MultipleMyelomaHub

Relapsed/refractory patients

Sub-group analysis of the PANORAMA-1 Trial: panobinostat plus bortezomib and dexamethasone by prior MM treatment

Fiona Chaplin | Mar 02, 2017

The PANORAMA-1 trial was a randomized, double-blind phase-3 study to assess the efficacy of a triple drug regimen of panobinostat, bortezomib and dexamethasone, in patients with relapsed, or relapsed and refractory, Multiple Myeloma (MM). In a sub-group analysis of this trial, Paul G. Richardson from the Dana-Faber Cancer Institute and collaborators, assessed the effect of this triplet drug regiment according to the number of prior treatments received, and published their findings in the February 2016 edition of Blood. Patients were randomly assigned into two treatment groups: panobinostat, bortezomib and dexamethasone (PAN-BTZ-Dex) or placebo, bortezomib and dexamethasone (Pbo-BTZ-Dex). The study design is summarized in a previous MMHub article.

Key Findings:

- Pts enrolled:
  - pts that received prior IMiD (Immunomodulatory drugs) = 485 (PAN-BTZ-Dex, n = 245; Pbo-BTZ-Dex, n = 240)
  - pts that received prior BTZ plus IMiD = 193 (PAN-BTZ-Dex, n = 94; Pbo-BTZ-Dex, n = 99)
  - pts that received ≥2 prior regimens including BTZ and an IMiD = 147 (PAN-BTZ-Dex, n = 73; Pbo-BTZ-Dex, n = 74)
- All data are given as PAN-BTZ-Dex *vs.* Pbo-BTZ-Dex:
- Median PFS:
  - prior IMiD: 12.3 months *vs.* 7.4 months; HR = 0.54 (95% CI, 0.43-0.68)
  - prior BTZ plus IMiD: 10.6 months *vs.* 5.8 months; HR = 0.52 (95% CI, 0.36-0.76)
  - prior regimens (≥2 including BTZ and an IMiD): 12.5 months *vs.* 4.7 months; HR = 0.47 (95% CI, 0.31-0.72)
  - no prior exposure to BTZ: 12.6 months *vs.* 9.2 months; HR = 0.69; (95% CI, 0.53-0.88)
  - no prior history of IMiDs: 11.4 months *vs.* 12.0 months; HR = 0.78; (95% CI, 0.57-1.08)
- nCR/CR rate:
  - prior regimens (≥2, including BTZ and an IMiD): 21.9% (95% CI, 13.1-33.1) *vs.* 8.1% (95% CI, 3.0-16.8)
- Response duration:
  - prior BTZ plus an IMiD: 11.99 months (95% CI, 9.69-13.90) *vs.* 8.31 months (95% CI, 6.14-12.32)
  - prior regimens (≥2, including BTZ and an IMiD): 11.99 months (95% CI, 9.69-13.37) vs. 6.97 months (95% CI, 4.86-13.40).
- Safety:
  - Dose changes and delays were mostly due to AEs

- Treatment Free Interval (TFI, calculated as Mean PFS – Mean treatment duration):
  - Pbo-BTZ-Dex was lower than PAN-BTZ-Dex across all groups
  - prior regimens (≥2, including BTZ and an IMiD): 4.69 months *vs.* 1.92 months
- Safety profile of PAN-BTZ-Dex was similar among prior treatment subgroups
- Grade 3/4 diarrhea:
  - prior IMiD = 26.1% *vs.* 7.9%
  - prior bortezomib plus IMiD = 30.4% *vs.* 13.1%
  - prior regimens (≥2 including bortezomib and an IMiD = 33.3% *vs.* 15.1%
- Grade 3/4 thrombocytopenia:
  - prior IMiD: 61% *vs.* 36%
  - prior BTZ plus IMiD: 68.5% *vs.* 48.0%
  - ≥2 prior regimens including BTZ and an IMiD: 68.1% *vs.* 44.4%
- Treatment-related deaths (or up to 28 days after treatment) prior IMiD: n = 17; 7.1% *vs.* n = 10; 4.2%
- Deaths due to other causes (primarily AEs): n = 14 *vs.* n = 6

This study confirmed that the addition of panobinostat - a potent oral pan-deacetylase inhibitor – to the regimen of bortezomib plus dexamethasone, leads to a specific PFS of 7.8 months among patients that have been heavily treated and for whom obvious therapeutic avenues are largely exhausted (those who have received ≥ 2 prior treatment regimens). Increased median PFS was also observed across all previous treatment groups, suggesting a benefit of panobinostat in general to this drug regimen. Indeed, data from the PANORAMA-1 study was used to support approval of panobinostat (for use in combination with bortezomib and dexamethasone, for the treatment of patients who have received ≥ 2 prior treatments), by the US FDA and the EMA.

Abstract

Panobinostat is a potent pan-deacetylase inhibitor that affects the growth and survival of multiple myeloma (MM) cells through alteration of epigenetic mechanisms and protein metabolism. Panobinostat plus bortezomib and dexamethasone (PAN-BTZ-Dex) led to a significant increase in progression-free survival (PFS) vs placebo plus bortezomib and dexamethasone (Pbo-BTZ-Dex) in patients with relapsed or relapsed and refractory MM in the phase 3 PANORAMA 1 trial. This subgroup analysis evaluated outcomes in patients in the PANORAMA 1 trial based on prior treatment: a prior immunomodulatory drug (IMiD; n = 485), prior bortezomib plus an IMiD (n = 193), and ≥2 prior regimens including bortezomib and an IMiD (n = 147). Median PFS with PAN-BTZ-Dex vs Pbo-BTZ-Dex across subgroups was as follows: prior IMiD (12.3 vs 7.4 months; hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.43-0.68), prior bortezomib plus IMiD (10.6 vs 5.8 months; HR, 0.52; 95% CI, 0.36-0.76), and ≥2 prior regimens including bortezomib and an IMiD (12.5 vs 4.7 months; HR, 0.47; 95% CI, 0.31-0.72). Common grade 3/4 adverse events and laboratory abnormalities in patients who received PAN-BTZ-Dex across the prior treatment groups included thrombocytopenia, lymphopenia, neutropenia, diarrhea, and asthenia/fatigue. Incidence of on-treatment deaths among patients who received prior bortezomib and an IMiD (regardless of number of prior regimens) was similar between treatment arms. This analysis demonstrated a clear PFS benefit of 7.8 months with PAN-BTZ-Dex among patients who received ≥2 prior regimens including bortezomib and an IMiD, a population with limited treatment options and poorer prognosis. This trial was registered at www.clinicaltrials.gov as #NCT01023308.

References

1. Richardson PG. *et al.* Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. Blood. 2016 Feb 11;127(6):713-21. DOI: 10.1182/blood-2015-09-665018. Epub 2015 Dec 2.
