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Examining Real-World Ibrutinib Outcomes in R/R MCL: Findings from a Danish Study

Dr. Maeusli:

You're listening to *Project Oncology* on ReachMD, and this is an *AudioAbstract*. I'm Dr. Mimi Maeusli, and today, I'll be reviewing a nationwide Danish study on real-world outcomes with ibrutinib in relapsed or refractory mantle cell lymphoma. Published in *Blood Neoplasia* in August 2025, the study compared outcomes in clinical practice with results reported in previous trials.

So let's start with some background. Ibrutinib was first approved in the U.S. back in 2013 for relapsed or refractory mantle cell lymphoma on the strength of early clinical data. These findings demonstrated an overall response rate of 68 percent, a median progression-free survival of nearly 14 months, and overall survival of more than 22 months.

But later confirmatory trials raised concerns about generalizability to older or comorbid patients—groups that are often excluded from clinical research—leading to FDA withdrawal in 2023. The drug remains approved in the E.U., and so this Danish study aimed to fill this evidence gap by evaluating outcomes, adverse events, and prognostic factors among patients treated outside clinical trials between 2010 and 2022.

The cohort included 146 patients with a median age of 73 years and a median time from diagnosis to starting ibrutinib of 2.7 years. High-risk features were common amongst patients. In fact, 58 percent had Ki67 proliferation indices of at least 50 percent, 40 percent had blastoid or pleomorphic morphology, 29 percent were refractory to their prior line of therapy, and 56 percent had progressed within 24 months of frontline treatment.

In terms of treatment patterns, ibrutinib was administered as second-line therapy in 62 percent of cases and in later lines for the rest. About 70 percent of patients received it as a monotherapy, and the other 30 percent received it in combination with additional agents.

Now, if we turn to the results, efficacy outcomes were lower than what's been previously reported in clinical trials. The overall response rate was 56 percent. That included 22 percent complete responses, 22 percent partial responses, and 12 percent clinical remissions. In terms of durability, the median duration was just over 14 months.

And when evaluating survival outcomes, progression-free survival was about six months compared with the 11 to 15 months seen in clinical trials, while overall survival came in at 12 months versus 20 to 27 months in trial data. And when we extend the follow-up to three years, fewer than 20 percent of patients were progression-free and only about a quarter remained alive.

The investigators also conducted a multivariable analysis. They found that several factors were associated with significantly worse progression-free survival—specifically, a Ki67 of 50 percent or higher, blastoid or pleomorphic morphology, early relapse, and refractory disease. By contrast, the timing of ibrutinib, whether used in the second-line setting versus later, or whether it was given as monotherapy versus in combination, didn't appear to significantly affect outcomes.

Now, shifting over to safety, adverse events were both common and clinically significant. 68 percent of patients experienced at least one adverse event, and of those, more than three-quarters were grade three or higher. By the three-year mark, 22 percent had required dose reductions due to toxicity, and 19 percent had discontinued treatment altogether. Outcomes after discontinuation were poor, with a median overall survival of just under two months. And notably, older age was associated with a higher likelihood of treatment discontinuation.

So compared with clinical trials and other observational studies, these real-world data highlight a clear efficacy gap. Several factors may explain this difference, including the older median age of the study population, the higher prevalence of adverse disease characteristics,

and a shorter median treatment duration of just under five months, compared with eight to 16 months in trials. In addition, during the study period, access to novel therapies such as CAR T-cell products, bispecific antibodies, and non-covalent BTK inhibitors was limited.

That said, the authors did note study limitations, including the absence of *TP53* mutation data, non-standardized assessment of Ki67, retrospective attribution of adverse events, and the inherent constraints of an observational design.

So in summary, this nationwide Danish analysis confirms that ibrutinib retains activity in relapsed or refractory mantle cell lymphoma. However, survival and tolerability in real-world settings were lower than those reported in clinical trials. Patients with high-risk features, such as Ki67 at or above 50 percent, blastoid or pleomorphic subtype, early relapse within 24 months, or refractory disease, experienced especially poor outcomes and may warrant prioritization for clinical trial enrollment. And finally, the frequency of dose-limiting toxicities points to the need for close monitoring and proactive supportive care, particularly in older patients.

This has been an *Audio Abstract* for *Project Oncology*, and I'm Dr. Mimi Maeusli. To access this and other episodes in our series, visit ReachMD dot com, where you can Be Part of the Knowledge. Thanks for listening!

Reference

Trab T, Chanchiri I, Al-Mashhadi AL, et al. Real-world outcomes with ibrutinib in relapsed or refractory mantle cell lymphoma: a Danish population-based study. *Blood Neoplasia*. 2025;2(3):100128. Published 2025 Jun 9.