MultipleMyelomaHub

Relapsed/refractory patients

Pivotal MM-003 trial to compare pomalidomide in combination with high or low-dose dexamethasone

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The MM-003 clinical trial carried out by Jesus San Miguel, Meletios Dimopoulos and colleagues, compared the efficacy of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone, in patients with refractory Multiple Myeloma (MM) who had failed therapy with both bortezomib and lenalidomide, administered either alone or in combination. This randomized phase 3 trial was carried out in 93 centres worldwide and enrolled 455 patients between March 2011 and August 2012 and the results were published in Lancet Oncology in October 2013. The primary endpoint was progression-free survival (PFS) and the key secondary endpoint was overall survival (OS). Other secondary endpoints were overall response rate (ORR), time to progression (TTP), duration of response (DR), safety, and quality of life. Analysis was carried out on the intention to treat (ITT) population.

Study Design

- Pts were assigned in a 2:1 ratio to one of two groups: pomalidomide plus low-dose dexamethasone (POM+LoDEX) or pomalidomide plus high-dose dexamethasone (POM+HiDEX)
- Oral pomalidomide - 4 mg on days 1-21 of each 28-day cycle
- POM+LoDEX (302 pts):
  - oral dexamethasone - 40mg/day on days 1, 8, 15, and, 22
- POM+HiDEX (153 pts):
  - oral dexamethasone - 40mg/day on days 1-4, 9-12, and 17-20
  - dex was reduced to 20mg/day in pts older than 75 years

Key Findings

- Data cut-off (Sept 7th, 2012) = 267 PFS events had occurred; deaths = 134
- Primary endpoint was met and upper boundary for superior OS achieved
- Data points are given as: POM+LoDEX *vs* POM+HiDEX
- Pts discontinued study at interim analysis: 242 pts (80%) *vs* 142 (93%)
- Median follow-up at 4.2 months (IQR 2.0–7.1) (Final PFS and interim OS):
  - median PFS = 3.8 months (95% CI 3.4–4.6) *vs* 1.9 months (95% CI 1.9–2.1); p<0.0001; HR= 0.41 (0.32–0.53); (p<0.001)
  - OS = 11.9 months (95% CI 10.4–15.5) *vs* 7.8 months (95% CI 6.4–9.2); 0.53 (0.37–0.74); p=0.0002

- Median follow-up 10.0 months (IQR 7.2-13.2) (Updated PFS and final OS):
    - PFS = 4.0 months (95% CI 3.6–4.7] *vs* 1.9 months [1.9–2.2]; HR = 0.48 (95% CI 0.39–0.60); p<0.0001;

Subgroup Analysis

- refractory to lenalidomide: 3.9 months [3.5–4.6] *vs* 1.9 months [1.9–2.2]; p<0.0001)
- refractory to both bortezomib and lenalidomide: 3.7 months (3.0-4.6) *vs* 2.0 months (1.9-2.2); p<0.0001)
- intolerant to bortezomib: 4.0 months (2.8-6.7) *vs* 2.0 months (1.9-3.7); p=0.0073
- lenalidomide as last treatment: 4.6 (3.5-6.0) *vs* 1.9 (1.1-2.5)
- bortezomib as last treatment: 3.8 months (2.8-4.9) *vs* 1.9 months (1.8-2.6); p<0.0001
- Final OS = 12.7 months [95% CI 10.4–1.5] *vs* 8.1 months [6.9–10.8]; HR = 0.74 (0.56–0.97]; p=0・0285
    - refractory to lenalidomide: 12.7 months (10.4-15.5) *vs* 8.0 months (6.4-10.1); p=0.0234
    - lenalidomide as last treatment: 12.3 months (9.8-16.4) *vs* 7.3 months (4.5-10.1); p=0.0097
    - No significant differences between pts refractory to both lenalidomide and bortezomib

- TTP = 4.7 months (95% CI, 4.0-6.0) *vs* 2.1 months (1.9-2.5); HR = 0.46 (0.36-0.59) p<0.0001
- ORR (at 10 months follow-up) = 31% *vs* 10% (odds ratio (OR) = 4.22 (2.35–7.58) p<0.0001
- pts with at least partial response, median response duration = 7.0 months (5.8–9.0) *vs* 6.1 months (1.4–8.5); HR = 0.52 (0.25–1.05); p=0.0631
- OR subgroup analysis:
    - refractory to lenalidomide: 30% *vs* 9%; OR= 4.16 (2.13-7.77); p<0.0001
    - intolerant to bortezomib: 31% *vs* 13%; OR = 3.01 (0.77-11.82); p=0.1423
    - refractory to both bortezomib and lenalidomide: 28% *vs* 12%; p=0.0003
    - lenalidomide as last treatment: 33% *vs* 6%; p=0.0003
    - bortezomib as last treatment: 34% *vs* 12%; p=0.0011

Safety

- Discontinuation due to treatment-related AEs: 4% *vs* 6%
- Grade 3-4 hematologic toxicities: neutropenia (48% *vs* 16%); anemia (33% *vs* 37%); thrombocytopenia (22% *vs* 26%)
- Other toxicities (grade 3-4): pneumonia (13% *vs* 8%); infections (30% *vs* 24%); fatigue (5% *vs* 6%); bone pain (7% *vs* 5%)
- Treatment-related deaths = 4% *vs* 5%

The results from the interim analysis provided key data to recommend the use of with pomalidomide plus low dose dexamethasone in this patient set, as it was associated with significantly longer PFS and OS, when compared with high-dose dexamethasone. Data from this trial was critical in gaining approval by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for the use of pomalidomide (in combination with dexamethasone) to treat MM

patients who have received at least two prior therapies, including both lenalidomide and bortezomib, and whose disease progressed after the last treatment. Several sub-group analyses of this trial have since been published (see other MM Hub articles).

References

1. San Miguel J. *et al*. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-66. DOI: 10.1016/S1470-2045(13)70380-2. Epub 2013 Sep 3.