MultipleMyelomaHub

Patients eligible for transplant

ASH 2018 | Ixazomib maintenance for patients with newly diagnosed multiple myeloma: results from the Tourmaline-MM3 trial

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The 60th American Society of Hematology (ASH) Annual Meeting was held in San Diego, California, from 1–4 December 2018. On Sunday 2 December 2018, an oral abstract session was held entitled: *Myeloma: Therapy, excluding Transplantation: Novel Targeted Combinations in Myeloma*, which focused on updates of clinical trials using novel combination regimens for patients with multiple myeloma (MM).

Meletios A. Dimopoulos from the School of Medicine, Athens, Greece, presented results from the phase III Tourmaline-MM3 clinical trial.[1] This randomized, placebo-controlled study examined the safety and efficacy of maintenance therapy using the proteasome inhibitor (PI) ixazomib.

The rationale behind this study relies on the fact that lenalidomide, the approved immunomodulatory (IMiD) drug for maintenance therapy, results in treatment-emergent adverse events (AEs) in 29% of the treated patients. It is possible that a PI, which has a different mode of action to that of lenalidomide, may be better tolerated and may provide a more effective maintenance alternative, at least to a subgroup of patients.

The primary endpoint was progression-free survival (PFS) and the key secondary point, overall survival (OS). The results presented at ASH 2018 were recently published at *Lancet*.[2]

Results are presented as ixazomib maintenance *versus* (*vs*) placebo.

Study Design:

- Key inclusion criteria:
  - Induction therapy comprised of a PI and/or IMiD but not vincristine, doxorubicin, and dexamethasone (VAD)
  - A single autologous stem cell transplant (ASCT) with a high-dose melphalan 12 months prior to maintenance treatment
- Key exclusion criteria:
  - Patients relapsed or unresponsive to primary treatment
  - Double ASCT
  - Post-ASCT consolidation therapy
- Randomization = 3 *vs* 2

- Treatment: Given for up to 26 cycles or until disease progression (DP) or unacceptable toxicity; 28-day cycles
  - Cycles 1–4: Ixazomib, 3 mg orally on days 1, 8, and 15
  - Cycles 5–26: Ixazomib, 4 mg orally on days 1, 8, and 15
  - Placebo treatment given on days 1, 8, and 15

Key Data:

- Number of patients = 395 *vs* 261
- Age = 58 years (range, 24–73) *vs* 60 years (range, 37–73)
- International Staging System (ISS) stage: ISS I = 38% *vs* 36%; ISS II = 33% *vs* 35%; ISS III = 29% *vs* 29%
- Minimal residual disease (MRD) status at study entry, assessed by 8-color flow cytometry; sensitivity 10^{-5}:
  - Number of patients tested = 90% *vs* 87%
  - MRD-negative = 33% *vs* 33%
  - MRD-positive = 63% *vs* 61%
  - Not evaluable = 4% *vs* 6%
- Median follow-up = 31 months
- PFS = 26.5 months *vs*3 months (HR, 0.72; 95% confidence interval [CI], 0.582–0.89, $P = 0.002$); there was a significant 39% improvement in overall PFS from time of randomization for the ixazomib group compared to the placebo group
- PFS benefit was seen across subgroups of patients
- Median OS = Not reached for either group; 14% deaths reported
- Higher rates of deepened response in the ixazomib group compared to the placebo (relative risk, 1.41; 95% CI, 1.10–80, $P = 0.004$)
- Rate of conversion of MRD-positivity to negativity = 12% *vs* 7%
- Discontinuation due to AEs = 7% *vs* 5%
- AEs, grade ≥ 3 = 42% *vs* 26%
- Treatment-related AEs = 19% *vs* 5%
- Serious AEs = 27% *vs* 20%
- AEs resulting in dose reduction of the study drug = 19% *vs* 5%
- Common grade ≥ 3 AEs:
  - Infections = 15% *vs* 8%, including pneumonia = 6% *vs* 4%
  - Gastrointestinal disorders = 6% *vs* 1%
  - Neutropenia = 5% *vs* 3%
  - Thrombocytopenia = 5% *vs* 1%
- Rate of second primary malignancies = same for both arms (3%)
- Quality of life scores (EORTC QLQ-C30 and EORTC QLQ-MY-20) = similar for both groups

Conclusions

The TOURMALINE-MM3 trial met its primary endpoint. Ixazomib maintenance was well tolerated and significantly improved PFS for 24 months compared to placebo.

References

1. Dimopoulos M.A. *et al.* Maintenance Therapy with the Oral Proteasome Inhibitor (PI) Ixazomib Significantly Prolongs Progression-Free Survival (PFS) Following Autologous Stem Cell Transplantation (ASCT) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): Phase 3 Tourmaline-MM3 Trial. 2018 Dec 2; Oral Abstract #301: ASH 60th Annual Meeting and Exposition, San Diego, CA.
2. Dimopoulos M.A. *et al.* TOURMALINE-MM3 study group. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2018 Dec 10. pii: S0140-6736(18)33003-4. DOI: 10.1016/S0140-6736(18)33003-4. [Epub ahead of print].

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