A New Study Published in the Journal Blood Demonstrates that Measuring Minimal Residual Disease Negativity Using Adaptive Biotechnologies' Next-Generation Sequencing Platform is a Major Predictive Indicator in Multiple Myeloma

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Deep MRD Negativity was the Strongest Prognostic Factor of PFS Regardless of Treatment, Risk Factor and Disease Stage

SEATTLE, WA, September 28, 2018 – Adaptive Biotechnologies today announced that Blood, the Journal of the American Society of Hematology (ASH), published online an analysis of patient samples from the Intergroupe Francophone du Myéloma (IFM) 2009 trial. The analysis confirms the value of minimal residual disease (MRD) as a prognostic indicator in multiple myeloma (MM) measured by next-generation sequencing (NGS), using a prior version of Adaptive's highly sensitive NGS platform to detect the presence of disease before and after maintenance therapy. The analysis looked at the impact of achieving MRD negativity on progression free survival (PFS) and overall survival (OS). MRD status was shown to be prognostic of PFS and OS. Deep assessment of MRD negativity using this assay, defined in the analysis as less than one myeloma cell in 1 million healthy cells (or 10-6) was the strongest prognostic factor for PFS, regardless of treatment, cytogenetics (risk factors) or stage of the disease. Achieving and maintaining MRD negativity regardless of treatment, resulted in significantly superior PFS and OS compared to those patients who remained MRD-positive.1

Myeloma is an incurable cancer of the plasma cells that typically develops in the bone marrow. It is the second most common form of blood cancer, affecting 1.5 times more men than women. MRD refers to the small number of cancer cells that can remain in a patient's body after treatment, which often cause no signs or symptoms, but eventually can lead to recurrence of the disease. These residual cells can be present at very low levels and require highly sensitive tests to identify them. Even very small amounts of MRD during and after treatment can have a profound effect on treatment success and patient outcomes. A test that can reliably determine the presence and amount of MRD at very low levels can be used in clinical trials and in the clinic to predict clinical outcomes, guide management and improve patient care.

"The IFM 2009 analysis demonstrates that MRD is the most important prognostic indicator in myeloma clinical trials when it is measured by a highly sensitive NGS MRD test," said Hervé Avet-Loiseau, MD, PhD, Head of the Laboratory for Genomics in Myeloma, University Cancer Center Toulouse, and co-corresponding author. "In the study, patients who achieved MRD negativity with NGS MRD testing, which is able to detect a single myeloma cell among 1 million healthy cells, had better outcomes, regardless of treatment, risk factors or disease stage. Given that MRD-negative patients can still relapse, these results demonstrate the importance of evaluating patients at diagnosis and monitoring them throughout treatment and remission, and it suggests this approach could be used to adapt treatment strategies in future clinical trials."

Study Results
The IFM 2009 study analyzed the relationship between MRD status, OS and PFS between two treatment arms. In the analysis published in Blood, a subset of patients (N=224) were analyzed using NGS MRD testing prior to maintenance and 183 patients were assessed after maintenance. DNA was extracted from frozen bone marrow samples and sequenced using an earlier version of Adaptive's NGS MRD assay developed by Sequenta Inc., which Adaptive Biotechnologies acquired in January 2015. Since the acquisition, Adaptive has combined the technologies into its current MRD assay known as clonoSEQ®.

MRD negativity was associated with prolonged PFS prior to (P<0.001) and after completion (P<0.001) of maintenance therapy, demonstrating that NGS MRD testing is highly predictive of outcomes. The PFS was significantly longer in patients who achieved and maintained MRD negativity (<10-6) than in patients who were MRD-positive (P<0.001). The risk of progression was nearly doubled in patients with an MRD level of 10-6−10-5 versus those who were MRD negative (<10-6) at the start of maintenance therapy (HR=1.94; 95% CI: 1.03 to 3.63; P=0.04) and was almost three-fold higher when MRD was detected after the completion of maintenance therapy (HR= 2.81; 95% CI: 1.50 to 5.24; P=0.001).

Overall survival was also significantly prolonged in MRD-negative patients compared to MRD-positive patients. The overall survival at 4 years after the start of maintenance therapy was 94% among MRD-negative patients, and 79% among MRD-positive patients (HR=0.24; 95% CI:0.11 to 0.54; P=0.001). The overall survival at 3 years after the completion of maintenance therapy was 96% among MRD-negative patients, and 86% among MRD-positive patients (HR= 0.26; 95% CI: 0.10 to 0.68; P=0.008). PFS and OS were significantly superior for patients who had sustained MRD negativity or became MRD-negative at the end of maintenance, indicating the clinical need for measuring MRD over time (P<0.001; P=0.004).

In the IFM 2009 trial, MRD was also assessed using conventional multiparametric flow cytometry, which can detect one myeloma cell in 10,000 healthy cells (10-4). Flow results were previously reported in the New England Journal of Medicine.2 Of the 233 patients who were previously identified as MRD-negative in the IMF 2009 trial by multiparametric flow cytometry, 113 patients (48%) were found to be MRD-positive using NGS MRD testing.

"The IFM 2009 analysis underscores the need for a deeply sensitive, highly accurate and reliable NGS MRD test that can detect and monitor disease burden throughout the treatment continuum. This study adds to the growing body of evidence that MRD is a critical endpoint that should routinely be incorporated into clinical trials and clinical practice to ensure the best patient outcomes," said Charles Sang, senior vice president of Diagnostics, Adaptive Biotechnologies. "Adaptive remains committed to providing physicians and their patients with a validated, specific and standardized NGS MRD assay that meets regulatory standards and can be used to assess burden of disease and guide disease management for patients living with multiple myeloma."

MRD is also being examined by the FDA and the EMA as a surrogate or primary endpoint in multiple myeloma and other lymphoid malignancies. The recent FDA review and approval of drugs with MRD included as a clinical endpoint, as well as the agency's inclusion of MRD in acute lymphoblastic

leukemia (ALL) on the recently released list of surrogate endpoints, demonstrates the clinical actionability of MRD and reinforces the need for accurate and standardized NGS MRD testing.3,4

Adaptive platform uses NGS to precisely identify and monitor MRD in patients throughout treatment and remission with meaningful sensitivity. Determining MRD status with deep sensitivity can help physicians better manage multiple myeloma and other lymphoid malignancies.

About Minimal Residual Disease
Minimal residual disease (MRD), also referred to as measurable residual disease, refers to cancer cells that remain in the body after treatment for patients with lymphoid cancers. These cells can be present at levels undetectable by traditional morphologic methods, microscopic examination of blood, or a bone marrow or a lymph node biopsy.

MRD is used by physicians to detect and monitor disease burden in patients and to inform their treatment decisions. Clinical practice guidelines5,6 recommend assessing MRD at multiple time points during treatment and maintenance in multiple myeloma and acute lymphoblastic leukemia (ALL), and guidelines include next-generation sequencing (NGS) as a recommended testing method. The prognostic value of MRD assessment has been demonstrated in multiple lymphoid cancers.7,8 Controlled trials have shown that even small amounts of disease are profoundly significant for predicting a patient's long-term clinical outcomes.1,9,10,11,12 Therefore, highly sensitive, standardized molecular technologies are needed for reliable detection of MRD.

Measurement of MRD is currently being evaluated as a way to measure efficacy in drug trials, with the potential to expedite the approval of emerging therapies.13

About IFM 2009
The latest clinical data from the IMF 2009 trial was published in the April 6, 2017 issue of New England Journal of Medicine (N Eng J Med;376:1311-20). The study evaluated the role of transplantation in patients with newly diagnosed myeloma under the age of 66 treated with lenalidomide, bortezomib, and dexamethasone (RVD). The primary endpoint was PFS. Secondary endpoints include OS and MRD assessment using conventional multiparametric flow cytometry (one myeloma cell in 10,000 healthy cells or 10-4). NGS MRD testing was not available when the trial was initiated in 2008. Details of MRD assessment using the multiparametric flow cytometry technique have been previously published.2

About the clonoSEQ® Assay
The Adaptive Biotechnologies clonoSEQ® Assay enables physicians to utilize a molecular, next-generation sequencing-based minimal/measurable residual disease (MRD) detection method. The clonoSEQ Assay detects and quantifies DNA sequences found in malignant cells which can be tracked throughout treatment. This robust assay provides consistent, accurate measurement of disease burden which potentially allows physicians to visualize response to treatment over time.

The clonoSEQ® Assay is regulated under CLIA and has not been cleared or approved by the FDA. The assay should only be used taking into account all available information and should not be used as the sole determinant to guide patient care. Results may vary. False positive or false negative results may occur for reasons including, but not limited to: sample mix up, misidentification, contamination, technical, and/or biological factors.

About Adaptive Biotechnologies
Adaptive Biotechnologies is the pioneer and leader in combining next-generation sequencing (NGS) and expert bioinformatics to profile T-cell and B-cell receptors. Adaptive is bringing the accuracy and sensitivity of its immunosequencing platform to researchers and clinicians around the world to drive groundbreaking research in cancer and other immune-mediated diseases. Adaptive also translates immunosequencing discoveries into clinical diagnostics and therapeutic development to improve patient care. For more information, please visit adaptivebiotech.com.

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