MultipleMyelomaHub

Relapsed/refractory patients

The CASTOR Clinical trial for daratumumab in combination with bortezomib and dexamethasone

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In August 2016, Antonio Palumbo from the Department of Hematology in Turin, Italy, and a wide group of collaborators, published the findings of the CASTOR clinical trial - to assess the efficacy of daratumumab on a background treatment of bortezomib and dexamethasone – in the *New England Journal of Medicine*. This study built upon the previous success of daratumumab as a monotherapy in patients with newly diagnosed multiple myeloma (NDMM). In the CASTOR phase 3, open-label trial, 498 patients with relapsed or relapsed and refractory MM, were recruited between September 2014 and September 2015, at 115 centers in 16 countries. The primary end point was progression free survival (PFS); secondary end points were time to disease progression (TTP), overall response (OR) rate, the proportion of patients who achieved very good partial response (PR) or better and duration of response, time to response, and overall survival (OS).

Treatment:

- Patients were given up to 8 cycles (21 days per cycle) of bortezomib (dosing schedule based on the pivotal SUMMIT trial18) and dexamethasone.
- Daratumumab was administered intravenously once per week at a dose of 16 mg/kg:
  - Cycles 1-3: on days 1, 8, and 15,
  - Cycles 4 to 8: once every 3 weeks on day 1
  - Cycle 9 onwards: once every 4 weeks until the patient withdrew consent, the disease progressed, or unacceptable toxic effects developed
- Bortezomib was administered subcutaneously at a dose of 1.3 mg/m^2: Cycles 1-8: on days 1, 4, 8, and 11
- Dexamethasone was administered orally or intravenously at a dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12, for a total dose of 160 mg per cycle
- Dexamethasone could be reduced to 20 mg/week for patients who were 75 years or older, had a BMI < 18.5, or had previous unacceptable side effects associated with glucocorticoid therapy
- Median age of the patients was 64 years (range, 30 to 88)

Key Findings:

- All data is given in the order daratumumab group (251 pts) *vs* control group (247):
- Median follow-up period = 7.4 months
- Events of disease progression or death = 67 *vs* 122
- Rate of PFS (12-month): 60.7% (95% confidence interval [CI], 51.2 to 69.0) *vs* 26.9% (95% CI, 17.1 to 37.5)

- Median PFS = not reached (95% CI, 12.3 to not estimable) *vs* 7.2 months (95% CI, 6.2 to 7.9)
- HR for disease progression or death with daratumumab *vs* control = 0.39; 95% CI, 0.28 to 0.53; P<0.001
- Patients who were free from disease progression after 12 months = 65.4% (95% CI, 56.1 to 74.8) *vs* 28.8% (95% CI, 17.8 to 39.8)
- HR for disease progression = 0.30; 95% CI, 0.21 to 0.43; P<0.001
- ORR = 82.9% *vs* 63.2% (P<0.0001)
- PR or better = 59.2% *vs* 29.1% (P<0.001)
- CR or better = 19.2% *vs* 9.0% (P= 0.001)
- Similar results were observed in the ITT population
- Median time to the first response = 0.9 months *vs* 1.6 months
- Median duration of response = not reached (95% CI, 11.5 months to not estimable) *vs* 7.9 months (95% CI, 6.7 to 11.3)
- Sub-group analysis confirmed the overall benefit of daratumumab:
    - Patients with ISS stage I disease (HR for progression or death with daratumumab vs. control = 0.25)
    - Patients that received one previous therapy: 12-month PFS = 77.5% (95% CI, 65.2 to 86.0) *vs* 29.4% (95% CI, 12.5 to 48.7); HR = 0.31; 95% CI, 0.18 to 0.52; P<0.001
    - Patients who had received two or three previous lines of therapy: median PFS = 9.3 months (95% CI, 7.6 to not estimable) *vs* 6.5 months (95% CI, 5.7 to 8.1); HR = 0.52; 95% CI, 0.33 to 0.81; P=0.004
- Following the interim analysis, daratumumab monotherapy was offered to patients in the control group who had disease progression (as the pre-specified statistical boundary for PFS had been crossed)
- PFS 2 (TTP or death while patients were receiving the next line of therapy) = not reached
- Events of progression or death (while receiving the next line of therapy) = 31 *vs* 49; HR = 0.57; 95% CI, 0.37 to 0.90
- Deaths during study = 29 *vs* 36; HR = 0.77; 95% CI, 0.47 to 1.26

Safety Analysis:

- Grade 3 or 4 AEs: 76.1% *vs* 62.4%
- Thrombocytopenia: 45.3% *vs* 32.9%; Anemia: 14.4% vs. 16.0%; Neutropenia: 12.8% *vs* 4.2%
- Hematologic AEs: any grade of thrombocytopenia (58.8% vs. 43.9%), neutropenia (17.7% *vs* 9.3%), and lymphopenia (13.2% *vs* 3.8%)
- Nonhematologic AEs: any grade of peripheral sensory neuropathy (47.3% *vs* 37.6%), grade 3 or 4 peripheral sensory neuropathy (4.5% *vs* 6.8%)
- Grade 3 or 4 infections and infestations: 21.4% *vs* 19.0%
- Bleeding events of any grade: 7.0% *vs* 3.8%
- Rates of secondary primary cancers: 2.5% *vs* 0.4% (most developed within the 6 months after trial initiation and occurred in patients with previous exposure to immunomodulatory drugs and alkylating agents)

- Discontinuation due to AEs: 7.4% *vs* 9.3%
- Infusion-related reactions for daratumumab = 45.3%, but 98.2% occurred during the first infusion.

Distinct benefits in PFS were observed for the use of daratumumab in combination with bortezomib and dexamethasone (61.4% reduction in risk of disease progression), compared to treatment with bortezomib and dexamethasone alone. Responses were durable, extended into the next treatment phase and gave patients longer periods of remission. In general, daratumumab was associated with higher rates of thrombocytopenia and neutropenia and reactions to the infusion (usually for the first dose), but overall was well tolerated. This was similar to the POLLUX https://clinicaltrials.gov/ct2/show/NCT02076009 study, which assessed the efficacy of daratumumab in a triple therapy regimen with a backbone of bortezomib and dexamethasone (see MM Hub article). Data from this study led to a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), recommending the use of daratumumab in combination with bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy. This extended the previously approved indication for use as a monotherapy in RRMM patients, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and demonstrated disease progression on the last therapy.

References

1. Palumbo A.*et al.* Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Aug 25;375(8):754-66.DOI:10.1056/NEJMoa1606038.
2. Comment in: Progress in Myeloma - A Monoclonal Breakthrough. [N Engl J Med. 2016]