Venetoclax in Combination with Standard Intensive AML Induction/Consolidation Therapy with FLAG-IDA in Patients with Newly Diagnosed or Relapsed/Refractory AML

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Venetoclax is a very well-known drug and appears to be a major breakthrough in acute myeloid leukemia therapy and has been approved already in the frontline setting in older AML not fit for induction combined with either low-dose cytarabine or with hypomethylating agents such as azacitidine or decitabine. We sought to evaluate whether addition of venetoclax to a more traditional induction chemotherapy such as FLAG-IDA in a different population, in a younger and fitter AML population, could also improve either response rate, MRD negativity, response duration, and could it do this in newly diagnosed as well as in relapsed/refractory AML. So, this is a phase 1b/2 study done in MD Anderson as a single center study at this time, and the two primary objectives as for most phase 1b studies are assessment and evaluation of safety, tolerability, establishing a recommended phase 2 dose, and then, of course, to look at overall response rate which includes CR/CRi/PR and morphological leukemia-free state and survival. So, this study allowed patients who are younger than 60 years of age, patients had to have a performance state of 0 to 2, and a white count importantly had to be less than 25,000 so that we did not run into problems or tumor lysis, other eligibility were by standard criteria. In the relapsed/refractory AML arm, initially we were doing standard-dose FLAG-IDA as has been used at the MRC and MD Anderson and other centers in the U.S. with fludarabine 30/m^2 for five days, cytarabine 2 g/m^2 for five days, and idarubicin 6 mg/m^2 for three days. However, over time, what we saw is that in the initial eight or nine patients, four patients had quite severe myelosuppression associated infections during the first cycle, and those four required ICU stay with eventual recovery with antibiotics/pressors. We felt that this regimen was too intense at the doses of the standard FLAG-IDA and reduced the doses with Ara-C being dropped by 25% to 1.5 g/m^2 for five days and the idarubicin being maintained at 6/m^2 for two days. And we also reduced the venetoclax to only 14 days at a standard dose 400 mg without azole, 200 mg with azole (isavuconazole), 100 mg with the posaconazole or voriconazole with an option to go down to 50 mg.

Now looking at the efficacy of this regimen, this was a highly advanced population in the relapsed cohort. They had a median of two prior salvages, they were younger patients, median of 37 years of age, and importantly 43% had received a prior stem cell transplant which we know is a very high-risk group relapsed post-transplant. We did confirm that venetoclax 400 mg days 1-14 during the first cycle with the lower doses of cytarabine and idarubicin, as I discussed, was a tolerable phase 2 dose for expansion. Importantly, the 30-day and 60-day mortality were zero in the newly diagnosed cohort and 13% in the

relapsed/refractory cohort. Overall, at this time, we have about 25 relapsed/refractory patients treated. The CR/CRi/MLFS rate is quite impressive at about 75% and a number of these patients have been able to proceed with allogeneic stem cell transplant. To put this in perspective, we need to know that in the relapsed/refractory setting, the response rate with fludarabine-cytarabine alone or FLAG-IDA alone is about 25% to 35%. So, we are seeing what we think are doubling of response in relapse. The relapsed study unfortunately, in spite of the high response rate, shows median survival of about six to eight months. And I think hopefully with better monitoring and ongoing follow up, we will see improvement in that survival. The good thing was that the ANC and platelet recovery was between 27 and 35 days, so this was not significantly or unduly prolonged, and the median duration of response is not reached in the relapsed cohort. But, as I mentioned, the median overall survival is 7.1 months with slightly higher survival in salvage one of 9.4 months. And the newly diagnosed is very early data, but we had 11 patients, of which 10 became MRD negative and 10 of those have responded. All of them continue to have response. We need to wait until we have 30 to 40 patients to make a clear conclusion based on whether we think this is going to be better than FLAG-IDA in the frontline setting.

I think what's very important with this regimen to note for community physicians is that this was done in a very large academic center with very close monitoring with infectious disease support, ICU availability, consultation within a couple of hours, and we did have a number of patients, especially in the relapsed cohort, who had very severe cycle 1 myelosuppression, infections, bacteremia, sepsis. I think at this time I do not think this regimen is ready for community use, I would not recommend it. I think this is very encouraging early data. The trial is ongoing, maybe expand it potentially to other centers; and we need to treat a good number of patients before we are confident that the safety and the efficacy will be maintained. So, I do not think that this is something I would consider doing in community but is a great clinical trial for patients, especially young relapsed patients, who may have limited options to be referred for. Thank you.