TREATMENT UPDATE:

# Blood Cancers

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This special edition of the Cancer*Care* Connect® Booklet Series highlights cutting-edge research presented at the 2018 Annual Meeting of the American Society of Hematology, which took place December 1-4 in San Diego, California.

Some of the treatments discussed are still in the very early stages of research and may not be available to the general public outside of a clinical trial.

***The information contained in this e-booklet is intended for discussion with your doctor. He or she can let you know whether these advances in the treatment of blood cancers affect your treatment plan and whether a clinical trial is right for you.***

The Cancer*Care* Connect® Booklet Series offers up-to-date, easy-to-read information on the latest treatments, managing side effects and coping with cancer.

Founded in 1944, Cancer*Care*® is the leading national organization providing free, professional support services and information to help people manage the emotional, practical and financial challenges of cancer. Our comprehensive services include counseling and support groups over the phone, online and in person, educational workshops, publications and financial and co-payment assistance. All Cancer*Care* services are provided by oncology social workers and world-leading cancer experts.

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# Treatment Update: Blood Cancers

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# How To Use This Booklet

Each year, Cancer*Care*® publishes a special edition of the Cancer*Care* Connect® Booklet Series that presents research highlights from the Annual Meeting of the American Society of Hematology. The information contained in these pages is intended for discussion with your doctor. He or she can tell you whether these advances in cancer treatment affect your treatment plan and whether a clinical trial is right for you.

Some of the treatments discussed in this booklet are still in the very early stages of research and may not be available to the general public outside of a clinical trial. The advances in treatment that have come about are because of the many people who have taken part in such studies. If current drugs or other types of cancer treatment no longer benefit you, you may wish to explore joining a clinical trial. The members of your health care team will help you fully understand the possible risks and benefits involved.

On page 26 you will find a list of resources, including websites where you can search for a clinical trial. If your particular type of cancer is not discussed in this booklet and you wish to take part in a study, these websites can help.

# About the Editors

In compiling this report, we used content from the Cancer*Care* Connect Education Workshop titled "Update from the 2018 American Society of Hematology (ASH) Annual Meeting" held on December 6, 2018. We are indebted to the following individuals who were featured on this workshop:

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# The Importance of Clinical Trials

**Clinical trials are the standard by which we measure the worth of new treatments and the quality of life of patients as they receive those treatments. For this reason, doctors and researchers urge people with cancer to take part in clinical trials.**

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things that you should know:

- Often, people who take part in clinical trials gain access to and benefit from new treatments.
- Before you participate in a clinical trial, you will be fully informed of the risks and benefits of the trial, including any possible side effects.
- Many clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- Participation is voluntary and does not affect your access to treatment in other settings. You can stop taking part in a clinical trial at any time for any reason.

When considering participation in a clinical trial, it's important to consult with your primary care physician and your oncologist and make sure that all of your questions are answered.

This is a very exciting time in cancer research, and there are clinical trials underway to study newer treatment approaches, such as immunotherapy and targeted therapy. In immunotherapy, the immune system's ability to seek out and destroy cancer cells is enhanced. Targeted therapies are designed to target the specific cell mechanisms that are important for the growth and survival of tumor cells.

# Leukemia

**Researchers reported a number of important findings in leukemia treatment at the 2018 Annual Meeting of the American Society of Hematology:**

- **In November 2018, three targeted therapies were approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute myeloid leukemia** (page 9).
- **A phase I trial is evaluating the safety, tolerability and effectiveness of an oral tyrosine kinase inhibitor (TKI) in the treatment of resistant forms of chronic myeloid leukemia** (page 11).
- **A novel BCR-ABL inhibitor shows potential in a phase I trial for the treatment of TKI-resistant chronic myeloid leukemia** (page 11).
- **The investigational compound ABL001, a specific BCR-ABL inhibitor, is being studied for the treatment of patients with chronic myeloid leukemia and the T315I mutation** (page 12).
- **The FDA has approved the TKI nilotinib for treatment of pediatric patients with chronic Philadelphia chromosome-positive chronic myeloid leukemia** (page 12).

## Three targeted therapies approved in November 2018 for the treatment of acute myeloid leukemia (AML)

**Gilteritinib.** The FDA has granted approval to the targeted therapy gilteritinib for the treatment of adult patients with FLT3-mutated AML that has relapsed (recurred) or is refractory (not responding to treatment). The approval, which was granted on November 28, 2018, was in conjunction with an expanded approval being given to the LeukoStrat CDx FLT3 Mutation Assay as a companion diagnostic to predict responses in patients being treated with gilteritinib.

The approval of gilteritinib was based on an interim analysis of the ADMIRAL trial, which showed significantly more cases of complete remission (or complete remission with partial hematological recovery) among patients treated with gilteritinib, compared with those who received standard chemotherapy.

**Glasdegib.** Glasdegib, a targeted therapy that inhibits the Hedgehog pathway, was approved by the FDA on November 21, 2018 (in combination with low-dose cytarabine) for the treatment of newly-diagnosed AML in patients who are age 75 or older or who have conditions that prevent the administration of intensive chemotherapy.

Glasdegib is the only FDA-approved Hedgehog pathway inhibitor for the treatment of AML. The abnormal activation of the Hedgehog pathway is thought to contribute to the development and persistence of cancer stem cells.

**Venetoclax.** On November 21, 2018, the FDA granted accelerated approval to venetoclax, a targeted therapy, in combination with chemotherapy (azacitidine, decitabine or low-dose cytarabine), for

the treatment of newly-diagnosed AML in adults age 75 or older, or those who have conditions that preclude the use of intensive chemotherapy as an initial treatment. Many people with AML have a mutation of the BCL2 gene that prevents the death of cancer cells and is associated with a resistance to chemotherapy. Venetoclax, a BCL2 inhibitor, is designed to correct this mutation.

The approval of venetoclax was based on two open-label non-randomized trials. Efficacy (effectiveness) was determined by the rate and duration of complete remission.

### What Patients Need to Know

Gilteritinib, glasdegib and venetoclax are all oral drugs. Glasdegib and venetoclax are approved for the same population of patients: those with newly-diagnosed AML who are age 75 or older or who have comorbidities (existing conditions) that prevent the administration of intensive chemotherapy. Other targeted therapies for the treatment of AML are currently being studied in clinical trials.

## Safety, tolerability and effectiveness of TKI being studied for resistant forms of chronic myeloid leukemia (CML)

Chronic myeloid leukemia is caused by a mutation (change) in the genes of progenitor (early) cells. In CML, the ABL gene joins to the BCR gene, forming a mutated BCR-ABL "fusion gene."

A phase I trial is evaluating the safety, tolerability and effectiveness of PF-114, a third-generation oral tyrosine kinase inhibitor (TKI), in the treatment of resistant forms of CML. PF-114 is an inhibitor of the mutated BCR-ABL gene and is active against Philadelphia chromosome-positive (Ph-positive) leukemias.

### What Patients Need to Know

The trial is evaluating PF-114 in patients with Ph-positive CML who are resistant to at least one of the second-generation TKIs, intolerant to previous treatment with TKIs or who have the BCR-ABL mutation.

## Novel BCR-ABL inhibitor shows potential for the treatment of TKI-resistant CML

HQP1351, a novel (never-before-tested) third-generation TKI, has shown potential in a phase I trial as a treatment for TKI-resistant CML. HQP1351 targets a broad spectrum of BCR-ABL mutations, including the T315I mutation. Of note, a major response was seen in 78 percent of patients in the chronic phase with the T315I mutation, a mutation which is highly resistant to almost all TKIs.

### What Patients Need to Know

The phase I trial evaluating HQP1351 as a treatment for patients with CML resistant to the first-generation TKI imatinib has been completed, and a phase II trial has been initiated.

## First-of-its-type TKI compound being studied for treatment of CML with the T3151 mutation

The investigational compound ABL001 (asciminib) is being studied for the treatment of patients with chronic myeloid leukemia and the T315I mutation.

ABL001, a TKI, is the first BCR-ABL inhibitor of its type to be tested in humans. Designed to overcome resistance, ABL001 selectively binds to the ABL portion of the BCR-ABL fusion protein (which is produced by the mutated BCR-ABL gene) to make it inactive.

### What Patients Need to Know

The T3151 mutation causes resistance to most BCR-ABL tyrosine kinase inhibitors (TKIs) in the treatment of CML. Early-phase trials indicate that ABL001 has the potential to overcome TKI-resistant mutations, possibly in combination with existing TKIs. Evaluation is ongoing in a phase III trial.

## TKI nilotinib approved for treatment of pediatric patients with chronic Philadelphia chromosome-positive CML

In March 2018, the FDA approved nilotinib for the first-and second-line treatment of chronic-phase Philadelphia chromosome-positive CML in pediatric patients age 1 or over.

Nilotinib is a TKI that can stop the protein made by the BCR-ABL gene from working, causing CML cells to die. There are four other drugs of this type used to treat CML: bosutinib, imatinib, dasatinib and ponatinib.

### What Patients Need to Know

The approval was based on two trials with a total of 69 pediatric patients with chronic-phase Philadelphia chromosome-positive CML. The participants were newly diagnosed, could not tolerate or were resistant to prior treatment with another TKI.

# Lymphoma

**Researchers reported a number of important findings in the treatment of lymphoma at the 2018 Annual Meeting of the American Society of Hematology:**

- **Results of a phase III trial showed that ibrutinib, given with or without rituximab, provided longer progression-free survival compared with rituximab plus bendamustine in older patients with previously untreated chronic lymphocytic leukemia (CLL)** (page 15).
- **In patients age 70 or younger with previously untreated CLL, ibrutinib reduced the risk of disease progression or death compared to the chemotherapy regimen FCR** (page 15).
- **Promising results were seen in a phase II trial for ibrutinib/venetoclax combination in treatment of relapsed or refractory CLL** (page 16).
- **The FDA has approved brentuximab vedotin for use in combination with chemotherapy in patients with CD30-expressing peripheral T-cell lymphoma** (page 16).
- **Data from a phase III trial showed that lenalidomide, in combination with rituximab, demonstrated superior progression-free survival in patients with relapsed or refractory indolent lymphoma compared to rituximab alone** (page 17).
- **Follow-up data from the ZUMA-1 study showed CAR T-cell therapy had benefit in the treatment of relapsed or refractory large B-cell lymphoma** (page 18).

## Targeted therapy superior to chemoimmunotherapy in older patients with previously untreated CLL

According to results of a phase III trial, the kinase inhibitor ibrutinib (a targeted therapy) with or without rituximab (an immunotherapy) provided longer progression-free survival in previously untreated chronic lymphocytic leukemia (CLL), compared with rituximab combined with the chemotherapy bendamustine.

### What Patients Need to Know

The study participants were age 65 and older. A phase III trial is currently underway to evaluate whether ibrutinib plus rituximab offers an advantage over chemoimmunotherapy in younger adults.

## Ibrutinib superior to chemotherapy as initial treatment for CLL in patients age 70 or younger

In patients age 70 or younger with previously untreated CLL, a phase III trial showed that the targeted therapy ibrutinib reduced the risk of disease progression or death by 65 percent, compared to the chemotherapy regimen FCR. FCR consists of fludarabine, cyclophosphamide and the immunotherapy rituximab.

### What Patients Need to Know

Approved by the FDA in 2013, ibrutinib has become a standard treatment in CLL. However, it has been used primarily to treat older or less fit patients who are unable to tolerate the side effects associated with standard chemotherapy regimens.

## Combination of targeted therapies promising in treatment of relapsed/ refractory CLL

The phase II CLARITY trial showed a combination of the targeted therapies ibrutinib and venetoclax to be promising in the treatment of relapsed or refractory CLL. After 12 months of treatment with the combination, 54 percent of trial participants were in complete remission (CR) or complete remission with incomplete marrow recovery (CRi).

### What Patients Need to Know

The combination also induced minimal residual disease (MRD) negativity in the bone marrow of 39 percent of the participants after 12 months of treatment and was generally well tolerated.

## FDA approves brentuximab vedotin in combination with chemotherapy for treatment of CD30-expressing PTCL

In November 2018, the FDA approved brentuximab vedotin for use in combination with chemotherapy for the frontline treatment of patients with CD30-expressing PTCL. Brentuximab vedotin is an antibody-drug conjugate (ADC) that directs a medication called auristatin to cells that have CD30.

### What Patients Need to Know

The FDA approval was based on the results of the phase III ECHELON-2 trial, which showed the addition of brentuximab vedotin to the chemotherapy combination CHP (cyclophosphamide, doxorubicin and prednisone) led to improvement in progression-free survival and overall survival compared to treatment with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).

## Combination of lenalidomide and rituximab doubled progression-free survival in relapsed or refractory indolent lymphomas

Results from the phase III AUGMENT trial showed that the targeted therapy lenalidomide, used in combination with the immunotherapy rituximab, more than doubled progression-free survival (PFS) in patients with relapsed or refractory follicular or marginal zone lymphoma when compared to treatment with rituximab alone.

Follicular and marginal zone lymphomas are indolent (slow-growing) types of non-Hodgkin lymphoma.

### What Patients Need to Know

In addition to more than doubling PFS, AUGMENT showed a favorable trend for overall survival and no new safety concerns were identified.

## CAR T-cell therapy effective in treatment of relapsed or refractory large B-cell lymphoma

Axicabtagene ciloleucel, a CAR T-cell therapy, was approved by the FDA in October 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma who had previously received at least two other kinds of therapy.

Follow-up data from the ZUMA-1 study indicated that, after a single infusion, 42 percent of patients in this population continued to respond to therapy after more than one year, including 40 percent who experienced a complete remission.

### What Patients Need to Know

CAR T-cell therapy is a type of immunotherapy that follows certain steps, which include drawing blood, separating out and genetically modifying the T-cells, multiplying those cells in a laboratory and infusing them back into the patient, where they attack cancer cells.

# Multiple Myeloma

**Researchers reported a number of important findings in the treatment of multiple myeloma at the 2018 Annual Meeting of the American Society of Hematology:**

- **A phase III trial showed encouraging data when daratumumab was added to standard of care lenalidomide and dexamethasone** (page 20).
- **The phase III TOURMALINE-MM3 trial evaluated ixazomib as maintenance treatment for multiple myeloma** (page 20).
- **The FDA has granted selinexor a Priority Review designation as treatment for penta-refractory multiple myeloma** (page 21).
- **Promising results have been seen with venetoclax in combination with other drugs as treatment for patients with relapsed or refractory multiple myeloma** (page 22).
- **The investigational CAR T-cell immunotherapy P-BCMA-101 was studied in a phase I trial** (page 22).
- **The investigational anti-B-cell maturation antigen (anti-BCMA) drug AMG 420 is being evaluated in a phase I trial** (page 23).

## Immunotherapy daratumumab showed progression-free survival benefit compared to standard of care in patients with newly diagnosed multiple myeloma

The phase III MAIA trial evaluated the addition of the immunotherapy daratumumab to the combination of lenalidomide (a targeted therapy) and dexamethasone (a corticosteroid) in treatment of newly diagnosed multiple myeloma patients who are not candidates for high dose chemotherapy and autologous stem cell transplant (in which a person's own stem cells are used).

The results demonstrated a benefit in progression-free survival when daratumumab was added to the standard of care combination of lenalidomide and dexamethasone. Analysis of safety and efficacy data is ongoing.

### What Patients Need to Know

Daratumumab, a monoclonal antibody, was approved by the FDA for the treatment of multiple myeloma in 2015. It is a type of immunotherapy that helps the body's immune system find and destroy cancer cells.

## Proteasome inhibitor studied as maintenance therapy in multiple myeloma

TOURMALINE-MM3, a phase III trial, evaluated the proteasome inhibitor ixazomib (a type of targeted therapy) as maintenance treatment in patients with multiple myeloma who previously responded to high-dose chemotherapy and autologous stem cell transplant.

Proteasomes are a type of enzyme that breaks down proteins in cells. Proteasome inhibitors block proteasomes from working, causing a buildup of unwanted proteins in cancer cells, leading to their death.

### What Patients Need to Know

Compared to placebo, patients treated with ixazomib had a 28 percent reduction in risk of progression or death and a 39 percent improvement in progression-free survival.

## Priority Review granted to selinexor as treatment for penta-refractory multiple myeloma

In November 2018, the FDA granted selinexor a Priority Review as treatment for patients with penta-refractory multiple myeloma. The designation was based on data from the phase IIb STORM trial, which showed that the combination of selinexor and the corticosteroid dexamethasone demonstrated an overall response rate of over 26 percent.

Multiple myeloma is considered penta-refractory when the patient has not responded to three or more prior therapy regimens.

### What Patients Need to Know

Selinexor is a selective inhibitor of nuclear export (SINE) compound that blocks the transport of proteins between the nucleus and the cytoplasm, leading to the death of cancer cells while sparing normal cells.

## Venetoclax shows promise in treatment of relapsed or refractory myeloma when given in combination with other drugs

A phase Ib trial showed that venetoclax, in combination with the targeted therapy bortezomib and the corticosteroid dexamethasone, demonstrated promising efficacy and an acceptable safety profile as treatment for relapsed or refractory myeloma.

Some of the highest response rates were found in patients who had high levels of the protein BCL2, which can prevent the death of cancer cells. Venetoclax, a targeted therapy, is a BCL2 inhibitor.

### What Patients Need to Know

Venetoclax is approved by the FDA for the treatment of certain types of chronic lymphocytic leukemia (CML) and acute myeloid leukemia (AML).

## Investigational CAR T-cell immunotherapy studied in early-phase trial

The investigational CAR T-cell immunotherapy P-BCMA-101 was evaluated in a phase I trial as a treatment for multiple myeloma. At the highest dose given, the objective response rate (the percentage of patients whose cancer shrunk or disappeared) was 100 percent. At lower doses, the objective response rate was close to 70 percent. No serious side effects were observed at any dose.

P-BCMA-101 is designed to boost patients' own T-cells to safely eliminate tumor cells carrying B-cell maturation antigen (BCMA), which is expressed (seen) on virtually all multiple myeloma tumor cells.

### What Patients Need to Know

Enrollment in the study is continuing and a phase II trial is being initiated. Based on the expected timelines, a biologics licensing application could be submitted for P-BCMA-101 in 2020.

## Anti-BCMA drug evaluated in early-phase trial

A phase I trial is evaluating the effectiveness and safety of the investigational immunotherapy AMG 420 (an antibody) in the treatment of multiple myeloma. At the optimal dose tested, AMG 420 achieved an objective response rate of 70 percent.

AMG 420 targets the B-cell maturation antigen (BCMA) expressed on multiple myeloma tumor cells.

### What Patients Need to Know

AMG 420 has received Fast Track status from the FDA (a process designed to facilitate the development and expedite the review of drugs that treat serious conditions) and an expanded trial is planned.

# Myeloproliferative Neoplasms

**Researchers reported a number of important findings in the treatment of myeloproliferative neoplasms (MPNs) at the 2018 Annual Meeting of the American Society of Hematology:**

- **The final analysis of a randomized trial revealed that, in patients with high-risk essential thrombocythemia or high-risk polycythemia vera, rates of complete remission were similar when treated with either pegylated interferon-alpha-2a or hydroxyurea** (page 24).
- **The investigational drug PRM-151 is being studied as treatment for myelofibrosis** (page 25).
- **Prognostic model MIPSS70 studied as predictor of overall survival in patients with myelofibrosis** (page 25).

## Results of trial comparing PEG with HU in patients with high-risk ET/PV revealed

The Myeloproliferative Neoplasms-Research Consortium 112 (MPN-RC 112) is a randomized trial that compared the use of pegylated interferon-alpha-2a (PEG) with hydroxyurea (HU) therapy in patients with high-risk essential thrombocythemia (ET) or high-risk polycythemia vera (PV).

### What Patients Need to Know

The results of MPN-RC 112 showed that the rates of complete remission in this group of patients were similar when treated with either PEG or HU, although PEG was associated with a higher rate of side effects.

## Investigational drug PRN-151 being evaluated for the treatment of myelofibrosis (MF)

In a phase II trial, the efficacy and safety of investigational drug PRM-151, alone and in combination with the immunotherapy ruxolitinib, is being evaluated for the treatment of primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF.

Early results were encouraging. A subsequent trial of single-agent PRM-151 given at three dose levels is ongoing.

### What Patients Need to Know

PRM-151 is a recombinant (resulting from new combinations of genetic material) form of the protein PTX-2, which circulates in the bloodstream and helps to regulate tissue repair. PTX-2 levels have been found to be lower in patients with myelofibrosis.

## Prognostic model useful in predicting overall survival in patients with myelofibrosis

MIPSS70 is an international prognostic scoring system, based on clinical and genetic data, for transplant-age (70 and over) myelofibrosis patients. A recent study concluded that MIPSS70 is useful in predicting overall survival in myelofibrosis patients treated with JAK1/2 inhibitor therapy.

### What Patients Need to Know

The study data also suggest that an enhancement of MIPSS70 may be possible by integrating the patient's transfusion status into the scoring system.

# Resources

**CancerCare®**
800-813-HOPE (800-813-4673)
www.cancercare.org

**American Cancer Society**
800-227-2345
www.cancer.org

**Be the Match® Patient Services**
800-627-7692
www.bethematch.org

**Blood & Marrow Transplant Information Network**
888-597-7674
www.bmtinfonet.org

**The Bone Marrow Foundation**
800-365-1336
www.bonemarrow.org

**Cancer.Net**
Patient information from the American Society of Clinical Oncology
888-651-3038
www.cancer.net

## CLINICAL TRIALS WEBSITES

**EmergingMed**
www.emergingmed.com

**National Cancer Institute**
www.cancer.gov

**Cancer Support Community**
888-793-9355
www.cancersupportcommunity.org

**National Bone Marrow Transplant Link**
800-546-5268
www.nbmtlink.org

**National Cancer Institute**
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www.cancer.gov

**The Leukemia & Lymphoma Society**
800-955-4572
www.lls.org

**Leukemia Research Foundation**
847-424-0600
www.allbloodcancers.org

**Lymphoma Research Foundation**
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