MultipleMyelomaHub

Relapsed/refractory patients

PANORAMA-1 study to assess efficacy of panobinostat in combination with dexamethasone and bortezomib

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The PANORAMA-1 trial was a pivotal study to assess the efficacy of panobinostat (a potent oral pan-deacetylase inhibitor) in combination with dexamethasone and bortezomib. Between January 2010 and February 2012, 768 patients (with relapsed or relapsed and refractory (R/R) Multiple Myeloma (MM), with one to three previous treatments) were recruited. Patients (pts) were randomly assigned (1:1) into one of two groups receiving panobinostat (n=387) or placebo (n=381), plus bortezomib and dexamethasone, and were stratified according to the number of previous treatments. The results of the study, conducted by Jesús F. San-Miguel and collaborators, were published in Lancet Oncology in October 2014. The primary endpoint was progression-free survival (PFS) and overall survival (OS) was a secondary endpoint.

Treatment

Two treatment phases were carried out:

- Phase 1: eight 3-week cycles, in which panobinostat (20 mg orally) or placebo was administered three times a week for the initial two weeks of every cycle (days 1, 3, 5, 8, 10, and 12) and bortezomib (1.3 mg/m^2 intravenously) on days 1, 4, 8, and 11, with dexamethasone (20 mg orally) on days 1, 2, 4, 5, 8, 9, 11, and 12
- Patients (pts) were allowed to continue to phase 2 if they showed no change per modified EBMT criteria
- Phase 2: four 6-week cycles of a '2 weeks on, 1 week off' rotation for all drugs. Consistent dosing of panobinostat continued, while bortezomib was given once a week on day 1 and dexamethasone on days 1 and 2

Key Findings

All data are given as panobinostat group *vs* placebo group:

- Median duration of treatment = 5.0 months (IQR 2.23–10.75) *vs* 6.1 months (2.82–10.75)
- Treatment termination due to adverse events (AEs): 34% *vs* 17%
- Treatment termination due to disease progression: 21% *vs* 40%
- Dose changes (in safety set):
  - panobinostat group: panobinostat = 51%, bortezomib = 61%, dexamethasone = 24%
  - placebo group: placebo = 23%, bortezomib = 42%, dexamethasone = 17%
- Median follow-up (at data cut-off for PFS analysis = Sept 10, 2013) was 6.47 months (IQR 1.81–13.47) *vs* 5.59 months (IQR 2.14–11.30); patients remain in follow-up for OS

- Median PFS (investigator review): 11.99 months [95% CI 10・33–12・94] *vs* 8.08 months (7.56–9.23]; HR = 0.63, 95% CI 0.52–0.76; p<0.0001; PFS as measured by independent assessment gave comparable data
- PFS (2 year): 20.6% (95% CI 15・4–26.4) *vs* 8.4% (5.1–12.7), although should be interpreted with caution as number of pts at risk at 2 years for PFS were fairly low (pan = 26; placebo = 12)
- PFS effect was observed across all pre-specified subgroups such as (pts with RRMM, stage II–III myeloma, aged ≥ 65 years and previously treated with bortezomib)
- Multivariate Cox model analysis for PFS: HR = 0.58, 95% CI 0.48–0.71; p<0.0001
- Deaths at data cut-off: total = 286 deaths; 35% *vs* 40%
- Median OS = 33.64 months (95% CI 31.34–not estimable) *vs* 30.39 months (26.87–not estimable); HR = 0.87, 95% CI 0.69–1.10; p=0.26; final OS data to be assessed when 415 deaths recorded (see MMHub article for update)
- Overall response (partial response or better): 60.7% (95% CI 55.7-65.6) *vs* 54.6% (95% CI 49.4-59.7)
- Median time to response (TTP): 1.51 (95% CI 1.41-1.64) *vs* 2.00 (95% CI 1.61-2.79) months
- Median time to first progression, relapse or death: 12.71 (95% CI 11.13-14.06) *vs* 8.54 (95% CI 7.66-9.72)
- Among patients who achieved at least near-complete response (CR), median PFS = 19.38 months (95% CI 15.90–26.61) *vs* 15.21 months (14.09–19.58)

Safety analysis set (n = 381 pts panobinostat and 377 pts placebo):

- Adverse events (AEs) occurred in ≥25% of patients in either treatment group
- Grade 3–4 AEs: 96% *vs* 82%
- Common grade 3–4 non-haematological AEs: diarrhoea, asthenia or fatigue, and peripheral neuropathy, all of which were more common for panobinostat *vs* placebo
- Grade 3–4 haemorrhage: 45% *vs* 2%
- Grade 3–4 haematological laboratory abnormalities more common for panobinostat *vs* placebo included: thrombocytopenia, lymphopenia, and neutropenia
- Serious AEs: 60% *vs* 42%
- Discontinuation due to:
  - AEs: 36% *vs* 20%
  - study drug: 24% *vs* 12%
  - Grade 3–4 AEs: 25% *vs* 13%
- Most common AEs leading to discontinuation:
  - panobinostat group: diarrhoea 4%, peripheral neuropathy 4%, asthenia or fatigue 6%, thrombocytopenia 2%, and pneumonia 1%
  - placebo group: fatigue 3%, pneumonia 2%, peripheral neuropathy 2%, and diarrhoea 2%
- Deaths during treatment: 8% *vs* 5%
- Deaths due to progressive disease: 4 pts *vs* 6 pts

- Treatment-related deaths: 11 *vs* 7

This study indicted a clear benefit of adding panobinostat to dexamethasone and bortezomib across all patient subgroups, and was pivotal in driving approval of this triplet drug regimen by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Updated results of this trial are reported in a separate MMHub article.

Abstract

Background
Panobinostat is a potent oral pan-deacetylase inhibitor that in preclinical studies has synergistic anti-myeloma activity when combined with bortezomib and dexamethasone. We aimed to compare panobinostat, bortezomib, and dexamethasone with placebo, bortezomib, and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma.

Methods
PANORAMA1 is a multicentre, randomised, placebo-controlled, double-blind phase 3 trial of patients with relapsed or relapsed and refractory multiple myeloma who have received between one and three previous treatment regimens. Patients were randomly assigned (1:1) via an interactive web-based and voice response system, stratified by number of previous treatment lines and by previous use of bortezomib, to receive 21 day cycles of placebo or panobinostat (20 mg; on days 1, 3, 5, 8, 10, 12, orally), both in combination with bortezomib (1·3 mg/m(2) on days 1, 4, 8, 11, intravenously) and dexamethasone (20 mg on days 1, 2, 4, 5, 8, 9, 11, 12, orally). Patients, physicians, and the investigators who did the data analysis were masked to treatment allocation; crossover was not permitted. The primary endpoint was progression-free survival (in accordance with modified European Group for Blood and Marrow Transplantation criteria and based on investigators' assessment) and was analysed by intention to treat. The study is ongoing, but no longer recruiting, and is registered at ClinicalTrials.gov, number NCT01023308.

Findings
768 patients were enrolled between Jan 21, 2010, and Feb 29, 2012, with 387 randomly assigned to panobinostat, bortezomib, and dexamethasone and 381 to placebo, bortezomib, and dexamethasone. Median follow-up was 6·47 months (IQR 1·81-13·47) in the panobinostat group and 5·59 months (2·14-11·30) in the placebo group. Median progression-free survival was significantly longer in the panobinostat group than in the placebo group (11·99 months [95% CI 10·33-12·94] vs 8·08 months [7·56-9·23]; hazard ratio [HR] 0·63, 95% CI 0·52-0·76; p<0·0001). Overall survival data are not yet mature, although at the time of this analysis, median overall survival was 33·64 months (95% CI 31·34-not estimable) for the panobinostat group and 30·39 months (26·87-not estimable) for the placebo group (HR 0·87, 95% CI 0·69-1·10; p=0·26). The proportion of patients achieving an overall response did not differ between treatment groups (235 [60·7%, 95% CI 55·7-65·6] for panobinostat vs 208 [54·6%, 49·4-59·7] for placebo; p=0·09); however, the proportion of patients with a complete or near complete response was significantly higher in the panobinostat group than in the placebo group (107 [27·6%, 95% CI 23·2-32·4] vs 60 [15·7%, 12·2-19·8]; p=0·00006). Minimal responses were noted in 23 (6%) patients in the panobinostat group and in 42 (11%) in the placebo group. Median duration of response (partial response or better) was 13·14 months (95% CI 11·76-14·92) in the panobinostat group and 10·87 months (9·23-11·76) in the placebo group, and median time to response (partial response or better) was 1·51 months (1·41-1·64) in the panobinostat group and 2·00 months (1·61-2·79) in the placebo group. Serious adverse events were reported in 228 (60%) of 381 patients in the panobinostat group and 157 (42%) of 377 patients in the placebo group. Common grade 3-4 laboratory abnormalities and adverse events (irrespective of association with study drug) included thrombocytopenia (256 [67%] in the panobinostat group vs 118 [31%] in the placebo group), lymphopenia (202 [53%] vs 150 [40%]), diarrhoea (97 [26%] vs 30 [8%]), asthenia or fatigue (91 [24%] vs 45 [12%]), and peripheral neuropathy (67 [18%] vs 55 [15%]).

Interpretation

Our results suggest that panobinostat could be a useful addition to the treatment armamentarium for patients with relapsed or relapsed and refractory multiple myeloma. Longer follow up will be necessary to determine whether there is any effect on overall survival.

References

1. San-Miguel JF. *et al.* Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1195-206. DOI: 10.1016/S1470-2045(14)70440-1. Epub 2014 Sep 18.