<td>▪ Treatment of adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy</td>
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<tr>
<td></td>
<td></td>
<td>▪ Newly diagnosed adult patients with Ph+ CML in chronic phase</td>
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<tr>
<td>hydroxyurea (Hydrea®)</td>
<td>Bristol-Myers Squibb, generic</td>
<td>▪ Resistant CML</td>
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<td>▪ Locally advanced squamous cell carcinomas of the head and neck (excluding lip), in combination with concurrent chemoradiation</td>
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<tr>
<td>ibrutinib (Imbruvica®)</td>
<td>Pharmacyclics/ Janssen</td>
<td>▪ Mantle cell lymphoma (MCL) in patients who have received at least 1 prior therapy</td>
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<td></td>
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<td>▪ <strong>Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma</strong></td>
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<td></td>
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<td>▪ Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma with 17p deletion</td>
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<td></td>
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<td>▪ Waldenström’s macroglobulinemia</td>
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<tr>
<td>idelalisib (Zydelig®)</td>
<td>Gilead</td>
<td>▪ Relapsed chronic CLL in combination with rituximab (Rituxan) in patients for whom rituximab (Rituxan) alone would be considered appropriate therapy due to other co-morbidities</td>
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<td>▪ Relapsed follicular B-cell non-Hodgkin’s lymphoma (FL) in patients who have received at least 2 prior systemic therapies</td>
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<tr>
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<td></td>
<td>▪ Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies</td>
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<tr>
<td>imatinib (Gleevec®)</td>
<td>Novartis, generic</td>
<td>• Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase&lt;br&gt;• Patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy&lt;br&gt;• Adult patients with relapsed or refractory Ph+ ALL&lt;br&gt;• Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy&lt;br&gt;• Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFRA) gene re-arrangements&lt;br&gt;• Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown&lt;br&gt;• 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&lt;br&gt;• Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP)&lt;br&gt;• Patients with Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)&lt;br&gt;• Adjuvant treatment of adult patients following resection of Kit (CD117)-positive gastrointestinal stromal tumors(GIST)</td>
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<tr>
<td>ixazomib (Ninlaro®)</td>
<td>Takeda</td>
<td>• In combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received at least 1 prior therapy</td>
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<tr>
<td>lenalidomide (Revlimid®)</td>
<td>Celgene</td>
<td>• In combination with dexamethasone for the treatment of multiple myeloma&lt;br&gt;• 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&lt;br&gt;• Treatment of mantle cell lymphoma after relapse or disease progression after 2 prior therapies, 1 of which included bortezomib</td>
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<tr>
<td>melphalan (Alkeran®)</td>
<td>generic</td>
<td>• Palliative treatment of multiple myeloma&lt;br&gt;• Palliation of non-resectable epithelial carcinoma of the ovary</td>
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<tr>
<td>mercaptopurine (Purixan®)</td>
<td>generic (tablets) Rare Disease Therapeutics (suspension)</td>
<td>• Maintenance treatment of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen</td>
</tr>
<tr>
<td>nilotinib (Tasigna®)</td>
<td>Novartis</td>
<td>• Accelerated phase and chronic phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib (Gleevec)&lt;br&gt;• Newly diagnosed adult patients with Ph+ CML in chronic phase</td>
</tr>
<tr>
<td>panobinostat (Farydak®)</td>
<td>Novartis</td>
<td>• Treatment of multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent</td>
</tr>
<tr>
<td>pomalidomide (Pomalyst®)</td>
<td>Celgene</td>
<td>• Treatment of multiple myeloma, in combination with dexamethasone, for patients who have received at least 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</td>
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**FDA-Approved Indications (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
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</table>
| ponatinib (Iclusig®)  | Ariad        | • 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 tyrosine kinase inhibitor (TKI) is indicated‡  |
| procarbazine (Matulane®) | Sigma-Tau   | • 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®)  | Incyte       | • Intermediate or high-risk myelofibrosis (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 |
| thalidomide (Thalomid®) | Celgene      | • Treatment of newly diagnosed multiple myeloma in combination with dexamethasone  
• Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprom (ENL)††  
• Prevention and suppression of cutaneous manifestations of ENL recurrence as maintenance therapy |
| thioguanine (Tabloid®) | Prasco Labs  | • For remission induction and remission consolidation of acute nonlymphocytic leukemias§§  |
| tretinoin             | 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®) | AbbVie      | • Treatment of CLL in patients with 17p deletion, as detected by an FDA-approved test, who have received at least 1 prior therapy |
| vorinostat (Zolinza®) | 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 |

Ph+ = Philadelphia chromosome positive; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia

* 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.

† The approved indications for hydroxyurea have changed; the use of this drug in either melanoma or ovarian cancer is no longer indicated. 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.

†† Accelerated approvals for these indications were granted based on overall response rate. Improvements in survival or disease-related symptoms have not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.

‡‡ Ibrutinib was previously only approved for CLL in patients who had received at least 1 prior therapy

†§ Indication approved via accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The indications for ponatinib (Iclusig) are based upon response rate; there are no trials verifying an improvement in disease-related symptoms or increased survival. Ponatinib (Iclusig) is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

‡‡‡ Ruxolitinib (Jakafi) has shown reduction in spleen volume and relief of symptoms. However, it does not reverse bone marrow fibrosis or result in cytogenetic or molecular remission. Drug discontinuation is typically associated with full relapse of disease symptoms, and severe anemia or thrombocytopenia occurs in the majority of patients.

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

†‡ 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. 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, and thioguanine will not be discussed in detail in this therapeutic class review.

OVERVIEW

Leukemias

**Chronic Myelogenous Leukemia (CML)**

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. The majority of patients suffering from CML possess a gene mutation called the Philadelphia (Ph) chromosome. In this genetic abnormality, a section of chromosome 9 and a section of chromosome 22 switch places and, as a result, the breakpoint cluster region (BCR) gene from chromosome 22 is fused with the ABL gene on chromosome 9. As the ABL gene carries a domain that can add phosphate groups to tyrosine residues, transcription of this BCR-ABL fusion gene produces a protein, p210BCR-ABL, which has constitutive abnormal tyrosine kinase activity that results in uncontrolled hematopoietic cell proliferation. Identification of the adenosine triphosphate binding site on the BCR-ABL tyrosine kinase has provided a target for inhibition with tyrosine kinase inhibitor (TKIs).

Three phases are used to classify CML; these are chronic phase (CP), accelerated phase (AP), and blast crisis (BC). The vast majority of patients are diagnosed in chronic phase. Chronic phase CML is characterized by the presence of less than 10% blast cells in blood and bone marrow. AP is defined as progressive disease and a loss of efficacy of drug therapy. Patients are found to have 10% to 19% blasts in the peripheral blood or bone marrow and often have exacerbation of splenomegaly, as well as constitutional symptoms such as fever, night sweats, and weight loss. Some patients in AP may also have bone marrow evidence of progression of the leukemic clone or new cytogenetic abnormalities. Blast cells of 20% or more in the peripheral blood or bone marrow represent blast crisis and a transformation that is akin to acute leukemia. Without treatment, CML-CP will eventually progress to CML-AP in about 3 to 5 years. The only proven therapy to cure CML, by eradicating the malignant clone, is an allogenic hematopoietic stem cell transplantation (HSCT). However, in the era of TKI therapy, HSCT is reserved for CML-CP patients who are refractory to TKI therapy and who have a suitable bone marrow donor. Although not curative per se, the introduction of TKI therapy has radically changed the clinical course of CML. Nearly 85% of patients demonstrate an initial response to imatinib (Gleevec) and 5-year survival with imatinib (Gleevec) therapy approaches 90%. With the introduction of later generation TKIs that may continue to show a response in imatinib (Gleevec)-resistant patients, life expectancy for patients with CML is now measured in years and perhaps decades. Prior to the introduction of TKIs, hydroxyurea played a role in selected patients, particularly in the chronic phase of CML. The use of hydroxyurea today is primarily reserved for patients who present with leukocytosis and/or thrombocytosis or possibly patients who are refractory to all TKI therapy. Busulfan was also used at one time in the treatment of CML but there is no role for busulfan (outside of hematopoietic cell transplantation) in the modern day management of CML.

Clinical response in CML is measured by standardized hematologic, cytogenetic, and molecular indices. Hematologic response is defined as the normalization of peripheral blood counts and occurs first in treated patients. 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. The most sensitive test to monitor disease status is molecular response as measured by quantitative reverse-transcription polymerase chain reaction (QPCR) standardized across different laboratories by using the International Scale (IS). A complete molecular response is the absence of BCR-ABL transcripts by QPCR (IS). A major molecular response is a ≥3-log reduction in BCR-ABL transcripts as measured by QPCR (IS). Peripheral blood is sometimes used to measure molecular responses as it correlates highly with bone marrow results.

There are currently 3 generations of TKIs marketed for use in CML patients. The original, first generation TKI is imatinib (Gleevec). Second generation TKIs include dasatinib (Sprycel), nilotinib (Tasigna), and bosutinib (Bosulif). The only third generation TKI currently on the market is ponatinib (Iclusig); however, the use of ponatinib (Iclusig) is now limited to select patients due to a high risk of toxicity. These later generation TKIs have been shown to be active against several resistance-associated mutations. Therefore, mutational analysis to identify point mutations is recommended if there is an inadequate initial response, a loss of response, or a 1-log increase in BCR-ABL1 transcripts with loss of MMR or disease progression. The selection of appropriate TKI therapy is dependent on the disease phase, its effectiveness against BCR-ABL1 specific mutations, and the drug’s side effect profile.

For patients newly diagnosed with Philadelphia chromosome-positive CML (Ph+CML) in the chronic phase, the 2016 National Comprehensive Cancer Network (NCCN) clinical guidelines recommend imatinib (Gleevec), dasatinib (Sprycel), or nilotinib (Tasigna) as standard first-line therapy (all category 1). While there are data indicating superior cytogenetic and molecular response rates at certain time points with dasatinib and nilotinib compared to imatinib, long-term survival benefit has not been established. Preliminary data suggest patients assessed to have intermediate or high risk disease per established risk scoring scales may preferentially benefit from dasatinib or nilotinib. Response to TKI therapy should be monitored every 3 months initially. Early molecular response (BCR-ABL1 transcripts <10% by QPCR [IS] at 3 and 6 months) to first-line TKI therapy is a positive prognostic indicator of long-term clinical outcomes. However, resistance to TKI therapy can develop and several resistant mutations have been identified that later generation TKIs may effectively overcome. If a patient does not experience at least a partial cytogenetic response (PCyR) or demonstrates greater than 10% BCR-ABL1 transcripts by QPCR (IS) at the 3-month milestone, then those patients receiving imatinib may be switched to nilotinib, dasatinib, or bosutinib (Bosulif) in the second-line setting. Alternatively, patients failing to meet the 3-month milestone to first-line imatinib may be treated with an increased dose of imatinib (as tolerated to a maximum of 800 mg daily) if they are not a candidate for an alternate TKI. These patients should also be evaluated for hematopoietic cell transplantation (HCT). Patients initially treated with nilotinib or dasatinib who fail to meet the 3-month milestone may continue the same dose of nilotinib or dasatinib or may be treated with an alternate TKI (other than imatinib) in the second-line setting. These patients should also be evaluated for HCT. At the 6-month evaluation, patients still not achieving a PCyR or with greater than 10% BCR-ABL1 transcripts by QPCR (IS) should be evaluated for lack of compliance with drug therapy, as well as potential drug interactions. Mutational analysis should be conducted as it may provide information regarding specific point mutations that may be actionable by a particular TKI. For example, dasatinib and nilotinib are effective against a majority of mutations resistant to imatinib and bosutinib is active in patients with point mutations resistant to dasatinib and nilotinib. Third-line therapy may involve changing to another
alternate TKI besides imatinib, including nilotinib, dasatinib, bosutinib, or ponatinib, depending on the previous therapy received.

**Acute Lymphocytic Leukemia (ALL)**

ALL is the most common form of childhood leukemia, with nearly 60% of patients diagnosed before the age of 20. Approximately 25% of cases of ALL are diagnosed at age 45 or older, with 11% 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 86% to 89% in children. Unfortunately, adolescents (5-year OS, 42% to 63%) and adults (5-year OS, 24%) do not fare as well with current therapies. Prognosis is also influenced by cytogenetic markers, including Philadelphia chromosome-positivity (Ph+) which is associated with a poorer prognosis. 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 is often included as part of a backbone treatment in the maintenance phase of ALL. Some protocols may utilize thioguanine during the induction or consolidation phases of ALL treatment but not during maintenance therapy due to the risk of toxicity with extended exposure to thioguanine.

**Ph+ ALL**

Ph+ ALL is rare in pediatric cases of ALL, occurring in approximately 3% of cases. In contrast, approximately 25% of adult cases of ALL are Ph+. The NCCN guidelines recommend incorporation of a 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) for patients with Ph+ ALL. Imatinib is the most commonly used TKI in this setting but data also support the use of dasatinib and smaller studies have demonstrated the activity of ponatinib in patients with Ph+ ALL harboring a T315I mutation. Mutation testing for the ABL gene should be considered as that can confer greater resistance or susceptibility to a particular TKI. Pediatric patients with Ph+ ALL are also candidates for imatinib therapy; 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.

**Acute Promyelocytic Leukemia**

Acute Promyelocytic Leukemia (APL) is a subtype of Acute Myeloid Leukemia (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. It is estimated that 80% of APL patients can now be cured. The median age of APL diagnosis (age 44) is younger than the median age of diagnosis for other subtypes of AML (age 67). 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 cells. Peripheral blood neutrophils that express PML-RARA rearrangements have been shown to differentiate to normal neutrophils during treatment with tretinoin. Another unique feature of APL compared to other subtypes of AML is the high risk of coagulopathy. This increased risk of coagulopathy 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.

Lymphomas

Hodgkin Lymphoma

Hodgkin lymphoma (HL) is most commonly diagnosed in patients who are between 15 and 30 years of age. While there are several different subtypes and 3 staging classifications (ranging from early stage favorable to advanced stage disease), HL is now curable in at least 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)

Lymphomas are a heterogenous 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. The majority of 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 is that of a solid tumor, but NHL can also present as circulating tumor cells in the peripheral blood. The presence or absence of Reed-Sternberg cells differentiates Hodgkin’s lymphoma (present) from Non-Hodgkin’s lymphomas (absent). NHLs are further classified into distinct clinical entities based on morphology, immunophenotype, genetic features, and clinical symptoms. All of the NHLs in this review (chronic lymphocytic leukemia [CLL], small lymphocytic lymphoma [SLL], hairy cell leukemia [HCL], follicular lymphoma [FL], and mantle cell lymphoma [MCL]) are classified as mature B-cell lymphomas with the exception of cutaneous T-cell lymphoma (CTCL) which is a T-cell lymphoma. NHLs can be further classified as indolent (e.g., FL) or aggressive (e.g., MCL). Indolent lymphomas can often be treated with single-agent therapy while aggressive lymphomas usually require complex, multi-agent chemotherapy regimens.

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

CLL is a lymphoproliferative disorder characterized by accumulation of clonal B lymphocytes that lack functionality due to lower levels of immunoglobulin M (IgM) and immunoglobulin D (IgD) compared to normal B cells. CLL is the most prevalent adult leukemia but is generally a disease of the elderly, with a median age of 72 years and less than 10% of patients diagnosed under the age of 50. A small percentage (< 4%) 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 patients may be candidates for cytotoxic or biologic therapies. CLL and SLL are different manifestations of the same disease. In CLL, the abnormal lymphocytes are found predominantly in the bone marrow and peripheral blood while in SLL the abnormal lymphocytes are
found predominantly in the lymph nodes. In the 1950s and 1960s, alkylating agents, including chlorambucil combined with corticosteroids, became the standard of care for patients requiring treatment for CLL. Later, the use of purine analog-based therapies with drugs like fludarabine became the standard of care for most patients. 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, such as rituximab (Rituxan) or obinutuzumab (Gazyva). The 2016 NCCN guidelines for CLL/SLL provide suggested treatment regimens for high risk CLL with del (17p), CLL with del (11q), as well as for standard risk CLL without del (11q) or del (17p). High risk patients with del (17p) have an approximate 32-month overall survival while standard risk patients may expect an overall survival approaching 10 years. Therefore, the intensity of treatment regimens, as well as whether or not the treatment is being utilized in the first-line setting or for relapsed/refractory disease, varies accordingly. While the established first-line therapy for fit patients with standard risk CLL who require treatment is fludarabine, cyclophosphamide, and rituximab, there are several approved drugs and combination regimens that may be utilized in the treatment of CLL; this review will focus only on those agents (mostly oral medications) that are included in this therapeutic class review. For high risk patients with CLL del (17p), ibrutinib or chlorambucil plus obinutuzumab are recommended in the first-line setting while ibrutinib, venetoclax (Venclexta), idelalisib monotherapy, or idelalisib plus rituximab (Rituxan), are options in the relapsed/refractory setting for patients with CLL del (17p). Patients with CLL with del (11q) mutations who are less than 70 years old without significant comorbidities should receive chemoimmunotherapy which may contain chlorambucil as first-line treatment, while those patients who are 70 years of age or older with significant comorbidities should receive chlorambucil plus obinutuzumab (Category 1), ibrutinib (Category 1), chlorambucil monotherapy, or chlorambucil combination therapy with either ofatumumab or rituximab. For patients with CLL del (11q) who are receiving treatment for relapsed or refractory disease, ibrutinib or idelalisib plus rituximab are both Category 1 recommendations regardless of age or comorbid conditions. If the CLL del (11q) patient is 70 years or older and has significant comorbidities, single agent idelalisib, rituximab plus chlorambucil, or lenalidomide with or without rituximab are all Category 2A options. Single agent idelalisib or lenalidomide with or without rituximab (both Category 2A) are also options for patients younger than 70 years who do not have significant comorbidities. First-line therapy options for patients with CLL without del (11q) or del (17p) include ibrutinib (Category 1) or chlorambucil alone (Category 2B) or in combination with obinutuzumab (Category 1), ofatumumab or rituximab (both Category 2A). For relapsed/refractory disease, ibrutinib (Category 1) or idelalisib with rituximab (Category 1), are recommended therapy while idelalisib monotherapy is a Category 2A recommendation regardless of age or comorbid condition for relapsed/refractory therapy of CLL without del (11q) or del (17p) mutations. For CLL patients without del (11q) or del (17p) who are either 70 years of age or older or who have significant comorbidities, cladribine has been removed from the NCCN guidelines as a treatment option.

**Hairy Cell Leukemia (HCL)**

HCL is classified as a non-Hodgkin’s lymphoma and is so named based on the characteristic appearance of the cells obtained from peripheral blood and bone marrow of patients afflicted with HCL. Cladribine is recommended as initial treatment of HCL in patients who display systemic symptoms such as bone marrow hypoplasia, splenic discomfort, or recurrent infections.
**Follicular Lymphoma (FL)**

FL is the most common subtype of indolent NHL and accounts for about 22% of all newly diagnosed cases of NHL. Idelalisib (Zydelig) is approved for the treatment of FL in patients who have received at least 2 prior systemic therapies.\(^4^4\) The 3.2016 NCCN guidelines list lenalidomide plus rituximab as a Category 3 recommendation for first-line therapy and as a Category 2A recommendation for second-line and subsequent therapy. Chlorambucil, with or without rituximab (Category 2A), is a first-line therapy option for the elderly or infirm. Idelalisib is another second-line or subsequent therapy option (Category 2A) for follicular lymphoma.

**Mantle Cell Lymphoma (MCL)**

MCL, while technically classified as an aggressive lymphoma, possesses characteristics of both indolent and aggressive NHLs. MCL is highly resistant to conventional chemotherapy and yet displays an aggressive disease course.\(^4^5,4^6\) Cladribine plus rituximab \((\text{Category 2B})\) may be utilized for induction therapy or second-line therapy while ibrutinib (Imbruvica) at a dose of 560 mg daily or lenalidomide (Revlimid), with or without rituximab, are options for second-line therapy of MCL (category 2A).\(^4^7\)

**Cutaneous T-cell Lymphoma (CTCLs)**

CTCLs are a group of NHL 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 it 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 3.2016 NCCN guidelines recommend vorinostat (Zolinza) for those patients requiring systemic therapy of CTCLs including MF or SS.\(^4^8\)

**Multiple Myeloma**

Multiple myeloma is a malignant neoplasm of plasma cells that results in accumulation of plasma cells in bone marrow, leading to bone destruction, hypercalcemia, cytopenias, and renal failure. 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 multiple myeloma 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 due to newer and more effective treatments and now is estimated to be 8 to 10 years among patients with standard-risk disease but significantly lower in patients that exhibit high-risk features.\(^4^9\) Melphalan and prednisone (MP) have been the historical standard treatment of multiple myeloma since 1960, resulting in an average 60% response rate with duration of 18 months and an OS of 24 to 36 months.\(^5^0\) Several trials have demonstrated significantly higher overall response rates (ORR) when thalidomide is added to melphalan and prednisone (MPT).\(^5^1\) MP has also been compared to melphalan/prednisone/bortezomib (MPB), as well as melphalan/prednisone/lenalidomide (MPL).\(^5^2,5^3\) All 3 of these regimens (MPT, MPB, and MPL), as well as bortezomib/lenalidomide/dexamethasone, are preferred regimens and are \(\text{designated Category 1}\).
NCCN recommendations as primary therapy for multiple myeloma patients who are non-transplant candidates.\textsuperscript{54} Other regimens that may be utilized as primary therapy in non-transplant candidates include ixazomib (Ninlaro)/lenalidomide/dexamethasone (Category 2A) or thalidomide/dexamethasone (Category 2B). High-dose therapy with stem cell support (bone marrow transplant) is a critical component in the modern treatment plan for eligible multiple myeloma patients. Melphalan-containing regimens should not be utilized in transplant eligible candidates due to the toxicity of melphalan on the patient’s stem cell reserve. Regimens containing bortezomib/dexamethasone as a backbone, with or without doxorubicin, lenalidomide, or thalidomide, as well as lenalidomide/dexamethasone, are preferred regimens for primary therapy (Category 1) in transplant eligible patients. Other regimens that may be utilized as primary therapy for transplant eligible candidates include ixazomib (Ninlaro)/lenalidomide/dexamethasone or carfilzomib/lenalidomide/dexamethasone (both Category 2A) or thalidomide/dexamethasone (Category 2B). Single agent lenalidomide or thalidomide are the preferred drugs for maintenance therapy of multiple myeloma (Category 1). Bortezomib or prednisone may be added to single agent thalidomide as another option for maintenance therapy (Category 2B). There are several preferred regimens for the treatment of progressive or relapsed myeloma. Many of these combinations include thalidomide or lenalidomide with other active agents against multiple myeloma, such as bortezomib and carfilzomib. Ixazomib (Ninlaro)/lenalidomide/dexamethasone is a preferred regimen (Category 1) in this setting while ixazomib (Ninlaro)/dexamethasone or ixazomib monotherapy are both Category 2A recommendations as preferred regimens. Panobinostat (Farydak)/bortezomib/dexamethasone is also a preferred regimen (Category 1) for use in patients with progressive disease who have received at least 2 prior therapies for multiple myeloma. Pomalidomide/dexamethasone is another preferred option for patients who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy (Category 1). Lenalidomide/bendamustine/dexamethasone, bortezomib/vorinostat, and panobinostat/carfilzomib (all Category 2A) are all listed as possible regimens but are not designated preferred regimens. Single agent lenalidomide, pomalidomide, or thalidomide may be considered for steroid-intolerant individuals in the setting of previously treated multiple myeloma.\textsuperscript{55}

**Waldenström’s Macroglobulinemia**

Waldenström’s Macroglobulinemia is a B-cell disorder presenting as bone marrow infiltration with lymphoplasmacytic cells that are CD19+, CD20+, and CD22+. The 2.2016 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 (Imbruvica) is listed as an option for both primary treatment and for use in patients who have received previous therapies for Waldenström’s Macroglobulinemia. Thalidomide with or without rituximab, cladribine with or without rituximab, and single agent chlorambucil are also considered possible primary treatment options or treatment options for patients who have received previous treatment (all Category 2A).\textsuperscript{56}
Myelodysplastic Syndromes

Myelodysplastic Syndromes are associated with profound cytopenias and patients are subject to the morbidity associated with refractory anemia, neutropenia, and thrombocytopenia. According to the 1.2016 NCCN guidelines, there are numerous categories/subtypes of myelodysplastic syndromes. One of these subtypes, chronic myelomonocytic leukemia (CMML), may be associated with a 5q31-33 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 (Gleevec). 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.58

Myelofibrosis

The diagnosis of myelofibrosis requires evidence of grade 3 or above bone marrow fibrosis and a pathogenetic mutation, such as JAK2. These patients may also have palpable splenomegaly, anemia, night sweats, weight loss, unexplained fever, and diffuse bone pain. The 2014 revision of the British Committee for Standards in Hematology Guidelines for Investigation and Management of Myelofibrosis provides recommendations regarding the use of ruxolitinib in the management of myelofibrosis.59 According to these guidelines, treatment with ruxolitinib should be considered in patients with symptomatic splenomegaly (Evidence grade 1A) and in patients with hepatomegaly and portal hypertension (Evidence grade 2B). The guideline further states that treatment with ruxolitinib in asymptomatic patients and/or patients who lack bothersome splenomegaly is not currently recommended.

Gastrointestinal Stromal Tumors (GIST)

The 2.2016 NCCN guidelines for Soft Tissue Sarcomas recommend imatinib (Gleevec) 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 (Category 1). Imatinib may also be utilized in patients with persistent gross residual disease after surgery (Category 2A). Mutational testing is recommended because patients with advanced GISTs have different responses to imatinib based on detectable mutations. While most KIT and PDGFRα mutations are associated with a response to imatinib, certain variants have a much lower response rate to imatinib and a higher dose of imatinib may be warranted in these patients. If neither KIT nor PDGFRα mutations are present, the likelihood of response to imatinib is less than 50%. According to the guidelines, preoperative imatinib may prohibit accurate assessment of recurrence risk and therefore imatinib (Gleevec) should only be considered preoperatively if surgical morbidity would be reduced by downstaging the tumor. 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.60
Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans is an uncommon tumor that arises in the dermis layer of the skin. Imatinib (Gleevec) is recommended for consideration in the setting of positive margins post-resection or in the setting of recurrence or metastasis by 1.2016 NCCN guidelines.61

No current United States (U.S.) guidelines exist for the treatment of polycythemia vera, aggressive systemic mastocytosis, erythema nodosum leprosum, hypereosinophilic syndrome, or chronic eosinophilic leukemia.

PHARMACOLOGY

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, cladribine, hydroxyurea, and mercaptopurine.

Cladribine is phosphorylated intracellularly to produce the active moiety chlorodeoxyadenosine triphosphate which inhibits DNA polymerase, DNA ligase, and ribonucleotide reductase, all of which are enzymes important in DNA maintenance and repair.81

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 affects on cells in the S-phase, especially in cells rapidly synthesizing DNA.

Melphalan, chlorambucil, and busulfan 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 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.

Thalidomide and its analogues, lenalidomide and pomalidomide, 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.82
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 promyelomoyocytic 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 bosutinib (Bosulif), dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), ponatinib (Iclusig), ruxolitinib (Jakafi), ibrutinib (Imbruvica), ixazomib (Ninlaro), venetoclax (Venclexta), and idelalisib (Zydelig).

Despite high imatinib (Gleevec) efficacy in chronic phase (CP) CML, resistance, particularly secondary resistance, or loss of response has been documented. The most common mechanism for secondary resistance is the reactivation of activity either by development of mutations in the BCR-ABL tyrosine kinase domain that impair imatinib (Gleevec) binding or, less frequently, by increased BCR-ABL gene expression. Dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib (Iclusig) are potent and selective BCR-ABL kinase inhibitors that have been effective in CP CML patients with imatinib (Gleevec) resistance or intolerance. They are active against many of the imatinib (Gleevec)-resistant BCR-ABL kinase domain mutations. A patient’s mutation status at time of loss of response to the first generation tyrosine kinase inhibitor may be helpful in selecting subsequent tyrosine kinase inhibitor therapy.

Ruxolitinib (Jakafi), an oral kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Myelofibrosis (MF) is a myeloproliferative neoplasm associated with dysregulated JAK1 and JAK2 signaling.
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.\(^9^1\) Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity.

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) inhibits phosphatidylinositol 3-kinase (PI3K), expressed in both normal and malignant B-cells inducing apoptosis and inhibiting proliferation. Idelalisib inhibits 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.

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 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.\(^9^2\)

<table>
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<th>BTK</th>
<th>SRC</th>
<th>ABL</th>
<th>PI3K</th>
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<th>VEGF</th>
<th>c-kit</th>
<th>EPHA2</th>
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ABL = Abelson; BCR = breakpoint cluster region; c-kit = stem cell factor c-kit; CSF-1R = colony stimulating factor Type 1; EPHA = ephrin A; JAK = janus associated kinase; PDGF = platelet derived growth factor; RET = glial cell-line derived neurotrophic factor.
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<th>Drug</th>
<th>Half-Life (hr)</th>
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<td>2</td>
<td>19</td>
<td>Methylation Oxidation</td>
<td>6-thioguanine nucleotides (6-TGNs)</td>
<td>Urine: 46</td>
<td>None</td>
</tr>
<tr>
<td>nilotinib (Tasigna)</td>
<td>17</td>
<td>98</td>
<td>Oxidation and hydroxylation</td>
<td>None</td>
<td>Feces: 93</td>
<td>AUC: ▲ 82</td>
</tr>
<tr>
<td>panobinostat (Farydak)</td>
<td>37</td>
<td>90</td>
<td>Oxidation, reduction, hydrolysis, glucuronidation, CYP3A</td>
<td>None</td>
<td>Urine:29-51</td>
<td>AUC: ▼6 Cmax: ▼4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feces: 44-77</td>
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</tbody>
</table>
Pharmacokinetics (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (hr)</th>
<th>Protein Binding (%)</th>
<th>Metabolism</th>
<th>Active metabolites</th>
<th>Elimination (%)</th>
<th>Effect of High Fat Meal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pomalidomide</td>
<td>9.5</td>
<td>12 to 44</td>
<td>CYP1A2 CYP3A4</td>
<td>None</td>
<td>Urine: 73</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CYP3A4 CYP2C8</td>
<td>None</td>
<td>Feces: 15</td>
<td></td>
</tr>
<tr>
<td>ponatinib</td>
<td>24</td>
<td>99</td>
<td>CYP3A4</td>
<td>None</td>
<td>Feces: 87</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CYP2C8</td>
<td>None</td>
<td>Urine: 5</td>
<td></td>
</tr>
<tr>
<td>procarbazine</td>
<td>7 min (parent; once reaches plasma)</td>
<td>Not described</td>
<td>Auto-oxidation</td>
<td>nr</td>
<td>Urine: 70</td>
<td>nr</td>
</tr>
<tr>
<td>ruxolitinib</td>
<td>3</td>
<td>97</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>Feces: 22</td>
<td>AUC: ▲ 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine: 74</td>
<td>Cmax: ▼ 24</td>
</tr>
<tr>
<td>thalidomide</td>
<td>5.5-7.3</td>
<td>55-66</td>
<td>Limited metabolism</td>
<td>None</td>
<td>Feces &lt; 2</td>
<td>Tmax ▲ to 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine: 93.6</td>
<td></td>
</tr>
<tr>
<td>tretinoin</td>
<td>0.5-2</td>
<td>&gt; 95</td>
<td>CYP enzymes</td>
<td>None</td>
<td>Feces: 31</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urine: 63</td>
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<tr>
<td>venetoclax</td>
<td>26</td>
<td>&gt; 99</td>
<td>CYP3A4/5</td>
<td>M27</td>
<td>Feces: &gt; 99.9</td>
<td>AUC ▲</td>
</tr>
<tr>
<td>vorinostat</td>
<td>2</td>
<td>71</td>
<td>Glucuronidation and hydrolysis followed by β oxidation</td>
<td>None</td>
<td>Urine: &lt; 1</td>
<td>AUC: ▲ 1.3 fold</td>
</tr>
</tbody>
</table>

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.
There are no contraindications with imatinib (Gleevec), dasatinib (Sprycel), ponatinib (Iclusig), vorinostat (Zolinza), ixazomib (Ninlaro), panobinostat (Farydak), ibrutinib (Imbruvica), or ruxolitinib (Jakafi).

Bosutinib (Bosulif), cladribine, hydroxyurea, idelalisib (Zydelig), melphalan, thalidomide, chlorambucil, lenalidomide, tretinoin, and mercaptopurine are contraindicated in patients with hypersensitivity to the active drug or any of the components.

Chlorambucil (Leukeran) 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.

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

Boxed Warnings

Thalidomide, lenalidomide, and pomalidomide all have a boxed warning regarding pregnancy. 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. Mortality at or shortly after birth has been reported in about 40% of infants exposed to thalidomide. Chlorambucil is probably mutagenic and teratogenic in human and produces human infertility. Melphalan is leukemogenic in humans and 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.

Ponatinib (Iclusig) has a boxed warning regarding the risk of vascular occlusion, heart failure, and hepatotoxicity. Arterial and venous thrombosis and occlusions have occurred in at least 27% of ponatinib-treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years
old, experienced these events. 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 8% 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.\textsuperscript{137}

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.

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

Cladribine’s boxed warning states that the drug should only be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. Serious neurological toxicity (including irreversible paraparesis and quadriplegia) has been reported in patients who received cladribine injection by continuous infusion at high doses (4 to 9 times the recommended dose for HCL). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurologic toxicity has been reported rarely following treatment with standard cladribine dosing regimens. Acute nephrotoxicity has been observed with high doses of cladribine (4 to 9 times the recommended dose for HCL), especially when given concomitantly with other nephrotoxic agents/therapies.

Idelalisib (Zydelig) has a boxed warning regarding fatal and/or serious toxicities, including hepatotoxicity (14% incidence), diarrhea/colitis (14% incidence), pneumonitis, and intestinal perforation.

Panobinostat’s 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.\textsuperscript{138}

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, it should not be used in patients with hypokalemia, hypomagnesemia, or in patients experiencing long QT syndrome. Before initiating therapy with nilotinib, hypokalemia and hypomagnesemia must be corrected, and monitoring of these electrolytes is recommended. Concomitant use of medications associated with QT prolongation and strong inhibitors of the CYP3A4 enzyme system should be avoided in patients taking nilotinib. Food should not be consumed 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.

Thalidomide, lenalidomide, and pomalidomide all carry a boxed warnings regarding embryo-fetal toxicity. Pregnancy must be excluded before starting treatment and the patient must use 2 reliable methods of contraception while taking any of these medications.

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. Lenalidomide also includes a boxed warning related to the risk of arterial thromboembolism, myocardial infarction, 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 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 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selected Warnings</th>
<th>Recommended Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosutinib</td>
<td>GI toxicity, myelosuppression, hepatotoxicity, fluid retention, embryo-fetal toxicity, renal toxicity</td>
<td>complete blood count (CBC), liver function tests (LFTs), bilirubin, renal function at baseline and during therapy</td>
</tr>
<tr>
<td>chlorambucil</td>
<td>Myelosuppression, seizures, infertility, secondary malignancies including leukemias, skin rash progressing to erythema multiforme, toxic epidermal necrolysis or Stevens-Johnson syndrome</td>
<td>CBC weekly, WBC 3 or 4 days after each CBC for the first 3 to 6 weeks of therapy</td>
</tr>
<tr>
<td>cladribine</td>
<td>Myelosuppression, fever, GI toxicity, renal dysfunction, neurologic toxicity, infections</td>
<td>CBC, renal function, neurological status, signs/symptoms of infection</td>
</tr>
<tr>
<td>dasatinib</td>
<td>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, arrhythmias, palpitations, peripheral arterial occlusive disease, transient ischemic attacks (TIAs), pulmonary arterial hypertension, embryo-fetal toxicity, severe dermatologic toxicity including Stevens-Johnson syndrome and erythema multiforme, tumor lysis syndrome</td>
<td>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/cardio pulmonary disease, electrolyte levels</td>
</tr>
<tr>
<td>hydroxyurea</td>
<td>Bone marrow suppression, most commonly leucopenia 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 leukemia’s; cutaneous vasculitic toxicities; <strong>embryo-fetal toxicity; avoid use of live vaccines</strong></td>
<td>CBC with differential, renal function</td>
</tr>
<tr>
<td>ibrutinib</td>
<td>Hemorrhage, infections, <strong>progressive multifocal leukoencephalopathy (PML)</strong>, cytopenias, atrial fibrillation, hypertension, second primary malignancies, embryo-fetal toxicity, prolonged hyperleukocytosis, tumor lysis syndrome</td>
<td>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, <strong>blood pressure</strong></td>
</tr>
</tbody>
</table>
### Selected Warnings and Recommended Monitoring (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selected Warnings</th>
<th>Recommended Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>idelalisib (Zydelig)</td>
<td>Hepatotoxicity, severe diarrhea or colitis, pneumonitis, intestinal perforation, severe cutaneous reactions, anaphylaxis, neutropenia, embryo-fetal toxicity</td>
<td>Liver function (alanine aminotransferase [ALT]/aspartase 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; skin reactions; CBC</td>
</tr>
<tr>
<td>imatinib (Gleevec)</td>
<td>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 Stevens-Johnson syndrome, 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</td>
<td>CBC, weight, signs/symptoms of fluid retention, signs/symptoms of cardiac failure, LFTs, ECG, serum troponin, thyroid function tests, growth monitoring in children</td>
</tr>
<tr>
<td>ixazomib (Ninlaro)</td>
<td>Thrombocytopenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy, peripheral edema, rash, hepatotoxicity, embryo-fetal toxicity</td>
<td>Platelet counts at least monthly; consider more frequent platelet count monitoring during the first 3 cycles of treatment; symptoms of neuropathy; LFTs</td>
</tr>
<tr>
<td>lenalidomide (Revlimid)</td>
<td>Embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism, increased mortality in patients with CLL, second primary malignancies (mainly AML and MDS), hepatotoxicity, angioedema, and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), tumor lysis syndrome, tumor flare reaction, impaired stem cell mobilization</td>
<td>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 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), signs and symptoms of thrombotic events, LFTs, signs of angioedema, exfoliative or bullous rash, signs/symptoms of tumor lysis syndrome</td>
</tr>
<tr>
<td>melphalan</td>
<td>Bone marrow suppression, secondary malignancies, anaphylaxis, impairment of fertility</td>
<td>CBC with differential</td>
</tr>
<tr>
<td>mercaptopurine (Purinethol) (Purixan)</td>
<td>Bone marrow suppression resulting in anemia, leucopenia, thrombocytopenia or any combination of these, life-threatening infections and bleeding, hepatotoxicity, immunosuppression, embryo-fetal toxicity, treatment related malignancies</td>
<td>CBC; consider thiopurine-5'-methyltransferase (TPMT) testing 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</td>
</tr>
</tbody>
</table>
## Selected Warnings and Recommended Monitoring (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selected Warnings</th>
<th>Recommended Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>nilotinib</td>
<td>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, 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) patients with resistant or intolerant Ph+ CML receiving nilotinib (Tasigna), the relative early occurrence of some of these deaths relative to the initiation of nilotinib (Tasigna) suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence, exposure of nilotinib (Tasigna) is reduced in patients with total gastrectomy, embryo-fetal toxicity</td>
<td>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, 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</td>
</tr>
<tr>
<td>panobinostat</td>
<td>Severe diarrhea, cardiac ischemia, arrhythmias, hemorrhage, hepatotoxicity, embryo-fetal toxicity, myelosuppression, infections, hepatotoxicity</td>
<td>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</td>
</tr>
<tr>
<td>pomalidomide</td>
<td>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</td>
<td>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 monthly thereafter, signs and symptoms of tumor lysis syndrome; LFTs monthly</td>
</tr>
<tr>
<td>ponatinib</td>
<td>Vascular occlusion including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, arterial occlusion including coronary artery occlusion and peripheral arterial occlusive events including fatal mesenteric artery occlusion, digital or distal extremity necrosis, renal artery stenosis and thrombosis, venous thromboembolism, heart failure, hepatotoxicity, hypertension, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, tumor lysis syndrome, comprised wound healing, gastrointestinal perforation, embryo-fetal toxicity, increased toxicity in newly diagnosed chronic phase CML</td>
<td>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</td>
</tr>
</tbody>
</table>
### Selected Warnings and Recommended Monitoring (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selected Warnings</th>
<th>Recommended Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>ruxolitinib (Jakafi)</td>
<td>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 ruxolitinib (Jakafi), progressive multifocal leukoencephalopathy, 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</td>
<td>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</td>
</tr>
<tr>
<td>thalidomide (Thalomid)</td>
<td>Embryo-fetal toxicity, venous and arterial thromboembolism, drowsiness and somnolence, peripheral neuropathy, dizziness and orthostatic hypotension, neutropenia, thrombocytopenia, increased HIV viral load, bradycardia, SJS and TEN, seizures, tumor lysis syndrome, contraceptive risks, hypersensitivity</td>
<td>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, HIV viral load after first and third months of treatment and every 3 months thereafter in HIV+ patients</td>
</tr>
<tr>
<td>tretinoin</td>
<td>Retinoic acid-acute promyelocytic leukemia (RA-APL) syndrome, leukocytosis, pseudotumor cerebri, hypercholesterolemia and/or hypertriglyceridemia, elevated LFTs</td>
<td>Signs of fever, dyspnea, weight gain, papilledema, headache, visual disturbances; monitor lipid profiles, LFTs, CBC, coagulation parameters</td>
</tr>
<tr>
<td>venetoclax (Venclexta)</td>
<td>tumor lysis syndrome, neutropenia</td>
<td>Blood chemistries including uric acid, renal function, CBC</td>
</tr>
<tr>
<td>vorinostat (Zolinza)</td>
<td>PE, DVT, thrombocytopenia (severe thrombocytopenia with GI bleeding when given concomitantly with other HDAC inhibitors such as valproic acid), anemia, nausea, vomiting, diarrhea, hyperglycemia, electrolyte abnormalities</td>
<td>Signs and symptoms of thrombosis, CBC, serum electrolytes, and blood glucose every 2 weeks for first 2 months of therapy and then monthly thereafter</td>
</tr>
</tbody>
</table>
Risk Evaluation and Mitigation Strategy (REMS)\textsuperscript{140,141,142,143,144,145}

The ponatinib (Iclusig) REMS approved in December 2013 informs prescribers about the approved indications for use and the serious risk of vascular occlusion and thromboembolism associated with ponatinib. The REMS includes the following: REMS letter to healthcare professionals who are known or likely to prescribe ponatinib, REMS letter for professional societies to be distributed to their members, REMS fact sheet for health care professionals, an information piece which was mandated to be published quarterly for 1 year after REMS approval in several professional journals, information that was required to be prominently displayed at scientific meetings for 1 year after REMS approval, and Iclusig REMS website to provide access to all REMS materials for the duration of the REMS.

The idelalisib REMS program was approved in July 2014 with the FDA approval of the medication. 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, and fatal and serious intestinal perforation associated with idelalisib. The communication plan includes a REMS letter to oncologists and hematologists, who are likely to prescribe idelalisib, REMS letter distributed to professional societies, a REMS fact sheet to be distributed to healthcare providers, an information piece published quarterly for one year after REMS approval in applicable professional journals, information to be prominently displayed at scientific meetings for 1 year after REMS approval, information regarding REMS on the Zydelig website, and a patient safety information card.

Thalidomide is available only through a restricted program. The goal of the Thalomid 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 Thalomid 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 thalidomide.

Lenalidomide is available only through a restricted program. The Revlimid 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 is available only through a restricted program. The Pomalyst 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.

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), idelalisib (Zydelig), imatinib (Gleevec), nilotinib (Tasigna), panobinostat (Farydak), and ponatinib (Iclusig) can potentially increase and the combinations should generally be avoided or used with caution. In addition, patients taking these medications should avoid grapefruit juice as it can increase the plasma concentrations of these agents.

Concomitant administration of ibrutinib with potent inhibitors of CYP3A4 should be avoided, and selection of an alternate medication with minimal to no enzyme inhibition potential is recommended. 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 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.

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%.
Co-administration of CYP3A4 Inducers

Administration of ibrutinib (Imbruvica), bosutinib (Bosulif), dasatinib (Sprycel), venetoclax (Venclexta), imatinib (Gleevec), nilotinib (Tasigna), idelalisib (Zydelig), panobinostat (Farydak), ixazomib (Ninlaro), and ponatinib (Iclusig) 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 should be considered (except ponatinib [Iclusig]).

Substrates of CYP3A4, CYP2D6, CYP2C8

Dasatinib (Sprycel), 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).

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 INRs monitored closely.

Patients receiving concomitant cladribine, 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 (Venclexta) by at least 50%. Ponatinib (Iclusig), venetoclax (Venclexta), 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, cladribine, melphalan, and hydroxyurea.

**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) 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.

**Histamine-2 (H₂) Receptor Blockers/Proton Pump Inhibitors (PPIs)**

H₂ receptor blockers and proton pump inhibitors are associated with long-term suppression of gastric acid secretion which may result in reduced systemic exposure of dasatinib (Sprycel), nilotinib (Tasigna), and ponatinib (Iclusig). Concomitant use of H₂ receptor blockers or proton pump inhibitors with these agents is, therefore, not recommended.

Concomitant lansoprazole (PPI) decreased bosutinib (Bosulif) Cmax by 46% and AUC by 26% compared to bosutinib alone. Consider using short-acting antacids or H₂ blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H₂ 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) 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 post-marketing 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.

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 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 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.

There are no known drug/drug interactions with chlorambucil (Leukeran) or melphalan (Alkeran).
ADVERSE EFFECTS

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fluid Retention/ Edema</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Skin Rash</th>
<th>Nausea</th>
<th>Hemorrhage</th>
<th>Muscle Pain/ Myalgia</th>
<th>Stomatitis</th>
<th>↓ Hb/ Anemia</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosutinib (Bosulif) n=546</td>
<td>14</td>
<td>82</td>
<td>--</td>
<td>35</td>
<td>46</td>
<td>--</td>
<td>reported</td>
<td>--</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>CML-resistant/intolerant to imatinib (Gleevec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cladribine (Leustatin)</td>
<td>2</td>
<td>7</td>
<td>14</td>
<td>16</td>
<td>22</td>
<td>nr</td>
<td>6</td>
<td>nr</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>dasatinib (Sprycel)</td>
<td>21-35</td>
<td>18-31</td>
<td>15-33</td>
<td>15-21</td>
<td>18-23</td>
<td>11-26</td>
<td>0-19/3-13</td>
<td>1-&lt;10</td>
<td>13-74</td>
<td>1&lt;10</td>
</tr>
<tr>
<td>CML-resistant/intolerant to imatinib (Gleevec)</td>
<td>23</td>
<td>18 (19)</td>
<td>12 (10)</td>
<td>11 (17)</td>
<td>9</td>
<td>6 (5)</td>
<td>6-12 (12-16)</td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>CML-newly diagnosed imatinib (Gleevec)</td>
<td>23 (43)</td>
<td>18</td>
<td>12</td>
<td>11</td>
<td>9</td>
<td>6</td>
<td>6-12 (12-16)</td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>ibritinib (Imbruvica) – MCL</td>
<td>35</td>
<td>51</td>
<td>13</td>
<td>25</td>
<td>31</td>
<td>6</td>
<td>11</td>
<td>17</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>ibritinib (Imbruvica) CLL</td>
<td>23</td>
<td>63</td>
<td>19</td>
<td>27</td>
<td>21</td>
<td>nr</td>
<td>23</td>
<td>21</td>
<td>44</td>
<td>17</td>
</tr>
<tr>
<td>idelalisib (Zydelig) CLL</td>
<td>nr</td>
<td>21 (16)</td>
<td>nr</td>
<td>18 (6)</td>
<td>25 (21)</td>
<td>nr</td>
<td>7 (4)</td>
<td>6 (2)</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>idelalisib (Zydelig) CLL</td>
<td>nr</td>
<td>68 (47)</td>
<td>16 (11)</td>
<td>31 (21)</td>
<td>42 (29)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>idelalisib (Zydelig) Indolent NHL</td>
<td>15 (10)</td>
<td>68 (47)</td>
<td>16 (11)</td>
<td>31 (21)</td>
<td>42 (29)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>imatinib (Gleevec) CML</td>
<td>61.7-76</td>
<td>43-57</td>
<td>27-36</td>
<td>36-47</td>
<td>49.5-71</td>
<td>28.9-53</td>
<td>38-49/9-27</td>
<td>0.1-1</td>
<td>6-42</td>
<td>0.11</td>
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</tbody>
</table>
### Adverse Effects (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fluid Retention/Edema</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Skin Rash</th>
<th>Nausea</th>
<th>Hemorrhage</th>
<th>Muscle Pain/Myalgia</th>
<th>Stomatitis</th>
<th>↓ Hb/Anemia</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib (Gleevec) GIST</td>
<td>76.7-86.1</td>
<td>56.2-58.2</td>
<td>19.7-22</td>
<td>38.1-49.8</td>
<td>58.1-64.5</td>
<td>12.3-13.3</td>
<td>nr</td>
<td>9.2-10</td>
<td>32-34.8</td>
<td>0.1-1</td>
</tr>
<tr>
<td>ixazomib (Ninlaro) n=720</td>
<td>25 (18)</td>
<td>42 (36)</td>
<td>nr</td>
<td>19 (11)</td>
<td>26 (21)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>lenalidomide/dexamethasone (Revlimid) (dexamethasone/placebo) in multiple myeloma</td>
<td>26.3 (21.1)</td>
<td>38.5 (27.4)</td>
<td>nr</td>
<td>21.2 (9.4)</td>
<td>26.1 (21.4)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>31.4 (23.7)</td>
<td>7.9 (5.7)</td>
</tr>
<tr>
<td>nilotinib (Tasigna) n=438 CML resistant/intolerant to imatinib (Gleevec)</td>
<td>11</td>
<td>19-22</td>
<td>21-31</td>
<td>28-33</td>
<td>18-31</td>
<td>reported</td>
<td>14</td>
<td>reported</td>
<td>8-23</td>
<td>1-10</td>
</tr>
<tr>
<td>nilotinib (Tasigna) 300 mg twice daily CML-newly diagnosed (imatinib [Gleevec])</td>
<td>8 (37)</td>
<td>14 (37)</td>
<td>28 (16)</td>
<td>36 (16)</td>
<td>19 (38)</td>
<td>reported</td>
<td>14 (16)</td>
<td>reported</td>
<td>7 (all Grades) (5) (Grade 3/4)</td>
<td>1-10</td>
</tr>
<tr>
<td>panobinostat (Farydak) + bortezomib + dexamethasone (placebo + bortezomib + dexamethasone)</td>
<td>(19)</td>
<td>68 (42)</td>
<td>nr</td>
<td>reported</td>
<td>36 (21)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>62 (52)</td>
<td>reported</td>
</tr>
<tr>
<td>pomalidomide (Pomalyst) monotherapy in multiple myeloma</td>
<td>23</td>
<td>34</td>
<td>nr</td>
<td>22</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>38</td>
<td>nr</td>
</tr>
<tr>
<td>ponatinib (Iclusig) CML-any phase n=417 Ph+ALL n=32</td>
<td>19</td>
<td>26</td>
<td>39</td>
<td>54</td>
<td>32</td>
<td>11</td>
<td>22</td>
<td>23</td>
<td>55</td>
<td>71</td>
</tr>
<tr>
<td>ruxolitinib (Jakafi) n=155</td>
<td>nr</td>
<td>nr</td>
<td>14.8 (5.3)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>96.1 (86.8)</td>
<td>nr</td>
</tr>
</tbody>
</table>
**Adverse Effects (continued)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fluid Retention /Edema</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Skin Rash</th>
<th>Nausea</th>
<th>Hemorrhage</th>
<th>Muscle Pain/Myalgia</th>
<th>Stomatitis</th>
<th>↓ Hb/Anemia</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>thalidomide (Thalomid) plus dexamethasone (dexamethasone alone)</td>
<td>34 (25)</td>
<td>nr</td>
<td>nr</td>
<td>30 (18)</td>
<td>13 (12)</td>
<td>nr</td>
<td>17 (14)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>venetoclax (Venclexta) n=240</td>
<td>11</td>
<td>35</td>
<td>15</td>
<td>nr</td>
<td>33</td>
<td>nr</td>
<td>10</td>
<td>nr</td>
<td>29</td>
<td>nr</td>
</tr>
<tr>
<td>vorinostat (Zolinza) ^1^</td>
<td>13</td>
<td>52</td>
<td>12</td>
<td>nr</td>
<td>41</td>
<td>nr</td>
<td>20</td>
<td>nr</td>
<td>14</td>
<td>nr</td>
</tr>
</tbody>
</table>

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.
Adverse Effects (continued)

Hydroxyurea (Hydrea) – dermatological reactions, such as maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral and facial erythema.

The most frequent adverse reaction to hydroxyurea, mercaptopurine, melphalan, and cladribine is myelosuppression.192,193,194,195

Melphalan – nausea, vomiting, diarrhea, oral ulceration, and liver dysfunction have been reported. Other reported adverse reactions include pulmonary fibrosis (some with fatal outcomes), interstitial pneumonitis, and dermatologic issues, such as hypersensitivity rash.196

The revised prescribing information for ponatinib (Iclusig) reflects an increase in the incidence of certain Serious Adverse Reactions (SARs) in the patient population. These include arterial ischemic SARs increased from 8% to 12%, cerebrovascular SARs increased from 5% to 6%, peripheral vascular SARs increased from 2% to 4%, and the incidence of cardiac failure increased from 4% to 5%.197

Ruxolitinib (Jakafi) 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).

Vorinostat (Zolinza) – taste disorders were commonly reported.

Interstitial lung disease has been reported with ibrutinib (Imbruvica) in post-marketing reports.

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.

Eye disorders were reported in 26% of patients who received ixazomib (Ninlaro)/lenalidomide (Revlimid)/dexamethasone compared to 16% of patients who received placebo/lenalidomide (Revlimid)/dexamethasone in clinical trials. The most commonly reported events were blurred vision, dry eye, and conjunctivitis.

Serious adverse reactions were reported in 44% of patients who received venetoclax (Venclexta) 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 reaction to chlorambucil (Leukeran) is bone marrow suppression and gastrointestinal toxicities, such as nausea, vomiting, diarrhea, and oral ulceration. Urticaria and severe dermatologic hypersensitivities, such as erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have been reported. CNS side effects, including tremors, muscular twitching, myoclonia, 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.
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.

**SPECIAL POPULATIONS**

**Pediatrics**

Safe and effective use of the following agents in patients less than 18 years of age has not been established: hydroxyurea, panobinostat (Farydak), lenalidomide (Revlimid), pomalidomide (Pomalyst), dasatinib (Sprycel), chlorambucil (Leukeran), ixazomib (Ninlaro), ibrutinib (Imbruvica), venetoclax (Venclextra), melphalan, idelalisib (Zydelig), nilotinib (Tasigna), ponatinib (Iclusig), ruxolitinib (Jakafi), bosutinib (Bosulif), and vorinostat (Zolinza).

Safety and effectiveness of thalidomide have not been established in children below the age of 12 years.

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/m²/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, 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.

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/m²/day have not been established.
Pregnancy

Thalidomide, lenalidomide, and pomalidomide are all Pregnancy Category X and are contraindicated during pregnancy.

Bosutinib (Bosulif), dasatinib (Sprycel), ibrutinib (Imbruvica), thioguanine (Tabloid), idelalisib (Zydelig), imatinib (Gleevec), nilotinib (Tasigna), ponatinib (Iclusig), vorinostat (Zolinza), melphalan, chlorambucil (Leukeran), tretinoin, hydroxyurea, busulfan (Myleran), mercaptopurine, procarbazine (Matulane), and cladribine 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.

Ruxolitinib (Jakafi) is Pregnancy Category C.

Panobinostat (Farydak) can cause fetal harm when administered to pregnant women. Panobinostat has been found to be teratogenic in rats and rabbits.

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.

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.

Women of childbearing potential should continue to use effective contraception after ending therapy with any of these agents for varying lengths of time.

Renal Impairment

No clinical studies were conducted with 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.

Ibrutinib (Imbruvica) exposure is not altered in patients with creatinine clearance (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.

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

Reduce ruxolitinib (Jakafi) starting dose to 10 mg twice daily for the treatment of myelofibrosis in patients with moderate (CrCl = 30-59 mL/min) or severe renal impairment (CrCl = 15-29 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 = 30-59 mL/min) or severe renal impairment (CrCl = 15-29 mL/min) and a platelet count between 50 x 10^9 to 100 x 10^9. 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 = 30-59 mL/min) or severe renal impairment (CrCl = 15-29 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.

Avoid use of pomalidomide in patients with a serum creatinine greater than 3 mg/dL.

The starting dose of lenalidomide in patients with moderate renal impairment (CrCl = 30-60 mL/min) should be reduced to 10 mg daily for the treatment of mantle cell lymphoma (MCL) or multiple myeloma (MM) and to 5 mg daily for the treatment of myelodysplastic syndrome (MDS). 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 and to 2.5 mg once daily for the treatment of MDS. Patients receiving dialysis should be given lenalidomide 5 mg once daily for the treatment of MCL or MM; the dose should be administered after dialysis on the days the patient is being dialyzed and 2.5 mg daily in the same fashion for the treatment of MDS 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.
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.

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 $100 \times 10^9/L$ and $150 \times 10^9/L$ and to 5 mg daily in these same patients who have a platelet count of $50 \times 10^9/L$ to less than $100 \times 10^9/L$. Avoid ruxolitinib in patients with hepatic impairment with platelet counts < $50 \times 10^9/L$.

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 1-3 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 1-1.5 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 liver impairment (Child-Pugh A) receiving ibrutinib (Imbruvica) should be dose reduced to 140 mg once daily. The use of ibrutinib in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) should be avoided.

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). A recommended dose has not been determined for patients with severe hepatic impairment.

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

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

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.

**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.

**Geriatrics**

No difference in efficacy or safety between older and younger patients was observed with melphalan, nilotinib (Tasigna), ixazomib (Ninlaro), tretinoin, chlorambucil (Leukeran), venetoclax (Venclexta), ruxolitinib (Jakafi), or vorinostat (Zolinza).

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.\(^{217}\)

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 (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.

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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>CML</th>
<th>Ph+ ALL</th>
<th>CLL/SLL</th>
<th>NHL</th>
<th>MM</th>
<th>Other Diagnoses</th>
<th>Administration Comments</th>
<th>Dosage Forms</th>
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</thead>
<tbody>
<tr>
<td>bosutinib (Bosulif)</td>
<td>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</td>
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<td>Take with food</td>
<td>100, 500 mg tablets</td>
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<tr>
<td>busulfan (Myleran)</td>
<td>Remission induction: 60 mcg/kg or 1.8 mg/m²: usual dose between 4 and 8 PO daily</td>
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<td>2 mg tablets</td>
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<tr>
<td>chlorambucil (Leukeran)</td>
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<td>0.1 to 0.2 mg/kg once daily for 3 to 6 weeks</td>
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<td>HD: 0.1 to 0.2 mg/kg once daily for 3 to 6 weeks</td>
<td>Take entire daily dose at 1 time</td>
<td>2 mg tablets</td>
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<td>cladribine (Leustatin)</td>
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<td>HCL: 0.09 mg/kg/day continuous IV infusion x 7 days</td>
<td>The use of 5% dextrose as a diluent is NOT recommended</td>
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<tr>
<td>dasatinib (Sprycel)</td>
<td>CP CML: 100 to 140 mg daily AP CML: 140 to 180 mg daily BP CML: 140 mg daily</td>
<td>Ph+ ALL: 140 to 180 mg daily</td>
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<td>Swallow tablets whole; do not crush or cut; take with or without food either in the morning or in the evening</td>
<td>20, 50, 70, 80, 100, 140 mg tablets</td>
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<td>Drug</td>
<td>Administration Comments</td>
<td>Dosage Forms</td>
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<tr>
<td>hydroxyurea</td>
<td>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)</td>
<td>500 mg capsules</td>
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<tr>
<td>ibritunib (Imbruvica)</td>
<td>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)</td>
<td>140 mg capsules</td>
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<tr>
<td>idelalisib (Zydelig)</td>
<td>Prophylactic administration of folic acid is recommended; hydroxyurea capsules should not be opened</td>
<td>100, 150 mg tablets</td>
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### Dosages (continued)

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<thead>
<tr>
<th>Drug</th>
<th>CML</th>
<th>Ph+ ALL</th>
<th>CLL/SLL</th>
<th>NHL</th>
<th>MM</th>
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<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib (Gleevec)</td>
<td>CP CML: 400 to 600 mg daily</td>
<td>Ph+ ALL in adults: 600 mg daily</td>
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<td>MDS/MPD: 400 mg daily</td>
<td>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)</td>
<td>100, 400 mg tablets</td>
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<td></td>
<td>AP CML: 600 to 800 mg daily</td>
<td>Ph+ ALL in children: 340 mg/m²/day (not to exceed 600 mg/day)</td>
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<td>ASM: 100 to 400 mg daily</td>
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<td>BP CML: 600 to 800 mg daily</td>
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<td>HES/CEL: 100 to 400 mg daily</td>
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<td>Pediatric patients with Ph+ CML CP: 340 mg/m²/day (not to exceed 600 mg/day)</td>
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<td>DFSP: 800 mg daily</td>
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<td></td>
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<td>GIST: 400 to 800 mg daily</td>
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<tr>
<td>ixazomib (Ninlaro)</td>
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<td>4 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle</td>
<td>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</td>
<td>2.3, 3, 4 mg capsules</td>
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<tr>
<td>lenalidomide (Revlimid)</td>
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<td>25 mg once daily on days 1-21 of repeated 28-day cycles</td>
<td>MM diagnosis: Administer with dexamethasone per recommended dosing schedule</td>
<td>2.5, 5, 10, 15, 20, 25 mg capsules</td>
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<tr>
<td>melphalan (Alkeran)</td>
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<td>6 mg (3 tablets) daily</td>
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<td>2 mg tablet</td>
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<td>Ovarian CA: 0.2 mg/kg daily x 5 days</td>
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</table>
## Dosages (continued)

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<th>Other Diagnoses</th>
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</tr>
</thead>
<tbody>
<tr>
<td>mercaptopurine (Purinethol) (Purixan)</td>
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<td>Maintenance dose in ALL: 1.5 to 2.5 mg/kg/day (50 to 75 mg/m²/day) as a single dose; doses are adjusted based on patient response and toxicity</td>
<td>Procedures for proper handling and disposal of anticancer drugs should be considered; shake suspension vigorously for at least 30 seconds before administration</td>
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<tr>
<td>nilotinib (Tasigna)</td>
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<td>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</td>
<td>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</td>
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</table>
# Dosages (continued)

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<tr>
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<tbody>
<tr>
<td>panobinostat (Farydak)</td>
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<td>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</td>
<td>10, 15, 20 mg capsules</td>
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<td>pomalidomide (Pomalyst)</td>
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<td>Do not break, chew or open capsules; take without food (at least 2 hours before or 2 hours after a meal); give in combination with dexamethasone</td>
<td>1, 2, 3, 4 mg capsules</td>
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<td>Drug</td>
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<tr>
<td><strong>ponatinib</strong> (Iclusig)</td>
<td>May be taken with or without food; tablets should be swallowed whole, do not crush or dissolve tablets</td>
<td>15, 45 mg tablets</td>
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<tr>
<td>CML</td>
<td>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</td>
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<tr>
<td>Ph+ ALL</td>
<td>Ph+ ALL: Start dosing with 45 mg once daily</td>
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<td>CLL/SLL</td>
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<td>NHL</td>
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<td>MM</td>
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<td>Other Diagnoses</td>
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<tr>
<td><strong>procarbazine</strong> (Matulane)</td>
<td>HD: as part of a combination chemotherapy regimen (MOPP): 100 mg/m² daily for 14 days; all dosages are based on actual weight or lean body mass if patient is obese</td>
<td>50 mg capsules</td>
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<tr>
<td><strong>ruxolitinib</strong> (Jakafi)</td>
<td>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</td>
<td>5, 10, 15, 20, 25 mg tablets</td>
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<td>There are extemporaneous compounding instructions for administration through a nasogastric tube</td>
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### Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CML</th>
<th>Ph+ ALL</th>
<th>CLL/SLL</th>
<th>NHL</th>
<th>MM</th>
<th>Other diagnoses</th>
<th>Administration comments</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>thalidomide (Thalomid)</td>
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<td>200 mg once daily</td>
<td>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</td>
<td>50, 100, 150, 200 mg capsules</td>
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<td>thioguanine (Tabloid)</td>
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<td>Acute nonlymphocytic leukemias: Doses varies according to the stage and regimen being utilized; dose should be drive by chosen protocol</td>
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<td>40 mg tablets</td>
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<td>tretinoin</td>
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<td>APL: 45 mg/m²/day divided into two doses</td>
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<td>10 mg capsule</td>
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<tr>
<td>venetoclax (Venclexta)</td>
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<td>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 beyond</td>
<td>Take with a meal and water; tablets should be swallowed whole and not chewed, crushed or broken prior to swallowing</td>
<td>10, 50, 100 mg tablets</td>
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<tr>
<td>vorinostat (Zolinza)</td>
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<td>CTCL: 400 mg once daily</td>
<td>Take with food; capsules should not be opened or crushed</td>
<td>100 mg capsule</td>
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</table>

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; 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; NHL = non-Hodgkin’s lymphoma; Ph+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia; Ph+CML = Philadelphia chromosome-positive chronic myelogenous leukemia; SLL = small cell lymphocytic leukemia;

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

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled, Phase III trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% 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, placebo-controlled, and have drop out rates in excess of 20% have been included in this therapeutic class review. In addition, where published Phase III data for the FDA-approved indications is lacking, Phase I/II studies cited in the package insert are included in this therapeutic class review.

Clinical trials involving busulfan (Myleran), procarbazine (Matulane), hydroxyurea (Hydrea) 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 and melphalan will be limited in scope to the treatment of CLL and multiple myeloma, respectively where these agents still have a role in contemporary management of these disease states.

Leukemias

Chronic Myelogenous Leukemia (CML)

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.237 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 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.238 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%.239 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. 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. The primary endpoint was complete cytogenetic response (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 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. 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 progression free survival (PFS) (85% for dasatinib, 86% for imatinib) and overall survival (OS) (91% for dasatinib, 90% for imatinib) were equal in both arms.

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. 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. 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 major cytogenic response (MCyR) was attained or maintained by 59% (52%
imatinib resistant and 80% imatinib intolerant). Fifteen month PFS was 90% and overall survival was 96%.\textsuperscript{248} START-R compared dasatinib to high-dose imatinib (800 mg/day) in patients with CP-CML resistant to imatinib.\textsuperscript{249} At a minimum follow-up of 2 years, dasatinib demonstrated higher rates of complete hematologic response (CHR) (93% versus 82%), MCyR (53% versus 33%), and complete cytogenic response (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.\textsuperscript{250} 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%).\textsuperscript{251}

**imatinib (Gleevec) and interferon-alfa/low-dose cytarabine**

CML-Study IV was a 5-arm, randomized study that began in 2002. In 2005, recruitment to the arms that contained either cytarabine or interferon alfa were terminated. The remaining 2 arms compared imatinib 400 mg/day to imatinib 800 mg/day in newly diagnosed CML-CP patients. With 10 years of follow up data, PFS was 82% and overall survival 84%. Molecular and cytogenetic response levels were achieved faster with imatinib 800 mg/day versus imatinib 400 mg/day. The 8-year probability of experiencing a grade 3 to 4 toxicity in patients who only received imatinib monotherapy was 22% overall with 17.3% of patients who received imatinib 400 mg/day experiencing a grade 3 to 4 toxicity while 31.3% of patients who received imatinib 800 mg/day experienced a grade 3 to 4 toxicity (p<0.001). Most patients experienced their first adverse drug reaction early with decreasing frequency over the course of therapy. No new late toxicity was observed.\textsuperscript{252}

**nilotinib (Tasigna) and imatinib (Gleevec) – first-line therapy**

Evaluating Nilotinib Efficacy and Safety in Clinical Trials in Newly Diagnosed Patients (ENESTed) 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.\textsuperscript{253} 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 gastrointestinal 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 4-year PFS and OS rates were 92.7% and 94.3%, 96.3% and 96.7%, and 92% and 93.3% respectively for nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib, respectively.254

**nilotinib (Tasigna) – second-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.255,256 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.

**ponatinib (Iclusig) – refractory disease**

The PACE trial enrolled 449 adult patients onto a phase 2, single arm, open-label trial of ponatinib 45 mg given once daily.257 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 [Gleevec], dasatinib [Sprycel], nilotinib [Tasigna], or bosutinib [Bosulif]) 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.258 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 duration of response 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. The estimated 2-year OS rates were 72% for patients with AP-CML and 18% for patients with BP-CML.259 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%.

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

**Dasatinib (Sprycel)**

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.

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. 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. Similar to imatinib, dasatinib has also been incorporated into frontline regimens for adult patients with Ph+ ALL despite the lack of an FDA-approved indication in this setting.

The utilization of mercaptopurine in the treatment of acute lymphoblastic leukemia (ALL) dates back more than 50 years. Current ALL protocols utilize a backbone of mercaptopurine and methotrexate during extended maintenance therapy for 2 to 3 years to prevent disease relapse.

As described above, the phase 3 PACE trial included a subgroup of 32 patients with Ph+ ALL. 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 duration of response or OS outcomes compared to the other 10 patients who did not demonstrate a T315I mutation.

**Imatinib (Gleevec)**

Numerous phase 2 studies have evaluated the efficacy of imatinib as either monotherapy or combined with chemotherapy in adults with Ph+ ALL. 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. 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%). CCyR were 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-CR and 7.1 months for patients with a partial response, 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. This study was included due to the paucity of data and a lack of randomized trials supporting the use of imatinib in adult patients with relapsed/refractory Ph+ ALL. Despite being outside the current FDA-approved indications, the incorporation of TKIs, such as imatinib, in the frontline treatment regimen for adults with Ph+ ALL has become the established standard of care.266 Published phase 2 data supports the use of imatinib in newly diagnosed adult patients with Ph+ALL as well as in the post-HSCT setting even though these scenarios are outside the current FDA-approved indications.267

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

**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 (Gleevec) 340 mg/m²/day in combination with chemotherapy.268 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.

**Acute Lymphoblastic Leukemia (ALL)**

**mercaptopurine**

The utilization of mercaptopurine in the treatment of ALL dates back more than 50 years.269 Current ALL protocols typically utilize a backbone of mercaptopurine and methotrexate during extended maintenance therapy for 2 to 3 years after induction and consolidation therapy to prevent disease relapse.

**Acute Promyelocytic Leukemia**

**all-trans-retinoic acid/tretinoin**

A phase 3 trial randomized 346 patients with previously untreated acute promyelocytic leukemia (APL) to either all-trans-retinoic acid (tretinoin) or daunorubicin plus cytarabine as induction treatment.270 Patients who achieved a complete remission (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.

**Multiple Myeloma**

**Ixazomib (Ninlaro)/lenalidomide/dexamethasone versus placebo/ lenalidomide/dexamethasone**

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. 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%). Patients reported similar quality of life scores in the 2 groups.

**Lenalidomide (Revlimid)/ dexamethasone versus dexamethasone alone-progressive disease**

A randomized, double-blind, placebo-controlled, multicenter, phase 3 trial randomized 117 patients who had progressive multiple myeloma after at least 1 previous treatment. Patients were randomized to receive lenalidomide 25 mg daily or placebo on days 1 to 21 of a 28-day cycle. Both groups received dexamethasone 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles. After the fourth cycle, dexamethasone was only administered on days 1 through 4. Treatment was continued until the occurrence of disease progression or unacceptable toxic effects. The primary endpoint was time to disease progression. Secondary endpoints included overall response rate (ORR) and OS, as well as an assessment of safety. At a median follow up of 17.6 months, the median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the placebo group (p<0.001). Overall response rate was 61% in the lenalidomide group and 19.9% in the placebo group (p<0.001). Median overall survival times in the 2 groups were 29.6 months for lenalidomide and 20.2 months for the placebo arm (p<0.001). Grade 3 or 4 adverse events were reported in 85.3% of the lenalidomide group and in 73.1% of the placebo group resulting in study discontinuation in 19.8% and 10.2%, respectively. Grade 3 or 4 neutropenia, thrombocytopenia, and venous thromboembolism, as well as grade 2 infections, were statistically significantly more common in the lenalidomide group compared to the placebo group.

**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. 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.

**melphalan (Alkeran) versus melphalan (Alkeran) plus prednisone**

A randomized trial compared melphalan monotherapy versus melphalan plus prednisone versus melphalan, prednisone plus testosterone combination therapy. Patients were stratified according to good risk or poor risk multiple myeloma. Response was defined as a combination of objective parameters based on changes in hemoglobin, marrow plasma cells, serum and urinary protein, azotemia, pain, and performance. In good risk patients, the prednisone-melphalan arm was significantly better than melphalan alone (55% good responses versus 23% good responses, respectively). The melphalan prednisone combination was also associated with a longer survival (53 months versus 30 months). The same results were not demonstrated in poor-risk patients.

**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. 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). 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 overall response rate (ORR) did not differ between the 2 groups; however, 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**

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. 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). Therapy 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 (hazard ratio [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%).

**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. 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 recommend in all patients being treated with thalidomide/dexamethasone.
Waldenström’s Macroglobulinemia

**Ibrutinib**

Ibrutinib (Imbruvica) 420 mg daily was administered to 63 symptomatic patients with Waldenström’s macroglobulinemia who had received at least 1 previous treatment. 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 estimated 2-year PFS and OS rates were 69.1% and 95.2%, respectively. The most common adverse events of grade 2 or higher were neutropenia (22%) and thrombocytopenia (14%), which occurred more commonly in heavily pretreated patients.

Non Hodgkin’s Lymphomas

**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

chlorambucil versus chlorambucil plus rituximab (Rituxan) versus chlorambucil plus obinutuzumab (Gazyva)

A phase 3, randomized trial evaluated chlorambucil as monotherapy compared to chlorambucil in combination with a CD20 antibody (either rituximab or obinutuzumab). 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.

chlorambucil (Leukeran) versus Ibrutinib (Imbruvica)-first-line

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

**ibrutinib (Imbruvica) versus ofatumumab (Arzerra) – after at least 1 previous therapy**

The RESONATE trial was a multicenter, open-label, phase 3 trial that randomized 391 patients with relapsed or refractory CLL or SLL who had been treated with at least 1 previous therapy to receive daily oral ibrutinib 420 mg daily or intravenous ofatumumab administered weekly for 8 weeks and then every 4 weeks per the recommended ofatumumab dosing schedule. Patients enrolled in this trial were considered to be inappropriate candidates for purine analogue therapy because they had a short progression-free interval after chemoimmunotherapy or because they had coexisting illnesses, an age of 70 years or more, or a chromosome 17p13.1 deletion. Patients requiring warfarin or strong CYP3A4/5 inhibitors were excluded. The primary endpoint was duration of PFS; secondary endpoints were duration of OS and ORR. The median PFS in patients receiving ibrutinib had not been reached at a median follow-up of 9.4 months while the median duration of PFS with ofatumumab was 8.1 months (HR for progression or death in the ibrutinib group, 0.22; 95% CI, 0.15 to 0.32; p<0.001). At 6 months, 88% of patients in the ibrutinib group were still alive with no disease progression as compared to 65% in the ofatumumab group. Ibrutinib significantly prolonged the rate of OS (HR for death in the ibrutinib (Imbruvica) group, 0.43; 95% CI, 0.24 to 0.79; p=0.005). At 12 months, the OS rate was 90% in the ibrutinib group and 81% in the ofatumumab group. Patients were allowed to cross over to ibrutinib after confirmed disease progression on ofatumumab. The most frequent nonhematologic adverse events that occurred in at least 20% of patients were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatique, infusion-related reactions, and cough in the ofatumumab group. Adverse events of grade 3 or higher occurring more frequently in the ibrutinib group than in the ofatumumab group included diarrhea and atrial fibrillation. Bleeding-related adverse events of any grade were more common in the ibrutinib group than in the ofatumumab group. Major hemorrhage was reported in 2 patients (1%) in the ibrutinib group and 3 patients (2%) in the ofatumumab group. Other grade 1 to 2 adverse events that were more common in the ibrutinib group included rash, pyrexia, infections, and blurred vision.
ibrutinib (Imbruvica) /bendamustine/rituximab versus placebo/bendamustine/rituximab

HELIOS was an international, double-blind, placebo-controlled phase 3 trial in patients (n=578) with CLL or SLL who had measurable lymph node disease and had relapsed or refractory disease after at least 1 previous regimen where they received a minimum of 2 cycles of treatment.283 The study excluded patients with del (17p), as well as patients who had previously received bendamustine or ibrutinib or who had undergone hematopoietic stem cell transplant. Patients were stratified by number of previous lines of therapy. The primary endpoint was PFS as assessed by an independent review committee. Crossover to ibrutinib was permitted for patients in the placebo arm who experienced disease progression. At the preplanned interim analysis with a median follow up of 17 months, the primary endpoint was met; PFS was significantly improved in the ibrutinib group compared to placebo (not reached versus 13.3 months [95% CI, 11.3 to 13.9]; HR, 0.203, [95% CI 0.15 to 0.276]; p<0.001). In the ibrutinib group, the most common adverse events were neutropenia and nausea, grade 3 to 4 neutropenia occurred in 54% of the ibrutinib group and 51% of the placebo group.

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.284 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.
venetoclax (Venclexta)-refractory CLL/SLL

A phase 1 dose-escalation study in 56 patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) was conducted to assess the safety, pharmacokinetic profile, and efficacy of venetoclax. Patients received venetoclax in 1 of 8 dose groups that ranged from 150 mg to 1,200 mg per day. In an expansion cohort, 60 additional patients were treated with doses up to 400 mg per day following a weekly ramp-up dosing schedule. Venetoclax was active at all dose levels. Tumor lysis syndrome, including 1 death, occurred in 3 of 56 patients in the dose-escalation cohort. After adjustments to the dose-escalation schedule, TLS did not occur in any of the 60 patients in the dose expansion group. A maximum tolerated dose was not identified and 92 of the 116 patients (79%) had a response. The 15-month PFS estimate for the 400 mg dose groups was 69%. Other toxicities included mild diarrhea (52%), upper respiratory tract infection (48%), nausea (47%), and grade 3 or 4 neutropenia (41%).

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. 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 Independent Review Committee (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 duration of response had not been reached at time of data evaluation. The duration of response ranged from 2.9 months to over 19 months.
Hairy Cell Leukemia

cladribine

A prospective, randomized trial compared 2 different administration schedules of cladribine for the treatment of HCL.\textsuperscript{287} Previously untreated adult patients (n=132) were randomized to either standard dosing with cladribine, 0.12 mg/kg as a 2-hour IV infusion daily for 5 days or cladribine 0.12 mg/kg as a 2 hour IV Infusion once a week for 6 weeks. The objective of the study was to compare efficacy and toxicity with the 2 schedules since cladribine given in the standard dosing schedule is highly effective in the treatment of HCL but is associated with a risk of severe infections and death due to sepsis. Efficacy results were similar between the 2 groups with 76% of patients receiving the standard dose schedule achieving a complete response (CR) and 72% of patients in the weekly infusion schedule achieving a CR. ORR were also similar (95% versus 91%; p=0.41). A total of 25 grade 3 or 4 infections were observed in 24 patients (26%) receiving the weekly schedule compared with 18% of patients receiving the standard daily dosing schedule. The time to infection onset and the time of infection duration were similar in the 2 groups. The comparison of other grade 3 or 4 side effects, including anemia and thrombocytopenia, did not show significant differences either. The authors concluded the 2 dosing schedules were equally effective but the weekly dosing was not less toxic than the standard daily protocol.

Indolent NHLs – Follicular Lymphoma/ Small Lymphocytic Lymphoma

idelalisib (Zydelig)

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\textsuperscript{288}. 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 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 duration of response, 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 duration of response 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%).
**Mantle Cell Lymphoma**

**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. 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 (Imbruvica) 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 have a partial response (PR) and 21% of patients having a complete response (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 duration of response 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.

**ibrutinib (Imbruvica) versus temsirolimus (Torisel)- relapsed or refractory disease**

A phase 3, randomized, multicenter, open-label trial compared oral ibrutinib 560 mg daily or IV temsirolimus given on days 1, 8, and 15 of 21-day cycles in patients (n=280) with relapsed or refractory mantle cell lymphoma who had received 1 or more rituximab-containing regimens. Patients were stratified by previous therapy received. The primary endpoint was PFS assessed by an independent review committee. There was a significant improvement in PFS for patients treated with ibrutinib versus temsirolimus (14.6 months versus 6.2 months; HR, 0.43; 95% CI, 0.32 to 0.58; p<0.0001). Grade 3 or higher adverse events were reported in 68% of ibrutinib-treated patients compared to 87% of temsirolimus-treated patients; fewer patients discontinued ibrutinib (6%) than discontinued temsirolimus (26%) due to adverse events.

**lenalidomide (Revlimid) relapsed or refractory patients**

A multicenter, single-arm, open-label 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. Patients were dosed at either 10 mg or 25 mg once daily for 21 days every 28 days depending on their serum creatinine levels. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. The endpoints were overall response rate which was 26% and median duration of response which was 16.6 months.
**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 overall objective response rate 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 55 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.

**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 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.

**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. 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. 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 magnetic resonance imaging (MRI) or computerized tomography (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. RESPONSE is an on-going international trial.

Aggressive Systemic Mastocytosis

**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. 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 CHR and 32% a partial hematologic response. Patients that harbor the D816V mutation of c-Kit are not sensitive to imatinib.

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. Fourteen of these patients were diagnosed with HES/CEL. HES patients 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.
Myelofibrosis

ruxolitinib (Jakafi) and placebo

COMFORT-I: 296, 297, 298 This randomized, double-blind, placebo-controlled, phase 3, study, compared ruxolitinib to placebo in 309 myelofibrosis (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% Cl, 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. 299 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% Cl, 0.36 to 0.95; p=0.03).

COMFORT-II: 300, 301 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 duration of response 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. 302 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% Cl, 0.28 to 0.85; p=0.009).

A pooled analysis of OS in both the COMFORT I and the COMFORT II trials was conducted. 303 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% Cl, 0.46 to 0.9; p=0.01).
Dermatofibrosarcoma Protuberans (DFSP)
imatinib (Gleevec) monotherapy

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

Gastrointestinal Stromal Tumor (GIST)
imatinib (Gleevec) and placebo post-operatively

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 gastrointestinal stromal tumor (GIST) at least 3 cm in size and positive for the KIT protein by immunohistochemistry. 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; 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. Patients assigned to 3 years of imatinib had longer recurrence-free survival 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%).

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. 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 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.
A systematic review and meta-analysis was conducted of randomized controlled trials comparing frontline treatment with imatinib (Gleevec) 400 mg daily versus high-dose imatinib (≥600 mg daily) in patients with CP CML (4 trials; n=1,673). At 12 months, high dose compared with standard dose imatinib improved CCyR (risk ratio [RR], 1.17; 95% CI, 1.08 to 1.26), as well as major molecular response (MMR) (RR, 1.26; 95% CI, 1.12 to 1.42). There was no difference in all-cause mortality or disease progression at the end of follow-up. Adverse events leading to discontinuation were more common in the high-dose group (RR, 1.98; 95% CI, 1.2 to 3.26) as were grade 3 or 4 neutropenia and thrombocytopenia (RR, 1.56; 95% CI, 1.15 to 2.12 and RR, 1.86; 95% CI, 1.28 to 2.7, respectively). Based on this study, currently there is insufficient evidence to support the routine use of higher doses of imatinib as first-line treatment for CP CML. Long-term follow-up is needed to evaluate whether higher CCyR and MMR with higher doses of imatinib translate to long-term clinical benefit.

Two meta-analyses recently reviewed the question of optimal dosing of imatinib (Gleevec) for patients with advanced gastrointestinal stromal tumors (GIST). Both of these analyses reviewed studies that utilized doses of 400 mg/day, 600 mg/day, or 800 mg/day in terms of both efficacy and toxicity. Each of the 2 publications identified 5 studies that met their inclusion criteria. There was an overlap of 4 of these studies in both reviews. While the 1 meta-analysis concluded that there was a slight 2-year PFS advantage for high-dose imatinib, there was also an increase in toxic effects in the high-dose cohort. By contrast, the other meta-analysis concluded that imatinib at standard dose (400 mg daily) produces similar benefits to high-dose imatinib and concluded that severity of the toxicity is associated with the dose of imatinib.

Hematologic malignancies, usually involving aberrant bone marrow function, are a heterogenous 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 course 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, cladribine, hydroxyurea, melphalan, 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 [bosutinib (Bosulif), dasatinib (Sprycel), ibrutinib (Imbruvica), idelalisib (Zydelig), imatinib (Gleevec), ixazomib (Ninlara), nilotinib (Tasigna), panobinostat (Farydak), ponatinib (Iclusig), ruxolitinib (Jakafi), venetoclax (Venclexta), and vorinostat (Zolinza)] are small molecule inhibitors that affect multiple enzymatic sites by targeting a broad spectrum of intracellular kinases. After the establishment of imatinib (Gleevec) as the new standard of care for CML, several second generation tyrosine kinase inhibitors (TKIs), including dasatinib (Sprycel), nilotinib (Tasigna), and bosutinib (Bosulif), have been developed which are used in either the first-line setting instead of imatinib (Gleevec) or in imatinib
pomalidomide (Pomalyst) have become part of the standard of care for transplant-eligible multiple myeloma patients while 2 newer options, panobinostat (Farydak) and ixazomib (Ninlaro), are available for use in patients with refractory multiple myeloma. New options for the treatment non-Hodgkin’s lymphomas have also recently been approved. Ibrutinib (Imbruvica), idelalisib (Zydelig), and venetoclax (Venclexta) are indicated for the treatment of chronic lymphocytic leukemia (CLL). While idelalisib and venetoclax are reserved for patients who have received previous CLL treatments, ibrutinib is now approved for first-line use in newly diagnosed patients with CLL, and has been shown to be well tolerated even in elderly patients with comorbidities. Imbruvica is also FDA-approved for the treatment of mantle cell lymphoma and idelalisib (Zydelig) is approved for the treatment of follicular lymphoma. The continued development of these targeted agents provides many patients with hematologic malignancies the hope for prolonged treatment options and extended survival.

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