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DARATUMUMAB MAINTENANCE VS OBSERVATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH BORTEZOMIB, THALIDOMIDE, AND DEXAMETHASONE ± DARATUMUMAB AND ASCT: CASSIOPEIA PART 2 RESULTS

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

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Background: Daratumumab in conjunction with bortezomib, thalidomide, and dexamethasone (D-VTd) and autologous stem cell transplantation (ASCT) is approved for the treatment of transplant-eligible patients with newly diagnosed multiple myeloma (NDMM) based on results from CASSIOPEIA part 1.

Aims: To assess daratumumab maintenance vs observation (OBS) in patients with partial response or better (≥PR) in part 1, regardless of induction/consolidation treatment (CASSIOPEIA part 2 prespecified interim analysis).

Methods: CASSIOPEIA is a 2-part, open-label, randomized, phase 3 study in transplant-eligible patients with NDMM. Written informed consent was obtained from all patients. In part 1, patients received 4 cycles of induction and 2 cycles of consolidation with D-VTd or VTd alone. All responders in part 1 (≥PR; n=886) were rerandomized in part 2 to receive maintenance (intravenous daratumumab 16 mg/kg every 8 weeks for ≤2 years [n=442]) or OBS (n=444) until disease progression (IMWG criteria). Patients were stratified by induction (D-VTd vs VTd) and depth of response (minimum residual disease [MRD] status and ≥PR post consolidation). Progression-free survival (PFS) after rerandomization was the primary endpoint. The efficacy and safety were assessed after 281 PFS events. Key secondary endpoints (preplanned hierarchical order) were time to progression, complete response or better (≥CR), MRD negativity rates by next-generation sequencing, and overall survival (OS).

Results: Median PFS was not reached with daratumumab vs 46.7 months for OBS (median follow up, 35.4 months; hazard ratio [HR] 0.53 [95% CI 0.42–0.68]; $P<0.0001$). Daratumumab showed consistent PFS advantage across most subgroups, except for a significant interaction with induction/consolidation treatment arm ($P<0.0001$; prespecified analysis). The daratumumab vs OBS PFS HR was 0.32 (95% CI 0.23–0.46) in the VTd arm and 1.02 (0.71–1.47) in the D-VTd arm. The median time to progression was not reached for daratumumab vs 46.7 months for OBS (HR 0.49 [0.38–0.62]; $P<0.0001$). Compared with OBS, more patients with daratumumab maintenance achieved ≥CR (60.8% vs 72.9%; odds ratio [OR] 2.17 [1.54–3.07]; $P<0.0001$). In patients with ≥CR at 10^{-5}, the MRD negativity rate was 58.6% with daratumumab maintenance vs 47.1% with OBS (OR 1.80 [1.33–2.43]; $P=0.0001$). Median OS was not reached in either arm. Most common (≥2.5%) grade 3/4 adverse events (AEs) reported with daratumumab maintenance vs OBS were lymphopenia (3.6% vs 1.8%), hypertension (3.0% vs 1.6%), and pneumonia (2.5% vs 1.4%). Serious AEs were reported in 22.7% of patients with daratumumab maintenance vs 18.9% with OBS; the most common (≥2.5%) being pneumonia (2.5% vs 1.6%). Thirteen patients (3.0%) discontinued daratumumab due to an AE. The rate of infusion-related reactions (90% were grade 1/2) was 54.5% in daratumumab-naive patients and 2.2% in daratumumab-pretreated patients. Second primary malignancies occurred in 5.5% of patients with daratumumab maintenance vs 2.7% with OBS.

Summary/Conclusion: CASSIOPEIA part 2 interim analysis showed a significantly longer PFS with daratumumab maintenance vs OBS in transplant-eligible patients with NDMM. The maintenance PFS benefit appeared only in patients treated with VTd as induction/consolidation. Patients who received D-VTd induction/consolidation ± daratumumab maintenance achieved similar PFS; longer follow up is needed for OS and PFS2. Compared with OBS, daratumumab maintenance significantly increased deeper response and MRD negativity rates, and it was well tolerated with no new safety signals.

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