Partial response or better at 6 months is not a prognostic indicator of progression-free survival in Waldenström macroglobulinemia treated with zanubrutinib: a post hoc analysis of the ASPEN study

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Introduction: Attaining partial response (PR) or better at 6 months was associated with superior progression-free survival (PFS) in patients (pts) with Waldenström macroglobulinemia (WM) treated with ibrutinib (IBR) monotherapy (Castillo et al. *Br J Haematol.* 2021); it could be a surrogate for PFS in prospective clinical trials evaluating Bruton tyrosine kinase inhibitors (BTKis) in pts with WM. This post hoc analysis of the ASPEN study aimed to evaluate the PFS prognostic value of attaining PR or better at 6 months in pts with WM treated with zanubrutinib (ZANU), a second-generation BTKi with more selectivity and sustained BTKi occupancy than IBR. The PFS prognostic value of very good partial response (VGPR) or better at 12 months was also evaluated.

Methods: The methodology for the ASPEN study has been described previously (Tam et al. *Blood.* 2020). This post hoc analysis evaluated the attainment of PR or better at 6 months and VGPR at 12 months from therapy initiation. Responses were assessed based on criteria from the 11th International Workshop on Waldenstrom's macroglobulinemia (Treon et al. *Semin Hematol.* 2023). PFS was estimated starting at the 6-month mark in pts with response assessment at 6 months and the 12-month mark in pts with response assessment at 12 months. Since 2 analyses were done using the same dataset, *P* values <.025 were considered statistically significant.

Results: In the IBR arm, response data at 6 months were available for 86 pts, of whom 57 (66%) attained PR or better. PR or better at 6 months was associated with favorable PFS in pts with WM treated with IBR (hazard ratio [HR], 0.47; 95% CI, 0.21-1.06; *P*=.0697). In the ZANU arm, response data at 6 months were available for 93 pts, of whom 67 (72%) attained PR or better. The PFS in pts with WM treated with ZANU was similar between those who did and did not attain PR or better at 6 months (HR, 1.53; 95% CI, 0.43-5.41; *P*=.5113). The 3-year landmark PFS event-free rates from the 6-month mark with ZANU (attained PR at 6 months, 81%; did not attain PR at 6 months, 87%) were consistently similar to those in IBR-treated pts with PR or better at 6 months (80%). In contrast, the event-free rate was lower (65%) in pts treated with IBR who did not attain PR or better at 6 months. In the IBR arm, response data at 12 months were available for 81 pts, of whom 11 (14%) attained VGPR or better. In the ZANU arm, response data at 12 months were available for 85 pts, of whom 22 (26%) attained VGPR or better. Pts treated with IBR (HR, 0.77; 95% CI, 0.18-3.32; *P*=.7225) or ZANU (HR, 0.86; 95% CI, 0.24-3.14; *P*=.8248) had similar PFS rates regardless of whether they attained VGPR or better at 12 months.

Conclusions: Results of the ASPEN trial provide additional support for PR or better at 6 months as a positive prognostic factor for PFS in pts with WM treated with IBR. PFS in ZANU-treated pts, whether or not they attained PR or better at 6 months, was similar to PFS in IBR-treated pts with PR or better at 6 months.