The Emerging Role of Bispecific Antibodies in AML: Promising Early Trial Results

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25. A Phase 1 First-in-Human Study of AMG 330, an Anti-CD33 Bispecific T-Cell Engager (BiTE) Antibody Construct, in Relapsed/Refractory Acute Myeloid Leukemia (R/R AML)

Hello. My name is Farhad Ravandi I am at the University of Texas MD Anderson Cancer Center in Houston. I am at the 60th ASH Annual Meeting, and will be reviewing the presentation on data on the phase 1 first in-human study of AMG 330 and anti-CD33 BiTE antibody in relapsed and refractory acute myeloid leukemia.

CD33 is an antigen expressed on the surface of the vast majority of AML cases, over 99%, and has been a target of antibody development in AML for a long time. The BiTE platform is now established in acute lymphoblastic leukemia with the approval of blinatumomab in relapsed and minimal residual disease ALL and it has CD3 and CD19 targets. AMG 330 is a similar molecule where the targets are CD33 and CD3, and by engaging these targets, the molecule brings T-cells to the close proximity of CD33 expressing leukemia cells and activates the T-cells and results in T-cell mediated killing of leukemic cells. The study was a dose-finding study, a phase 1 trial in patients with relapsed and refractory AML, patients older than 18 who had either primary refractory or relapse disease could be enrolled. Patients with APL as well as patients with secondary AML were excluded, and the initial design of the study was dose escalation in single patient cohorts, but at the later cohorts, the design was a classical 3+3 design. After the fifth cohort, because of the occurrence of significant cytokine release syndrome, the study was amended to allow for predosing for dexamethasone and also there was an initial step-up dosing performed where the patients would receive a lower dose followed by bigger dose of AMG 330 after a few days, and this was in order to mitigate cytokine release syndrome. After cohort 10, where there was two dose-limiting toxicities at the high dose of 480 mcg/day, there was further adjustment to the schedule and a second step-up dosing was instigated and whereby the patients would receive lower initial dose of 10 mcg/day for a few days followed by 60 mcg/day for a few days, followed by the eventual high-target dose.

The study has been ongoing and about 40 patients had been accrued and apart from cytokine release syndrome, there was no other major significant toxicity. Cytokine release syndrome of grade 4 was seen in two earlier cohorts which led to the instigation of steroids as well as step-up dosing, and with appropriate measures, cytokine release syndrome was only seen as a dose

limiting toxicity at the dose of 480 mcg, and this time it was because it was persistent grade 2 CRS. Among the later cohorts, there have been responses including two CRs at the high doses of 102 mcg/day target dose and 240 mcg/day target dose, and also, there have been two CRi's at earlier cohorts 8 and 9. There was one morphological leukemia state achievement in one of the very early cohorts of the study. All in all, this study validates the use of the BiTE platform in acute myeloid leukemia. Cytokine release syndrome is an expected toxicity and we now have measures to try to minimize that. Neurological toxicity was seen but was only grade 1 and 2 mainly, and it was headaches and dizziness. Further dose and schedule adjustments are being conducted with eventually a dose expansion to see whether we can further establish its efficacy in treating patients with relapse and refractory AML.

Reference: Ravandi F, Stein A, Kantarjian H, et al. A Phase 1 First-in-Human Study of AMG 330, an Anti-CD33 Bispecific T-Cell Engager (BiTE®) Antibody Construct, in Relapsed/Refractory Acute Myeloid Leukemia (R/R AML). ASH 2018. Abstract 25.

763. Complete Responses in Relapsed/Refractory Acute Myeloid Leukemia (AML) Patients on a Weekly Dosing Schedule of XmAb14045, a CD123 x CD3 T Cell-Engaging Bispecific Antibody: Initial Results of a Phase 1 Study

I will be reviewing the data from the phase 1 study of bispecific antibody XmAb14045, a CD123 x CD3 T-cell engaging antibody, which is being evaluated in patients with relapsed and refractory CD123 expressing leukemias.

CD123, or the alpha subunits of interleukin 3 receptor, is present on the surface of leukemic stem cells as well as mature basophils. It is also expressed on a number of other hematological malignancies such as subsets of acute lymphoblastic leukemia as well as BPDCN. As such, this has been a target for antibody-based drug development. This was a phase 1 study to evaluate safety and to establish the first infusion and subsequent infusion maximum tolerated doses of XmAb14045. Patients older than 18 who had CD123 expressing leukemias who had failed prior therapy were eligible to participate; however, the vast majority of the patients who were enrolled on this study had relapsed and refractory acute myeloid leukemia. The initial doses in the dose escalation scheme were administered to single patient cohorts, but subsequently, the design was a classical 3+3 design. After the establishment of the dose of 1.3 mcg/kg/day as the maximum tolerated first infusion dose, a Part B was initiated to look at maximum tolerated dose for second and subsequent doses, and this is based on pre-clinical studies that have shown that the highest likelihood of cytokine release syndrome, the major toxicity of these agents, is in first dose infusion.

To date, 67 patients have been enrolled, but as I mentioned, one patient had relapsed B-cell ALL and was not reported on the study. The rest of the patients had relapsed and refractory

acute myeloid leukemia with a majority of the multiple prior therapies. The study drug has been well tolerated and the major toxicity has been the expected cytokine release syndrome, which occurred in about 55% of patients, but was grade 3 or 4 in only about 6% of patients. This has also led to risk mitigation measures which is administration of steroids and diphenhydramine and acetaminophen prior to administering the doses. Now, this molecule is an extended half-life molecule. It is a larger molecule which requires only short infusions as opposed to other DART and BiTE strategies which require continues intravenous infusion. We have now been able to see responses in about 28% of patients, and in some of these patients their responses have been durable, lasting several months. Two patients have been able to proceed to an allogeneic stem cell transplant, a third patient was referred for transplant but was unable to undergo it due to an unrelated cardiomyopathy. Overall, this study further establishes the potential role of bispecific antibodies, at this time with the CD3, CD123 molecule, and clearly these agents will hopefully have a role in AML, particularly in the area of my interest, which is measurable or minimal residual disease where these agents can have a very significant role in the future.

Reference: Ravandi F, Bashey A, Foran J, et al. Complete Responses in Relapsed/Refractory Acute Myeloid Leukemia (AML) Patients on a Weekly Dosing Schedule of XmAb14045, a CD123 x CD3 T Cell-Engaging Bispecific Antibody: Initial Results of a Phase 1 Study. ASH 2018. Abstract 763.