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What are the most exciting new agents in acute myeloid leukemia (AML) and where are they in clinical development?

Welcome to *Managing AML*. I am Dr. Naval Daver. I am frequently asked, "What are the most exciting new agents in acute myeloid leukemia (AML) and where are they in clinical development?" The last 3 to 4 years have been very beneficial for AML clinical trials and therapeutic innovations. For over the last 30 to 40 years, unfortunately, no drugs had been approved for AML with the exception of gemtuzumab (Mylotarg®) which was approved for a short while but then actually came off the market. However, in the last 5 years, there have been four major classes of new drugs that are coming into development for AML.

The first are novel cytotoxic agents, and one of these drugs is called CPX-351 or cytarabine and daunorubicin liposome (Vyxeos). This agent recently showed superiority in a phase 3 study in patients with AML who are between 60 to 75 years of age and had a secondary AML. Secondary AML is defined by an AML that arises from a preexisting MDS or myelofibrosis, or AML that arises in the patient who had prior chemotherapy for another tumor. In this group of patients with secondary AML, age 60 to 75, the CPX showed a survival benefit that was significantly better than with 7+3,* which would have been the standard treatment for those patients if they did not get CPX. Based on this, we expect that the CPX will become available in the United States for these patients with secondary AML who are between 60 to 75 years. Based on the data, it does show significant improvement in survival, as well as improvement in bridging to transplant and posttransplant outcomes.

The second major group of agents is the molecular-targeted therapies, and two of these include the FLT3-targeted as well as the IDH-targeted agents. Both of these as single agents have shown impressive response rates of 35% to 50%, but even more impressive when they are combined with cytotoxic therapies or with hypomethylating therapy. This has especially been shown in FLT3 inhibitors, with recent phase 3 data showing that adding a FLT3 inhibitor to standard cytotoxic therapy in a newly diagnosed young AML patient could improve overall survival. I think these should be considered standard of care across the board in new AML patients in the upcoming months.

The third group of drugs is the immune therapies, and these are really exciting and interesting. One of the major benefits of immune mechanisms, such as monoclonal antibodies to CD33, CD123, or immune checkpoint-based therapies or even CAR-T cells, is that they do

not depend on the molecular machinery. Mutation such as TP53 or MLL would usually make a person resistant to many of the targeted or cytotoxic therapies, but these patients are still sensitive to immune therapies because they are not resistant if you have these particular mutations. So, we think of these immune approaches as ways to overcome potential high-risk mutations in AML and so far, some of the data with the monoclonal antibodies are actually showing that to be true.

The fourth class of agents that is of interest and is also in development in phase 3 trials is the newer hypomethylation therapies, and these include specifically a drug called guadecitabine or SGI-110. This is a new version or a next-generation decitabine that produces more potent hypomethylation but additionally higher response rates than decitabine both in the relapsed as well as frontline AML. A large phase 3 study comparing guadecitabine versus either azacitidine or decitabine (which would be considered standard of care) has just completed accrual, and we expect these data to hopefully be available by the end of this year. If the guadecitabine does show survival improvement, then this will become available to be used next year and could become the hypomethylating agent of choice in elderly AML populations.

All in all, there is a lot of development in a number of ongoing phase 3 trials, and many drugs already showing benefit in phase 3, so it is a very exciting time in AML research, and many more options are becoming available for our patients, which is extremely exciting. Thank you for viewing this activity.

7+3, referred to in the video as 3+7, is most often used today as first-line induction therapy in AML, and consists of 7 days of standard dose cytarabine and 3 days of an anthracycline, most often daunorubicin.