Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Overall Survival in Alcyone

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Introduction:

Daratumumab (DARA) is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action. The addition of DARA to standard-of-care regimens in phase 3 studies reduced the risk of disease progression or death by ≥44%, nearly doubled the rate of complete response or better, and induced a ≥3-fold increase in minimal residual disease (MRD)-negativity rates versus standard of care alone in patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM) and relapsed/refractory multiple myeloma. In the primary analysis of the phase 3 ALCYONE study (median follow-up: 16.5 months), a significant progression-free survival (PFS) benefit (median not reached vs 18.1 months; hazard ratio [HR], 0.50; $P<0.001$) was observed with the addition of DARA to bortezomib/melphalan/prednisone (D-VMP) in patients with transplant-ineligible NDMM, without an increase in overall toxicity (Mateos MV, et al. *N Engl J Med*. 2018;378[6]:518-528). D-VMP continued to demonstrate a significant PFS benefit versus VMP alone after 1 year of additional follow-up, including in patients ≥75 years of age (Dimopoulos MA, et al. *Blood*. 2018;132[Suppl 1]:156). After a median follow-up of 27.8 months, D-VMP reduced the risk of disease progression or death by 57% versus VMP alone, with a 24-month PFS rate of 63% in the D-VMP group and 36% in the VMP group. This PFS benefit was observed regardless of patient age and was maintained during the subsequent line of therapy in patients with transplant-ineligible NDMM. Here, we present >36 months of follow-up from ALCYONE, including analysis of overall survival (OS) from a prespecified interim analysis.

Methods*:*

Patients with NDMM ineligible for high-dose chemotherapy and autologous stem cell transplantation due to age (≥65 years) or comorbidities were randomized 1:1 to receive up to nine 6-week cycles of VMP (bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and Days 1, 8, 22, and 29 of Cycles 2-9; melphalan 9 mg/m^2 orally and prednisone 60 mg/m^2 orally on Days 1-4 of Cycles 1-9) with or without DARA (16 mg/kg intravenously once weekly for Cycle 1, once every 3 weeks for Cycles 2-9, and once every 4 weeks for Cycles 10+ until disease progression). The primary endpoint was PFS. Secondary endpoints included overall response rate, rate of complete response or better, rate of very good partial response or better, MRD-negativity rate (10^{-5} threshold), PFS on subsequent line of therapy (PFS2), OS, and safety.

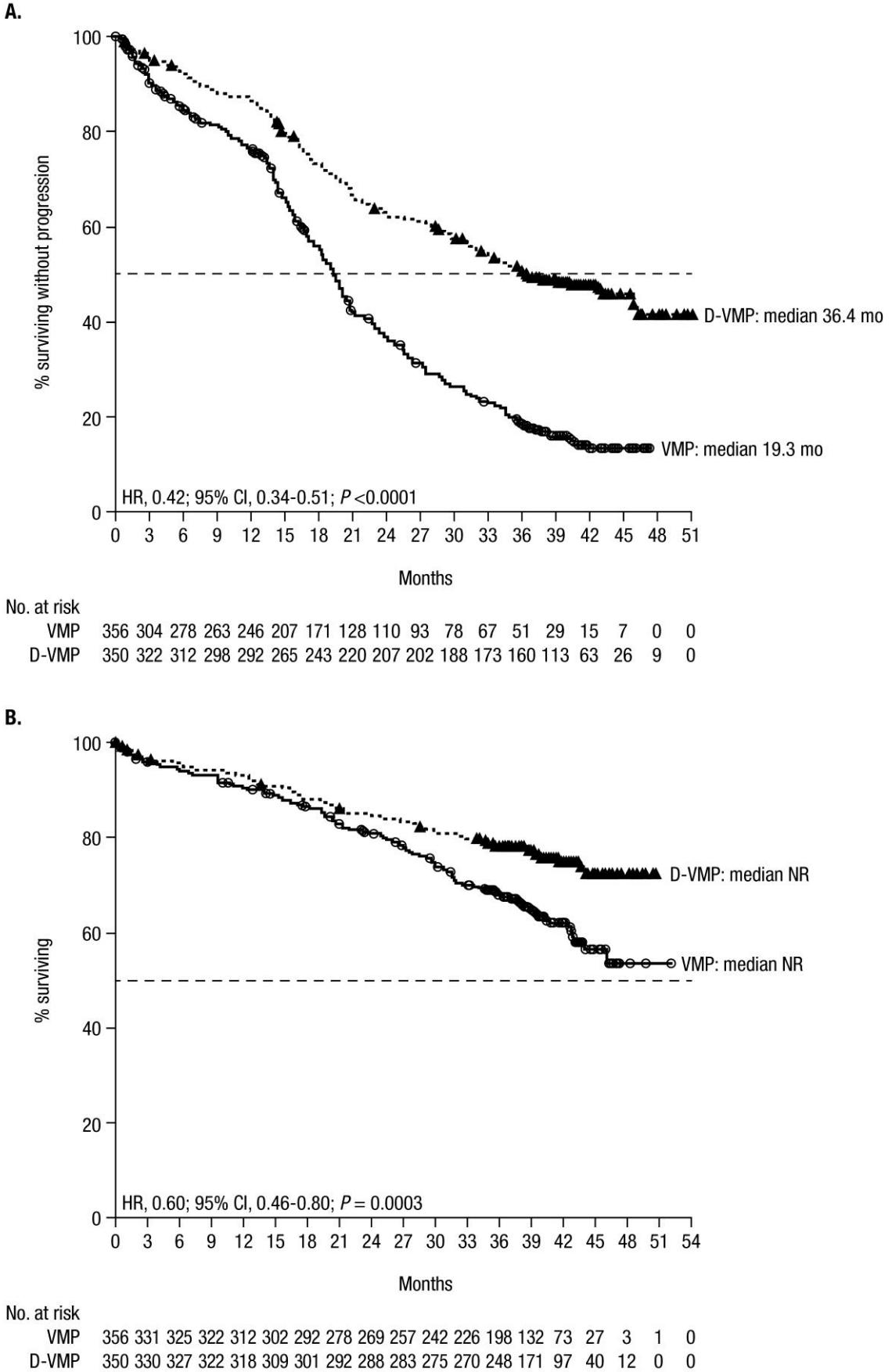
Results*:*

A total of 706 patients were enrolled in this study (D-VMP: n = 350; VMP: n = 356). Patient baseline characteristics were well balanced between treatment arms. The median (range) age was 71 (40-93) years, and 29.9% of patients were ≥75 years of age. 518 (84.1%) and 98 (15.9%) of 616 patients evaluated had standard and high (del17p, t[14;16], and/or t[4;14] positive) cytogenetic risk, respectively, as assessed via local fluorescence in-situ hybridization/karyotyping. Median PFS was 36.4 months with D-VMP versus 19.3 months with VMP after a median follow-up of 40.08 months (HR, 0.42; 95% confidence interval [CI], 0.34-0.51; P <0.0001; *Figure A*). Median PFS2 was not reached with D-VMP versus 42.3 months with VMP (HR, 0.55; 95% CI, 0.43-0.71; P <0.0001). The estimated 36-month OS rate was 78% with D-VMP versus 68% with VMP, with a significant benefit for OS observed for D-VMP versus VMP alone (HR, 0.60; 95% CI, 0.46-0.80; P = 0.0003; *Figure B*); median OS was not reached in either group and follow-up is ongoing. Additional efficacy data, including MRD negativity, and updated safety data will be presented at the meeting.

Conclusions:

For the first time, we demonstrate that the addition of DARA to VMP prolongs OS in patients with transplant-ineligible NDMM, with a 40% reduction in the risk of death versus VMP alone after a median follow-up of 40 months. D-VMP continued to demonstrate a significant PFS benefit, which was also maintained during the subsequent line of therapy. These findings, together with the phase 3 MAIA study (DARA plus lenalidomide/dexamethasone vs lenalidomide/dexamethasone), continue to support the addition of DARA to frontline treatment regimens in patients with transplant-ineligible NDMM.

Figure: Progression-free survival (A) and overall survival (B) with D-VMP and VMP.



D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; HR, hazard ratio; CI, confidence interval; NR, not reached.