



S. Bradbrook/NPC

Mantle-cell lymphoma (MCL), although rare, portends a poor prognosis and typically progresses rapidly despite multiple lines of therapy, which has led to its adoption as a model for accelerated drug development. Nevertheless, no standard-of-care treatment for relapsed MCL has been established. “Both ibrutinib and temsirolimus are registered for relapsed MCL in Europe, based on mostly phase II studies,” explains Martin Dreyling. “Thus, the obvious question was how these two approaches perform in direct comparison.” Dreyling and colleagues have now performed this comparison in an international phase III trial.

The investigators randomly assigned 280 patients who had previously received at least one rituximab-based regimen to receive either oral ibrutinib (560 mg daily), or intravenous temsirolimus (175 mg weekly for 3 weeks, then 75 mg weekly). The response rate was 72% in the ibrutinib arm versus 40% in the temsirolimus arm ( $P < 0.0001$ ), with 19% versus 1% of patients achieving

a complete response, respectively. The median progression-free survival (PFS) more than doubled with ibrutinib treatment (14.6 months versus 6.2 months; HR 0.43;  $P < 0.0001$ ), and 2-year PFS was 41% versus 7%. Of note, ibrutinib was also better tolerated than temsirolimus, with fewer grade 3 or higher adverse events, and was associated with a greater median relative dose intensity and a lower rate of treatment discontinuation.

These results will come as a surprise to few: as Dreyling notes, “the superior response rate and PFS, as well as tolerability, of ibrutinib was almost identical to what was expected based on the results of prior phase II studies.” Indeed, in a linked commentary, Peter Martin explains how phase II trials “brought outsized hope regarding the activity of temsirolimus”, and recounts the rapidity at which ibrutinib has surpassed this agent as the standard treatment for relapsed MCL — ibrutinib only entered clinical development in 2009.

“To date, ibrutinib is the only registered monotherapy with sufficient efficacy in relapsed MCL,”

Dreyling states. This fact does not, however, rule out a role for temsirolimus treatment; as Dreyling concludes, “temsirolimus will be explored in combinations; for example, in combination with bendamustine and rituximab, as in the recent BeRT trial, in which all evaluable patients with relapsed MCL responded.”

Importantly, these results pave the way for movement of ibrutinib to the first-line setting. As Martin highlights in his commentary, the SHINE trial of ibrutinib combined with standard frontline chemotherapy has already been completed and the results are eagerly anticipated — a brighter future for patients with MCL is on the horizon.

David Killock

“These results will come as a surprise to few...”

**ORIGINAL ARTICLE** Dreyling, M. et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* doi:10.1016/S0140-6736(15)00667-4

**FURTHER READING** Martin, P. Ibrutinib — a new standard treatment for relapsed mantle cell lymphoma? *Lancet* doi:10.1016/S0140-6736(15)01040-5