4. SPECIAL CONDITIONS

DARATUMUMAB MONOTHERAPY VERSUS ACTIVE MONITORING IN PATIENTS WITH HIGH-RISK SMOLDERING MULTIPLE MYELOMA: "AQUILA" OUTCOMES BASED ON MAYO 2018/IMWG 2020 RISK STRATIFICATION, IMWG 2020 PLUS CYTOGENETIC CRITERIA, AND AGE

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Introduction. Patients with high-risk smoldering multiple myeloma (SMM) may benefit from early treatment. With SMM risk stratification advancement, post hoc analysis of the AQUILA study using IMWG 2020 ("20/2/20") and other risk models was conducted to assess which patients benefited most from daratumumab. Safety and efficacy analysis by age and stem cell collection outcomes were also assessed.

Methods. Patients with confirmed high-risk SMM per IMWG 2014 criteria were randomized to receive subcutaneous daratumumab or active monitoring for 39 cycles, 36 months, or until confirmed disease progression, whichever came first. Primary endpoint was progression-free survival (PFS); secondary endpoints included time to 1L treatment and overall survival. Outcomes were assessed by age, IMWG 2020 high-risk SMM criteria, and IMWG 2020 plus cytogenetic criteria.

Results. Daratumumab showed PFS benefit across all IMWG 2020 subgroups (low-risk: HR=0.59; intermediate-risk: HR=0.70), with largest benefit in the high-risk subgroup; disease progression/death rate with active monitoring was ~1.6-fold greater than daratumumab (62.8% vs 37.5%; HR=0.36). Daratumumab benefit was durable, with 5-year PFS rates of 78.2% vs 71.6%, 56.2% vs 42.9%, and 60.4% vs 23.6% in IMWG 2020 low-, intermediate-, and high--risk groups, respectively. A favorable trend for daratumumab in time to 1L treatment was seen across all IMWG 2020 risk groups (low-risk HR=0.63; 95% CI, 0.22–1.80; intermediate-risk HR=0.57; 95% CI, 0.35–0.92; high-risk HR=0.39; 95% CI, 0.25–0.62). PFS benefit occurred regardless of age, in younger (<65y HR, 0.51; 95% CI, 0.32–0.79) vs older (≥65y, HR=0.50; 95% CI, 0.32–0.77) patients. Treatment-emergent adverse event (TEAE) incidence was consistent within <65, 65 to <75, and ≥75 year subgroups (82.7%, 81.1%, and 87.5% with active monitoring; 96.2%, 98.5%, and 95.2% with daratumumab). Serious TEAEs were more frequently observed in older active monitoring patients (12.2%, 18.9%, and 50.0% with active monitoring; 24.8%, 35.8%, and 28.6% with daratumumab). In daratumumab and active monitoring arms respectively, 23 (11.9%) and 41 (20.9%) patients received autologous stem cell transplant after active MM progression, with limited plerixafor use (daratumumab, 3 [1.6%] vs active monitoring, 9 [4.6%]). Median (range) CD34+ cell yield was 5.0 (2–20)×10^6 cells/kg body weight among 22 patients in the daratumumab arm and 5.1 (2–21)×10^6 cells/kg body weight among 39 patients in the active monitoring arm.

Conclusions. Patients receiving daratumumab experienced long-term PFS benefit across IMWG 2020 subgroups, with the largest benefit for high-risk patients. No notable differences in PFS or safety were observed across age subgroups. Early daratumumab treatment for high-risk SMM did not have a detrimental impact on stem cell yield. These results support early intervention with daratumumab monotherapy among patients with high-risk SMM.