The Role of Nivolumab in Maintenance Therapy; BCL-2 Inhibitor Studies in Newly Diagnosed AML; Impact of NGS on Therapy Selection

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My name is Naval Daver. Today, I am going to be talking about nivolumab maintenance therapy in patients with high-risk acute myeloid leukemia. This is an abstract that is going to be presented at the American Society of Clinical Oncology 2018. This study was conducted at MD Anderson. The study basically looked at patients with high-risk acute myeloid leukemia. High-risk was defined as patients who had either adverse cytogenetics, TP53 mutations, secondary AML, or relapsed AML (with up to first salvage being allowed). We know historically that the outcomes for these patients are quite poor, with CR durations at six months and one year of less than 50%, and overall survival at one year frequently below 50% to 60%. The primary endpoint of this study was whether we could use nivolumab, an anti-PD1 agent, to improve the T-cell activity and thereby prevent the relapse of acute myeloid leukemia. In this study, a total of 18 patients have been enrolled at this time. All of these patients had one or more high-risk feature as we discussed previously. The primary endpoint that we are seeing at this time (with the study ongoing) is that the overall survival at one year is about 86%, which is very encouraging compared to historical overall survivals that we had seen in this similar population at MD Anderson and also published by other groups who have done similar analysis. Also, the CR duration at both six months and one year was 78% and 72%, both of which are higher than what we would expect in similar high-risk patients who have completed treatment and are not going to stem cell transplant.

Overall, we did see immune side effects, and this has been described with nivolumab, both as a single agent and in combination with azacitidine in different AML patients. The most common immune effects that were seen were thyroid inflammation in two patients; we did have two patients with pneumonitis; we had one patient with skin rash; and also one with transaminitis. All of these events responded to steroids and when steroids were initiated rapidly, we did notice that immune toxicity responded quite quickly. No patients had to come off study and there were no fatalities from the immune toxicities. Overall, the study is ongoing. We are quite encouraged by both the overall survival and CR duration, but the follow-up at this time is short. We hope that if we continue to see, at two years and beyond, more than 60% of the patients having survival, this would make us encouraged that this is truly beneficial impact and then this could be evaluated in larger phase 2/phase 3 studies.

Next, I am going to be talking about the outcomes in a combination therapy of azacitidine or decitabine with a BCL-2 inhibitor venetoclax in patients with newly diagnosed AML who are elderly and not fit for intensive therapy. Venetoclax is a BCL-2 inhibitor and it has shown single-agent activity in AML in a phase 1 study that was led by Marina Konopleva at MD Anderson. The response rates with single-agent venetoclax in relapsed AML were about 18% to 19%. Based on this data, it was then subsequently moved into combination therapy. One of the combinations that has yielded very exciting results is the combination of azacitidine or decitabine – drugs that we call hypomethylating agents which we frequently use in both elderly AML and MDS – added with the venetoclax, the BCL-2 inhibitor, which was given as a pill. The venetoclax was evaluated at three different dose levels in the initial portion of the dose-finding portion of the study, and the three levels that were looked at were the 400, 600, and 800. The majority of the patients were either on the 400 or the 800 in combination with azacitidine and decitabine at the standard dose. The standard dose of azacitidine is 75 mg/m^2 days one through seven. The standard dose of decitabine is 20 mg/m^2 days one through five. The primary endpoint of this study, since this was a phase 1/2 study, was evaluation of safety, as well as response rates. Secondary endpoints included duration of response and overall survival.

Overall, what we noticed was the response rate across all patients – with a total of 145 patients being presented here – was 72%, which is very striking because historically, the response rates that we have seen with azacitidine or decitabine alone in similar elderly AML patients not fit for intensive chemo was about 20% to 25%. We are seeing not doubling, but tripling of the response rates, and this was very encouraging. The second thing that is also very important was the median survival. Historically in elderly AML, whether we use azacitidine or decitabine or low-dose cytarabine, which were the three standard approaches, the median survival is between 6 to 10 months. In this study, we are seeing a median survival of 18 months. What is impressive is that at two-and-a-half-year follow-up, we have almost 48% of the patients alive, which is much higher than the historical 10% to 15% who would be alive at two-and-a-half and three-year follow-up with azacitidine or decitabine alone. Overall, these are fantastic results. This regimen is being evaluated in a phase 3 study of azacitidine with venetoclax versus azacitidine alone. The study is enrolling very well. The other thing that was looked at was the safety profile. What was seen is that the main safety issue that is seen is neutropenia, which is an on-target effect, which is known to happen with BCL-2 inhibitors. We do see prolonged neutropenia as compared to what we would get with azacitidine alone, so now we are looking at different strategies at MD Anderson, as well as other institutions, to see if it would be possible to do dose interruptions of venetoclax once people are in remission. This has not yet been formalized, but down the line, there will be approaches looking at dose interruptions to allow count recovery. All in all, we do not see mucositis, we do not see skin rashes or diarrhea or any of the toxicities that are concerning with high-dose chemotherapy, and we at MD Anderson and many other major centers believe that this is going to be the new standard of care for elderly acute myeloid leukemia patients and it is going to be reviewed by the FDA quite soon. We are very excited about this data.

Finally, this abstract looked at the impact of next generation sequencing in identifying mutations on selection of therapy in patients with acute myeloid leukemia. The abstract was presented by MD Anderson and they looked at patients who were seen at MD Anderson for a diagnosis of acute myeloid leukemia between 2012 and 2017. They found a total of about 1450 patients. What they then look at was the prevalence or incidence of actionable mutations and these are defined as mutations for which some form of targeted therapy was available given in that time period. These could have been IDH1, IDH2, FLT3, RAS mutations, TP53 based mutations, NRAS mutations and others. What they showed was that if you looked at baseline testing, about 40% to 45% of patients would have an actionable mutation identified. What was also interesting is that the results of the mutation screen were available about 50% of the time after the patient had started some form of standard therapy, meaning that they would not then be eligible at that time for getting a targeted-based therapy. In all, they saw that about 35% of the patients received some form of targeted therapy for the actionable mutation that was identified, either in the newly diagnosed or relapsed setting. The majority of these treatments were done on a clinical trial basis with very few patients getting standard of care targeted therapies, which make sense because most of the targeted therapies in AML have just been approved or are in the process of being approved (such as IDH and FLT3 inhibitors).

The other interesting thing that they saw was that more physicians frequently treated relapsed refractory AML patients on clinical trials or on standard of care with targeted agents, rather than frontline patients. The reasons they cited for these are potentially not having the results available at the time of selection of frontline therapy; or urgency on the part of the treating physician to start treatment very early in a new AML; or potentially the lack of available mutational data or clinical trials in the frontline setting. In the relapsed setting, they did note that about 50% of patients were actually selected for trials because the mutational data had already become available, and so the selection process was quicker and the patients could have been screened for clinical trials early on. The bottom line is that it does seem even before these targeted therapies such as midostaurin, quizartinib, and gilteritinib (FLT3 inhibitors or IDH1 or IDH2 inhibitors recently approved), there has been – at least in large academic centers – an effort to match the patients' mutations with their therapy. I think this will only become more prevalent and in the near future, we will be able to see 70% to 80% or more of patients who have a potentially actionable mutation getting these therapies. The other important point I think from this abstract to take away is the importance of trying to get mutational data back quickly. This is something that at MD Anderson we have worked on. I know a lot of other institutions that have tightened their timelines where we get the data on the actionable mutations such as IDH, FLT3, TP53, RAS within five to six days. We often wait to get that data because that will help us triage the patients to appropriate trials. The reason we do that is because we are now seeing outcomes showing that the addition of FLT3 inhibitors in FLT3 mutated newly diagnosed AML, and potentially of IHD inhibitors in IDH mutated patients, may improve outcome. We feel it is more important to wait a few days if the patient is relatively stable to get the mutational data, and give them the correct clinical trial or targeted therapy off-trial, rather than starting treatment right away; and this is what most of the major academic

centers are leaning towards. I think we are really seeing an era of targeted personalized based therapy in acute myeloid leukemia that no longer is in the research arena, but is moving very quickly as a standard of care approach. Thank you.

Abstracts:

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