with time to neutrophil recovery consistent with the NSG engraftment result.

Conclusion: In these studies, we demonstrate that the expanded CD34+ cell fraction of MGTA-456 contains large numbers of CD34+CD90+ HSC, which are critical for long term engraftment in NSG mice and correlated with rapid neutrophil recovery clinically.

4

Final Evaluation of a Clinical Phase III Trial Comparing Treosulfan to Busulfan-Based Conditioning Therapy Prior to Allogeneic Hematopoietic Stem Cell Transplantation of Adult Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients Ineligible to Standard Myeloablative Regimens

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Background: Allogeneic hematopoietic stem cell transplantation (HCT) remains a challenge in elderly and comorbid AML and MDS patients. This patient population is at increased risk for non-relapse mortality (NRM) when treated with standard myeloablative conditioning and was selected to compare a newly developed treosulfan-based with a well-established reduced intensity busulfan-based preparative regimen in a prospective randomized clinical phase III trial.

Methods: Adult patients with AML in remission or MDS scheduled for HCT from matched related or unrelated donors, aged ≥50 years or with a comorbidity index (HCT-CI) of >2 were enrolled by a central stratified randomization procedure. Treatment arms consisted of intravenous (IV) treosulfan (10 g/m^2/day [d-4 to d-2]) or IV busulfan (3.2 mg/kg/day [d-4 to d-3]), both combined with IV fludarabine (30 mg/m^2/day [d-6 to d-2]). The primary objective was to compare event-free survival (EFS) at two years with relapse/progression of disease, graft failure, or death reported as events. Secondary endpoints were safety evaluation (according to CTCAE v4.03), engraftment, chimerism, overall survival (OS), relapse/progression incidence (RI), NRM and acute or chronic GvHD. After a previously conducted confirmatory interim analysis (based on 476 patients), which resulted in early termination of patient accrual due to significant non-inferiority of treosulfan treatment with improved EFS, NRM and OS (Beelen et al., ASH 2017), results of the final analysis of all 570 randomized patients including post surveillance data are provided here.

Results: Median age of the 551 patients (352 AML; 199 MDS) included in the full analysis set (268 treosulfan; 283 busulfan) was 60 years (range: 31, 70). Frequencies of early adverse events (d-6 to d+28) and incidences of acute and chronic GvHD were largely comparable between the two regimens, while extensive chronic GvHD was numerically in favor of treosulfan (19.7% vs. 26.7%; p=0.0750). Primary neutrophil recovery at day +28 was comparable, while the rate of complete donor-type chimerism (day +28) was higher after treosulfan (93.2% vs. 83.3%; p<0.0001). After a median follow-up of 29 months (range: 3.0, 54.3) the 2-year EFS was significantly higher in the treosulfan arm (65.7% vs. 51.2%; hazard ratio [HR] 0.64; p=0.0012) as was OS (72.7% vs. 60.2%; HR 0.64; p=0.0037) and NRM (12.0% vs. 20.4%; HR 0.63; p=0.0343). RI was comparable between both regimens (22.0% vs. 25.2%; HR 0.82; p=0.2631). Results were consistent within all pre-defined major prognostic subgroups of patients.

Conclusions: Final evaluation of this phase III trial substantiates the previous confirmatory analysis resulting in significantly improved survival after treosulfan-based conditioning. Due to the reduction of NRM a major clinical benefit of the new treosulfan conditioning regimen was demonstrated in the selected AML/MDS patient population.