MultipleMyelomaHub

Relapsed/refractory patients

ASCO 2018 | Phase I trial of ruxolitinib, lenalidomide, and methylprednisolone for RRMM

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Ruxolitinib (rux) is an orally administered agent that selectively inhibits both JAK1 and JAK2, and is currently approved by the FDA for the treatment of myelofibrosis and polycythemia vera. It has been shown to enhance the activity of lenalidomide and dexamethasone in suppressing the growth of both multiple myeloma cell lines, primary cell lines derived from patients, and in xenograft models in immunodeficient mice. In an oral abstract presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, data from a phase I study of ruxolitinib, lenalidomide, and methylprednisolone to treat relapsed and refractory multiple myeloma (RRMM) patients, was shown. The study was conducted by James R. Berenson from the Institute for Myeloma and Bone Cancer Research, California, US, and colleagues.

Dr Berenson began with an explanation as to the rationale behind this combination. It has been shown that MUC1 expression is increased in the bone marrow (BM) of myeloma patients, especially when these cells are bound to stromal cells, leading to translocation of beta-catenin to the nucleus and up-regulation of CD44, and in turn, this leads to lenalidomide resistance. Stromal cell interactions also drive increased expression of CXCL12, CXCR4, and TRIB1, leading to M2 polarization and further tumor cell stimulation. Ruxolitinib acts to suppress MUC1, PDL1/PD-1, CD44, and CX12/CXCR4, and down-regulates TRIB1, leading to a marked reduction of M2 expression. Overall, the outcome is depression of tumor stimulation and warranted further exploration of ruxolitinib a phase I trial in combination with lenalidomide, and methylprednisolone. The primary endpoint was to determine the maximum-tolerated dose (MTD) and to establish safety and tolerability at this dose; secondary endpoints include progression-free survival (PFS) and duration of response (DoR). The trial used a classic 3 + 3 dose escalation and recruited patients (pts) with progressive disease that had received 3 or more prior lines of therapy, and failed treatment with both lenalidomide and a proteasome inhibitor (PI).

Key Highlights:

- Ruxolitinib = 5 mg 2x daily, lenalidomide (R) = 5 mg initially on a 21-day on, 7-day schedule; methylprednisolone (MP) = 40 mg every other day
- No dose reductions required, ruxolitinib was administered at 15 mg 2x daily; lenalidomide = 10 mg daily
- N = 28 pts; 26 were evaluable for safety
- Mixed Ig isotypes: 50% = IgG, and approximately 25% = IgA or light chain only
- Median time since diagnosis = 56 months (7–132 months)
- High risk cytogenetics (32%): del(17p) = 5 pts; del(17p) and t(14;16) = 1 pt; t(14;16) = 1 pt; t(4;14) = 2 pts
- Median number of prior treatments = 6 (range 3–10); most had received bortezomib and failed carfilzomib
- Pts given MTD = 19; 9 pts remain active on the study
- Median follow up = 2.6 months (1 May 2018)

- Complete response (CR) = 1 pt; very good partial response (VGPR) = 1 pt with no measurble M-protein but residual myeloma cells in BM; partial response (PR) = 8 pts; minimal response (MR) = 3 pts; stable disease (SD) = 10 pts; progressive disease (PD) = 3 pts
- ORR = 10 pts (39%) and clinical benefit rate (CBR) = 13 pts (50%)
- Reductions in M-protein were observed in almost all responding pts
- Progression free survival (PFS) in all pts = 5 months; in all 13 responders = 5.6 months.
- Adverse events (AEs): Grade 3 thrombocytopenia = 3 pts, GI bleeding = 3 pts, anemia = 2 pts
- Serum BCMA was assessed at baseline and weekly up to Cycle 2 day 1, then once per cycle; pts were then divided into quartiles based on measurements
- Pts in the highest quartile (BCMA levels > 342 ng/ml): PFS = 1.1 months *vs* all pts in other quartiles: PFS = 5.1 months; thus higher BCMA at baseline predicts shorter PFS
- Change in serum BCMA during treatment also correlated with outcome: pts with an increase in BCMA during the first week of therapy had PFS = 1.4 months; pts with a decrease had PFS = 5.1 months
- Changes in BCMA levels were more dramatic and could predict response status more rapidly than other markers such as M-protein

This preliminary data is extremely promising in terms of both efficacy and safety and it is particularly encouraging that benefits were observed in heavily pre-treated patients that were refractory to lenalidomide. As an all-oral regimen, this offers convenience for patients and warrants further evaluation in a phase II trial. Interestingly, baseline BCMA measurements correlated with PFS and response, suggesting that BCMA could be a useful biomarker to track response to treatment. BCMA has the advantage of a higher turnover rate allowing quick assessment of response, is independent of renal function, and is more reliable than serum free light chain (SLFC) measurements.

References

1. Berenson J. *et al.* A phase 1 trial of ruxolitinib, lenalidomide, and methylprednisolone for relapsed/refractory multiple myeloma patients. Abstract #8005. 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, 2018 June 1–5; Chicago, IL, USA.