Developments in FLT3 Inhibitors, Chemotherapy, and Small Molecule Inhibitors

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Welcome to *Managing AML*. My name is Naval Daver, and I am one of the leukemia faculty at MD Anderson Cancer Center in Houston, Texas. Today I will be giving a brief overview on four abstracts that our group is presenting on the treatment of acute myeloid leukemia. The first one is an interim report of a phase 1/2 study looking at a combination of quizartinib (a potent second-generation FLT3 inhibitor) with either azacitidine or with low-dose cytarabine in patients with FLT3-ITD mutated acute myeloid leukemia.

This study was a study that was done in frontline newly diagnosed elderly patients with FLT3-ITD mutation or first-relapse FLT3-ITD mutated patients. We know that the FLT3 inhibitors are showing activity in these populations as a single agent, as well as with induction chemotherapy, as was shown in the RATIFY trial with midostaurin. The goal of this study was to see whether we could get similar efficacy when combining quizartinib – a very potent second-generation FLT3 inhibitor – with either azacitidine or low-dose cytarabine in the elderly population. Overall, we have enrolled at this time about 60 patients on the study. These patients included patients who were newly diagnosed who got either azacitidine or quizartinib, or low-dose cytarabine and quizartinib; as well as first-relapse patients. Among the newly diagnosed patients, we see an overall response rate (which includes a complete remission or complete remission with incomplete recovery, also called a CRC) of 65% to 75% with the combination of azacitidine and quizartinib. Interestingly, we also see an encouraging high response rate of about 60% to 65% in frontline elderly patients treated with low-dose cytarabine and quizartinib. What was more encouraging was that, even though we had small numbers, we are seeing an improved signal for survival with frontline elderly patients receiving aza/quizartinib, having a median survival greater than 21 months; and salvage patients with FLT3-ITD mutation receiving aza/quizartinib having a median survival of 12 months or higher. Overall, these findings do suggest that when we add hypomethylating agents to quizartinib, not only do we improve the response rate (as you may know, the response rates with quizartinib alone are in the range of 40% to 45%, and we are getting up to 60% to 65%) but more importantly, we seem to be improving the duration of response and overall survival. Single-agent quizartinib usually was associated with a duration of response of three to four months and survivals of six months in the salvage setting, and we are getting survivals of 12 months. I think this study, although a small phase 1/2, does give a signal that you could combine hypomethylating agents with FLT3 inhibitors, get higher response rates, and improve on the survival. At this time, quizartinib has completed its phase 3 study. This was an international study for salvage 1 AML, and the data of that study should be out

early next year. If it is approved, then there will be many approaches to consider, such as the hypomethylating agents plus quizartinib, low-dose cytarabine plus quizartinib, and others.

The next abstract I will discuss is a phase 2 study of azacitidine in combination with nivolumab, and included both a salvage cohort as well as a frontline cohort. The salvage cohort enrolled a total of 70 patients and has completed enrollment, and the frontline cohort has at this time enrolled 16 patients, of which the first 12 are evaluable. Overall, the goal of this study was to see if the addition of the PD-1 inhibitor nivolumab could improve the response rate, but more importantly, the duration of response and overall survival with azacitidine. As many of you may know, PD-1 inhibitors have now been approved in almost 20 indications in the last seven years, including solid and hematological malignancies. In AML, we have also presented at previous meetings; and at this meeting, we will have an oral presentation showing that the AML bone marrow environment does show an increase of T-cells that express PD-1, indicating that this may also be a potential inflamed tumor that could be targeted with immune checkpoint agents. Overall in the salvage patients which included 70 patients, we had a median age of 72 years, with half of them having secondary AML and about 35% with complex cytogenetics. The overall response rate we saw when we combined CR/CRi/PR and durable six-month or longer hematological improvement without progression was 35%, which included 25% CR/CRi/PR and 10% hematological improvement. What was interesting is that, in the early salvage population including salvage 1 and 2 who were above 70 years of age, we are seeing a median survival of 10.5 months. This is quite encouraging and compares similarly to frontline survival that has been seen with azacitidine or decitabine alone in a similar elderly high-risk population.

This is a phase 2 study but it needs to be confirmed, and indeed there is a phase 3 study that is ongoing with the SWOG group looking at azacitidine versus azacitidine/nivolumab versus azacitidine/midostaurin in elderly frontline AML populations. Additionally, we did see that there is evidence that patients who had higher CD3 and CD8 in the bone marrow aspirates to begin with had a better chance of achieving response. Those patients who did respond did have an increase in T-cell population in their bone marrow – especially in the CD8 population – and the increase was associated with increased expression of activation markers such as ICOS and OX40. This basically indicated that there was development of an active immune infiltrate in the bone marrow of patients who responded, but not in those who did not respond. There are other combinations that will be presented at this meeting with PD-1 inhibitors. One of them is a combination of high-dose chemo, idarubicin/cytarabine, with PD-1 that will be presented by Dr. Farhad Ravandi from our group; and there are other phase 1/2 studies ongoing of combinations of immune checkpoints such as PD-1 with CTLA-4, or PD-1 with OX40 (with or without azacitidine or chemo).

The third abstract I am going to talk about is a combination of a FLT3 inhibitor sorafenib (a multikinase inhibitor that has other targets beyond FLT3), and selinexor (an exportin inhibitor that is now being tried in multiple solid tumors, multiple myeloma, and acute myeloid leukemia).

This study was developed on preclinical work done by Dr. Michael Andreeff from our group who showed that the combination of sorafenib, a broad kinase inhibitor, with selinexor was able to show very potent inhibition of both cell lines and primary AML samples, including FLT3-ITD, but also FLT3-D835-mutated patients. This is important because in general, FLT3-D835 patients do not respond to sorafenib and this may be through the synergy with the exportin inhibitor that we are seeing this activity. The trial was a phase 1/2 study done in salvage populations including salvage 1, 2 and 3. In the initial portion, we did a dose finding and we noticed that we had difficulty in giving the full dose of selinexor 100 mg twice a week. We settled, after doing the dose escalation, at a dose of 60 mg twice a week in combination with sorafenib at a standard dose of 400 mg twice a day. At that dose, we have now enrolled a total of 18 patients. The overall response rate among the evaluable patients is quite high. We are seeing a response rate of 50% when we look at CR, CRi and PR. What is interesting is that all the responses seem to occur in patients who have received a prior FLT3 inhibitor.

In summary, at this time, we have small numbers of patients. However, there is evidence of efficacy and a higher response rate than we would expect with single-agent FLT3 inhibitors in the salvage setting with this combination. We are going to continue to enroll on this study to build further and see if we continue to see this signal; and if we do, then we may consider doing a similar study with some of the second-generation – and potentially more potent – FLT3 inhibitors such as quizartinib with selinexor, or gilteritinib with selinexor.

The fourth presentation is a new phase 1 study of a novel FLT3 inhibitor, FLX925. FLX925 is a FLT3 inhibitor that had activity against both ITD as well as D835; as well as some of the activation loop mutations such as X91, 691 and others. There was a lot of interest on this agent because of its broad FLT3 inhibitory activity as well as very potent preclinical data supporting it. The study we are presenting as a poster at this ASH is a phase 1 dose escalation. We went through eight different dose levels. The population included relapsed/refractory AML, and we allowed both FLT3 mutated as well as FLT3 unmutated patients in the dose escalation. Overall, what we noticed is that the response rate was very modest. We had only two patients who achieved a CRi among the 50 patients enrolled, indicating that we were not seeing the degree of efficacy that we would like to see in the current landscape with multiple active FLT3 inhibitors to take this agent forward. The agent in general was well-tolerated, although there was a signal for increased creatinine. In general, at this time, after discussing with the multiple investigators across the country who collaborated with us on this trial, as well as the sponsors, we do not plan to take this study further into phase 2 and beyond, as there are other FLT3 inhibitors that are approved or are close to approval.

With that, I would like to thank you all for viewing this activity; and I hope you enjoy the meeting.

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