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Studies Highlight Both Novel Treatments and Enduring Value of Older Approaches

Findings suggest "less is more" and "tried and true" may benefit select patients

(SAN DIEGO, Dec. 10, 2023) – Research findings being presented at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition highlight new treatment approaches that are enabling patients to live longer or better, judicious uses of older treatment approaches, and how a powerful, relatively new prognostic tool is helping identify patients who are more or less likely to benefit from both older and newer treatments.

"At the ASH annual meeting, we always get excited about new treatment approaches that promise better outcomes for patients both now and in the future," said press briefing moderator **Mikkael A. Sekeres, MD,** of the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine.

"Collectively, these studies draw attention not only to new approaches that show how far we've come from the past, but also to studies telling us that 'less is more' in some cases and 'tried and true' treatment approaches can still be of great benefit to carefully selected patients," he said.

In the first study, the addition of a second drug to standard therapy for previously untreated patients with myelofibrosis resulted in a clinically significant reduction in spleen size, compared with patients who received a placebo in addition to standard therapy.

Two other studies presented in this session spotlight ways in which a novel prognostic tool is demonstrating its value across a range of blood cancers. Measurable residual disease, or MRD (also sometimes called minimal residual disease) refers to cancer cells that remain in the blood or bone marrow at a level that can be detected only with highly sensitive tests. Previous studies have shown that patients who are "MRD negative" (i.e., for whom high-sensitivity testing finds no evidence of remaining cancer cells in the blood or bone marrow) have better outcomes than patients who are "MRD positive" (i.e., whose blood or bone marrow still harbors extremely low levels of cancer cells).

In the first of these MRD-related studies, patients with newly diagnosed chronic lymphocytic leukemia who were treated with a combination regimen of two targeted drugs saw significantly improved outcomes compared with similar patients who received standard-of-care chemotherapy. The researchers used MRD to determine how long patients in the targeted-agents group should continue treatment.

In the second, researchers showed that patients with acute myeloid leukemia and FLT3+ who were MRD positive benefited from a donor stem cell transplant, while those who were MRD negative derived no additional benefit from undergoing a transplant.

In the final study, researchers show that a subset of patients with lymphoma who are eligible for CAR T-cell therapy but face a wait to receive it can benefit from receiving an older treatment, namely a transplant of the patient's own stem cells.

TRANSFORM-1: Addition of second targeted agent doubles spleen volume reduction in myelofibrosis

620: TRANSFORM-1: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib Plus Placebo in Patients with Untreated Myelofibrosis

An enlarged spleen is a key disease feature in myelofibrosis, a rare blood cancer. Among patients with myelofibrosis who had not previously been treated with a targeted drug known as a *JAK* inhibitor, twice as many of those who received an investigational targeted agent in addition to standard therapy had a clinically significant reduction in spleen size, compared with patients who received a placebo plus standard therapy.

"Approximately twice the number of patients in the combination-treatment group, compared with the control arm, achieved the primary endpoint of spleen volume reduction of 35% or more by week 24 of treatment," said **Naveen Pemmaraju, MD**, professor of leukemia at the MD Anderson Cancer Center in Houston, and the study's lead author.

"This is one of two global randomized, double-blind, placebo-controlled clinical trials in our field to be reported that investigate the use of two targeted agents in patients with myelofibrosis who have not yet been treated with a *JAK* inhibitor," he said. "These results show the feasibility and tolerability of a frontline approach with this promising two-drug combination and potentially open a new era of combination therapy to modify the course of this disease."

However, symptom reduction with the two-drug combination regimen at week 24 of treatment has not yet reached statistical significance when compared with the control group, he said. "We will continue to monitor this and other key secondary endpoints over time."

Myelofibrosis is caused by a genetic mutation in blood-forming stem cells in the bone marrow. These cells develop into specialized blood cells, such as red and white blood cells and platelets, that also carry the mutation. As the mutated cells multiply, they cause scar tissue to form in the

bone marrow. With the bone marrow unable to produce enough normal blood cells, the spleen – a fist-sized organ located next to the stomach – tries to help out by starting to produce blood cells. This results in a buildup of blood cells that causes the spleen to enlarge, a condition known as *splenomegaly*. If the spleen continues to enlarge in myelofibrosis, it can be harmful to patients and it may cause early fullness feeling (early satiety), further lowering of blood cell counts, more infections, and increased bleeding or other hematologic complications.

Patients with myelofibrosis can present with varied symptoms that often develop slowly but can in some cases develop quickly. Symptoms may include fatigue or weakness (caused by anemia, a shortage of red blood cells) and pain in the abdomen or back due to an enlarged spleen. Some patients with myelofibrosis can go on to develop acute myeloid leukemia, a rapidly progressing blood cancer. Myelofibrosis is most often diagnosed in people over age 50 and occurs roughly equally in men and women.

In about half of patients, myelofibrosis is caused by a mutation in a gene known as *JAK2V167F*. In 2011, ruxolitinib, a *JAK* inhibitor, became the first targeted agent approved by the U.S. Food and Drug Administration to treat myelofibrosis and related conditions. Ruxolitinib reduces spleen enlargement and other symptoms, Dr. Pemmaraju said, but isn't a cure for the disease, and treatment with ruxolitinib alone doesn't work for all patients.

In 2022, Dr. Pemmaraju and his colleagues published the results of a phase II non-randomized study in which they added the investigational drug navitoclax to ruxolitinib therapy in patients with myelofibrosis whose response was suboptimal or whose cancer was progressing with ruxolitinib alone. Navitoclax belongs to a family of targeted drugs known as BCLxL inhibitors that work by blocking a protein that helps keep cancer cells alive. The two-drug combination produced benefits in many of the patients, including reduced bone marrow scarring, and decreased spleen size.

Following up on these results, the investigators launched the current study, TRANSFORM-1, a randomized controlled phase III trial that enrolled 252 patients (median age 69, 57% male) around the world with intermediate- or high-risk myelofibrosis who had not been previously treated with a JAK inhibitor. Patients were randomly assigned to treatment with either navitoclax plus ruxolitinib (NAV+RUX) or a placebo plus ruxolitinib (PBO+RUX). The study was double blinded, meaning that while patients were receiving treatment neither they nor their doctors knew which patients were in which treatment group.

The study's primary endpoint was a reduction in spleen enlargement of at least 35%, confirmed by radiological imaging, by 24 weeks of treatment. This endpoint was chosen because it roughly correlates with an approximate 50% reduction in spleen size on a physical exam, which is considered a clinically significant reduction, Dr. Pemmaraju said. Secondary endpoints included the change in total symptom score at week 24.

After a median follow up of 14.9 months, 79 patients (63.2%) in the NAV+RUX group had achieved a statistically significant reduction of at least a 35% in spleen enlargement at week 24,

compared with 40 patients (31.5%) in the PBO+RUX group. At week 24, the average change in the total symptom score was –9.7 for patients treated with NAV+RUX, compared with –11.1 for those treated with PBO+RUX, a difference that was found to not be statistically significant.

The most common adverse events included low blood cell counts and diarrhea. A total of 83 patients (33%) discontinued the study treatment, with the most common reason for discontinuation being adverse events. A total of 13 patients (10%) died 30 or fewer days after receiving their final dose of the study medication; six of those who died had received NAV+RUX and five PBO+RUX.

Monitoring of the trial will continue as the patient dataset matures over time, Dr. Pemmaraju said, to collect additional data on symptom scores and other secondary endpoints, including the duration of spleen volume reduction, the effect of treatment on bone marrow scarring, and patients' overall survival.

The study was funded by AbbVie, Inc., which manufactures navitoclax.

Naveen Pemmaraju, MD, of MD Anderson Cancer Center, will present this study during an oral presentation on Sunday, December 10, 2023, at 4:45 p.m. Pacific time in Ballroom 20CD in the San Diego Convention Center.

Ibrutinib plus venetoclax with duration of treatment determined by measurable residual disease outperforms standard therapy for newly diagnosed CLL

631: Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study

Among patients with newly diagnosed chronic lymphocytic leukemia (CLL) who were treated with two targeted agents and whose duration of treatment was determined by high-sensitivity testing for residual cancer cells in the blood, 97.2% were free of cancer progression and 2% had died at three years. By comparison, progression-free survival (PFS) for patients receiving the standard of care was 76.8% with a death rate of 7%.

"These results appear better than those seen in any previous phase III trial in CLL," said **Professor Peter Hillmen, MB ChB, PhD**, of the University of Leeds in the United Kingdom and principal investigator for the study. "They show that targeted therapy, with high-sensitivity testing used to individualize the duration of treatment, is a more effective approach than current standard therapy and represents a new gold standard for previously untreated CLL."

CLL is the most common blood cancer in adults. In the United States about 19,000 new cases of CLL are diagnosed every year. The median age at diagnosis is 70. Roughly half of patients with CLL have mutated immunoglobulin genes, also known as *IGHV*. Patients with mutated *IGHV* generally have a better outlook and longer survival compared with those who have unmutated

IGHV. Immunoglobulins (or antibodies) are proteins made by some lymphocytes that help protect the body against infection.

The FLAIR study is a large, ongoing randomized trial in the UK that is comparing novel treatments for newly diagnosed CLL against what has been considered a standard of care, a regimen consisting of the drugs fludarabine, cyclophosphamide, and rituximab (FCR). In the current study, 523 patients with untreated CLL (71.3% male, median age 62) were randomly assigned to receive FCR or two newer agents, ibrutinib and venetoclax (I+V). These drugs are types of targeted therapy – that is, drugs targeted to specific molecules or molecular pathways in cancer cells that the cells need to survive and spread. Ibrutinib blocks cell signals that encourage leukemia cells to multiply, while venetoclax blocks a protein that helps cancer cells survive, explained Dr. Hillmen.

A novel feature of the FLAIR trial is its use of measurable residual disease, or MRD, to determine how long patients should continue treatment. Previous studies in leukemia and other cancers have shown that patients who are "MRD negative" (those for whom high-sensitivity testing has found no evidence of remaining leukemia cells in the blood or bone marrow) have better outcomes than patients who are "MRD positive" (when the blood or bone marrow still harbors extremely low levels of leukemia cells that can be detected with high-sensitivity testing).

In FLAIR, patients in the I+V group underwent blood tests for MRD at one year and then every six months. If these tests found no evidence of remaining leukemia cells, the testing was repeated in both the blood and the bone marrow after another three months and again three months later. If all these tests were MRD negative, the patient was treated for twice the duration of time from the start of I+V treatment to the first MRD-negative test.

"Patients' duration of treatment was determined by how quickly they responded," said Prof. Hillmen. Duration of treatment ranged from two to six years. The trial's primary endpoint was PFS, while overall survival was one of several secondary endpoints.

At a median follow-up of 43.7 months, patients treated with FCR were approximately eight times as likely to have disease progression compared with patients who received I+V. This finding was consistent regardless of patient gender, age, or disease stage. Moreover, patients with a worse prognosis appeared to do particularly well.

"We found that the patients with disease features associated with a worse prognosis – such as those with unmutated *IGHV* or deletion of chromosome 11q – had even better outcomes when treated with I+V than the favorable-risk, *IGHV*-mutated patients," said Dr. Hillmen. "At three years follow up, patients with unmutated IGHV were about 14 times less likely to have progressed if treated with I+V than with FCR. At the latest follow-up, not a single patient with the 11q chromosome deletion who was treated with I+V had progressed or died, compared with 31.2% of patients with this deletion who were treated with FCR. This indicates that the

combination of I+V overcomes previously reported risk factors for a poor outcome in patients with CLL."

A limitation of the study, Prof. Hillmen said, is that patients were eligible to enroll only if they were deemed fit enough to undergo intensive chemotherapy with FCR. As a result, the median age of patients enrolled in the trial was 62 whereas the median age at which CLL is diagnosed is 70. Nevertheless, 31.2% of the patients enrolled were over age 65.

The study was funded by Cancer Research UK with additional support from Janssen, Inc., and AbbVie, Inc.

This study was also published in the *New England Journal of Medicine* at the time of the press program presentation.

Peter Hillmen, MB ChB, PhD, of the University of Leeds in the United Kingdom, will present this study during an oral presentation on Sunday, Dec. 10, 2023, at 3:30 p.m. Pacific time in Seaport Ballroom ABCD (Manchester Grand Hyatt San Diego).

Presence of measurable residual disease after two chemo cycles predicts benefit from donor transplant in AML with *NPM1* mutation

425: The Benefit of Allogeneic Transplant in 1st Complete Remission in NPM1 Mutated AML with or without FLT3 ITD Is Restricted to Those Testing MRD Positive after Induction – an Analysis of the UK NCRI AML17 and AML19 Studies

Among patients who have acute myeloid leukemia (AML) with genetic mutations in *NPM1*, those with no residual leukemia cells in the blood based on high-sensitivity testing after two cycles of chemotherapy achieved high rates of overall survival at three years and saw no additional survival benefit from undergoing a donor stem cell transplant. Conversely, among patients who had residual leukemia cells in the blood, those who received a donor stem cell transplant had improved survival compared with those who did not undergo a transplant.

"To our knowledge, this is the largest study to examine whether measurable residual disease (MRD) after two cycles of chemotherapy could identify which patients with *NPM1* mutated AML would benefit from a transplant," said **Jad Othman, MBBS**, of Guy's and St Thomas' NHS Foundation Trust in London and the study's presenting investigator. "In all of the disease subgroups we looked at, the answer is yes, it did – and it was the only thing that did."

In the current study, patients who were MRD positive had improved survival when they received a stem cell transplant, whereas among patients who were MRD negative, researchers could not identify any subgroup that showed a survival benefit from a transplant, Dr. Othman explained.

AML, a fast-growing cancer of the blood-forming cells in the bone marrow, is classified as favorable risk, intermediate risk, or adverse risk based on the presence or absence of certain genetic mutations, he said. While a transplant of healthy blood cells from a donor can

sometimes be a cure for AML, studies have shown that patients with a favorable risk generally do well with chemotherapy and that the risks and side effects of a transplant outweigh the benefits. On the other hand, patients with adverse-risk AML generally do poorly with chemotherapy and are likely to benefit from a transplant. For patients with intermediate-risk AML, Dr. Othman said, the relative benefits of chemotherapy and donor stem cell transplantation are unclear.

The *NPM1* mutation is the most common genetic risk factor seen in younger adult patients (that is, those aged under 60) with AML. Patients with the *NPM1* mutation are generally deemed to be favorable risk, whereas those with the *FLT3* mutation are considered intermediate risk. For the subgroup of patients with both mutations, however, it's been unclear whether chemotherapy alone or chemotherapy followed by a transplant is the best approach.

Othman and his colleagues analyzed MRD data from 737 patients with *NPM1*-mutated AML who had achieved a complete response after being treated in one of two large phase three randomized clinical trials, known as AML17 and AML19, that were conducted in the United Kingdom, Denmark, and New Zealand. Both trials enrolled adult patients fit for intensive chemotherapy with newly diagnosed AML. A subset of 238 patients had both *NPM1* and *FLT3* mutations. The researchers compared patients' outcomes based on their mutation status (*NPM1* only or both *NPM1* and *FLT3*), whether or not they underwent a donor transplant, and whether they were MRD positive or MRD negative when tested after two rounds of chemotherapy.

Across both trials, among MRD-negative patients, three-year overall survival was 75% for those enrolled in AML17 and 83% for those in AML19. Undergoing a donor transplant did not further improve survival for patients who were MRD negative. By contrast, three-year overall survival among MRD-positive patients who underwent a donor transplant was 61%, compared with 24% for those who did not receive a donor transplant.

In the subset of patients with both *NPM1* and *FLT3* mutations who were MRD-positive, three-year overall survival was 22% in AML17 and 31% in AML19, and patients undergoing transplant had improved survival. Among those with both mutations who were MRD negative, three-year overall survival was 75% in AML17 and 80% in AML19. Again, for those who were MRD negative, undergoing a donor transplant did not improve survival.

"Patients who are MRD negative after two courses of chemotherapy have a low risk for relapse," Dr. Othman said. "We saw no evidence that donor transplantation was of benefit to MRD-negative patients, including those with the *FLT3* mutation. By contrast, we saw a significant survival benefit for MRD-positive patients who underwent a donor transplant after achieving a complete response to chemotherapy. We think this supports making MRD status after two rounds of chemotherapy a major part of the process for selecting patients who are likely to benefit from transplantation."

A limitation of the study findings, he said, is that there are several methods of high-sensitivity testing for MRD, and it's unclear whether the use of a different testing method would have produced the same results. Moreover, not all cancer treatment centers currently have access to high-sensitivity testing.

The study was funded by the Cancer Research UK.

Jad Othman, MBBS, of Guy's and St Thomas' NHS Foundation Trust in London, will present this study during an oral presentation on Saturday, December 10, 2023, at 10:30 a.m. Pacific time in Marriott Grand Ballroom 8-9 (Marriott Marquis San Diego Marina).

For relapsed DLBCL patients who achieve complete remission, two-year outcomes are better with ASCT than with CAR-T

781: Autologous Transplant (auto-HCT) Is Associated with Improved Clinical Outcomes Compared to CAR-T Therapy in Patients (pts) with Large B-Cell Lymphoma (LCBL) Achieving a Complete Remission

For patients with a common type of lymphoma who have an early relapse or whose cancer doesn't respond to first-line treatment, randomized trials have shown that CAR T-cell therapy – which involves infusing the patient with their own genetically modified T cells – is superior to the historical standard of care, which included additional chemotherapy followed by high-dose chemotherapy plus a transplant of the patient's own stem cells. Due to the high demand for CAR T-cell therapy, however, patients often face long waits to receive it and need additional chemotherapy as a "bridge" to CAR-T. For some of these patients, that bridging chemotherapy may bring about a complete remission.

A new study based on data from the world's largest database of patients treated with stem cell transplants, CAR-T, and similar therapies finds that when patients in complete remission received high-dose chemotherapy plus a transplant of their own stem cells (known as an autologous transplant, or ASCT), they had fewer second relapses and their cancer stayed in remission for longer, compared with similar patients who received CAR T-cell therapy. Two years after treatment, 27.8% of patients treated with ASCT experienced another relapse, compared with 48% of those treated with CAR T-cell therapy.

Diffuse large B-cell lymphoma, or DLBCL, is one of the most common types of lymphoma, a cancer that starts in white blood cells. Around 60% of patients with newly diagnosed DLBCL respond well to chemotherapy and don't need further treatment, said **Mazyar Shadman, MD, MPH**, associate professor at Fred Hutchinson Cancer Center and the University of Washington in Seattle and the study's lead author. For patients whose disease either does not respond to initial chemotherapy or recurs within 12 months, high-dose chemotherapy plus ASCT has historically been the standard of care. Now, however, these patients are eligible to receive CAR T-cell therapy.

“Our findings support high-dose chemotherapy plus ASCT as a valid treatment option in real-world practice for patients who achieve a complete remission and also for the subset of patients who have relapsed and may be candidates for CAR T-cell therapy, but achieve a complete remission with bridging chemotherapy,” said Dr. Shadman. “ASCT also remains the treatment choice in patients with late relapse who achieve a complete remission as there is not data to suggest that CAR-T is more efficacious.”

The results are consistent with a previous finding by Dr. Shadman and his colleagues that relapsed patients who achieved partial remission had improved outcomes with ASCT compared with CAR T-cell therapy. Partial remission means tests show a reduction of 50% or more in the number of cancer cells. Complete remission means tests show no signs of cancer.

“If they relapse again after ASCT, they still have the option of undergoing CAR T-cell therapy – but it’s more difficult to do high-dose chemo plus ASCT if they relapse after CAR T-cell therapy,” he said.

Dr. Shadman and his colleagues analyzed data from the Center for International Blood & Marrow Transplantation Research (CIBMTR) database to compare outcomes for patients with relapsed DLBCL who were treated with either ASCT or CAR T-cell therapy. The CIBMTR database includes clinical information for more than 630,000 patients worldwide who have been treated with autologous or donor stem cell transplants, CAR T-cell therapies, and other cellular therapies, including most of those treated in the United States.

In 2022, Dr. Shadman and his team reported in the journal *Blood* their findings for 411 adult patients with relapsed DLBCL who received either CAR T-cell therapy or ASCT while in partial remission. They found that patients who received ASCT had fewer relapses and lived longer than those treated with CAR T-cell therapy.

For the current study, the researchers compared outcomes for 360 adult patients (average age about 62) with relapsed DLBCL who received either CAR T-cell therapy or ASCT while in complete remission. The study’s primary endpoints were the length of time patients stayed in remission (progression-free survival, or PFS) and patients’ overall survival (OS). Results showed that patients in the ASCT group had longer remissions and lived longer than those in the CAR T group (PFS, 66.2%; OS, 78.9% for the ASCT group versus PFS, 47.8%; OS, 65.6% for the CAR T group).

A limitation of the study is that it is based on a look back at outcomes for patients treated in the past, rather than a clinical trial in which patients were assigned at random to receive ASCT or CAR T-cell therapy, Dr. Shadman said.

Mazyar Shadman, MD, MPH of Fred Hutchinson Cancer Center and the University of Washington in Seattle, will present this study during an oral presentation on Monday, Dec. 11, 2023, at 10:30 a.m. Pacific time in the Pacific Ballroom Salons 18-19 (Marriott Marquis San Diego Marina).

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The American Society of Hematology (ASH) (hematology.org) is the world's largest professional society of hematologists dedicated to furthering the understanding, diagnosis, treatment, and prevention of disorders affecting the blood. For more than 60 years, the Society has led the development of hematology as a discipline by promoting research, patient care, education, training, and advocacy in hematology.

ASH's flagship journal, *Blood* (bloodjournal.org) is the most cited peer-reviewed publication in the field, and *Blood Advances* (bloodadvances.org) is an open-access, online journal that publishes more peer-reviewed hematology research than any other academic journal worldwide. Two new journals will be joining the Blood Journals portfolio in 2024, *Blood Neoplasia* (bloodneoplasia.org) and *Blood Vessels, Thrombosis & Hemostasis* (bloodvth.org).

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