Updates on the Most Anticipated Data Presented at ASH 2019

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Hello, I am Dr. Daver from the MD Anderson Cancer Center. I will be giving some updates on exciting studies that are being presented this year at the ASH 2019 meeting in Orlando, Florida, focusing on AML (acute myeloid leukemia) and MDS (myelodysplastic syndrome). There are a few special studies that I think are bringing in new drugs to the AML/MDS field hopefully in the next one or two years. These are, of course, in addition to the numerous breakthroughs that have occurred already in AML in the last three to four years such as the venetoclax-based therapies, FLT3 and IDH therapies, CD33 antibody-drug conjugates, hedgehog inhibitors, CPX-351, and others. But this year specifically among the new drugs, beyond these that we're aware, of are two agents that I think are especially active. One of them is in a drug called CD47. This is a type of immunotherapy. One of my primary areas of clinical research for many years has been developing immunotherapies that enhance the T-cell biology and the T-cell activity against tumors. So, the CD47 is a similar immune checkpoint antibody, but instead of activating T-cells, it's an immune checkpoint on surfaces of macrophages. And by using CD47 antibody, we are able to activate macrophages, the activated macrophages infiltrate into the leukemic marrow, and we actually can see and even visualize on photon microscopy, phagocytosis of the leukemia cells. This preclinical data that was very nicely developed by Irv Weissman, Ravi Majeti, and others in Stanford many years ago has now led to a clinical trial of azacitidine with CD47 in newly diagnosed frontline AML above 65 who are not candidates for induction chemotherapy, as well as in newly diagnosed intermediate-, high-, very high-risk IPSS-R MDS. The updated data were presented here at ASH and are quite striking and encouraging. Now with about 61 patients enrolled, we see that the 30-day mortality in this frontline population is zero. This is quite outstanding for a multicenter study better than we have seen with almost any other study. Also in general, quite well tolerated, we are not seeing any of the immune checkpoint associated toxicities we have seen with PD-1 and others, and the main thing that we do note is an early on-target anemia, as CD47 seems to be expressed on older red cells, and that actually may be the only other area in the normal human body it's expressed. So, we recommend early monitoring transfusions for these patients by day 10, after that they seem to tolerate things well. The response in MDS was shown to be about 90%, which is, of course, outstanding.

Looking at the efficacy data, this was quite encouraging in frontline MDS, the response rates were shown to be 92%. Responses are very durable, and it appeared that only two patients had lost response with a median follow up of eight and a half months, and that all the MDS

patients were alive. In AML, we saw the response rate was 66%, and the responses also seem to be durable here and the overall activity, especially in a TP53 population was separately shown, 7 out of 9 TP53 patients responded for a response rate of about 75%, and it appeared that only one of those had relapsed. So all in all, very encouraging early activity, and more importantly to me, very encouraging early safety, which is critical because this may be a very nice backbone for us to further combine drugs; and we can envision in the future combination of azacitidine-venetoclax with CD47 and potentially this will be curative for many of our MDS and AML patients.

The other very important study was a very large multicenter, multinational, randomized study looking at a very novel approach, which is maintenance in AML. This is something that has never really been established in AML. There have been phase 2 studies showing maintenance with IV azacitidine and decitabine, both European and American studies, can improve outcomes response, relapse-free survival and overall survival, but these were phase 2. This was the first large randomized phase 3 study giving agent oral azacitidine to patients above 55 years of age who had completed their planned induction consolidation, and the patients randomized either to give the oral azacitidine on the investigational arm versus best supportive care, which is the standard of care for completion of induction consolidation therapy. Importantly, these were patients who were not going to transplant, either because they were not candidates for transplant in the opinion of the physician, or they did not have a transplant donor, or the patient decided not to go to transplant. So this was an approach for patients who are not going for transplant. The study showed, in a randomized fashion, improvement in overall survival, both clinically and statistically, meaningful and significant, with a good tail to the curve and we think that this will be adopted very quickly once hopefully the drug is approved. So this is a late-breaker abstract at ASH presented by Dr. Andrew Wei, and this data, I think, for the first time establishes maintenance in AML as a standard approach in addition to induction consolidation. We have done this in ALL for 25 years. Now in AML we will also be using this concept.

So I think these are the two major studies for ASH this year, going forward next year in the ASH after that, I think we're going to see a lot of developments. We're already seeing it in the immunotherapy field. There are other novel targets such as TIM-3, PD-1 maybe a good combination partner with AZA-CD47, maybe with azacitidine and venetoclax, and those kind of triplet trials are ongoing. Of course, we will continue to identify biomarkers of response to different venetoclax combinations. We expect in the next year, in the next four to six months especially, a readout of another phase 3 study using MDM2 inhibitor idasanutlin in the relapsed AML. This is the MIRROS study and if it is positive, will bring yet another drug, the 10 drug, potentially idasanutlin for treatment of relapsed AML not FLT3, not IDH mutated, which remains an open area for development. So all in all, a lot of things to be expected and should be a very busy and exciting year for patients, physicians, and research in AML/MDS in 2020. Thank you.

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