

# **Efficacy and Safety of Ibrutinib Combined with Standard First-Line Treatment or As Substitute for Autologous Stem Cell Transplantation in Younger Patients with Mantle Cell Lymphoma: Results from the Randomized Triangle Trial By the European MCL**

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**INTRODUCTION:** High-dose cytarabine-containing immunochemotherapy followed by autologous stem cell transplantation (ASCT) and rituximab maintenance represents the current standard of care for younger mantle cell lymphoma (MCL) patients. The BTK-inhibitor ibrutinib has shown promising efficacy in relapsed (Dreyling et al, Hemasphere 2022) and previously untreated older MCL patients (Wang et al., NEJM 2022). In 2016, the European MCL Network initiated the randomized, open-label, 3-arm TRIANGLE trial to evaluate the addition of ibrutinib to standard treatment (arm A+I) in comparison to the previous standard treatment (arm A) and an ibrutinib containing treatment without ASCT (arm I).

**PATIENTS AND METHODS:** Patients with previously untreated, advanced stage II-IV MCL, up to 65 years and suitable for high-dose cytarabine and ASCT were randomized 1:1:1 to the 3 trial arms A, A+I, and I in 13 European countries and Israel. Study treatment consisted of 3 cycles R-CHOP/R-DHAP without (arm A) or with ibrutinib added to R-CHOP cycles and 2 years

maintenance (arms A+I, I). ASCT was planned for responding patients of arms A and A+I. Rituximab maintenance could be applied according to national guidelines in all responding patients irrespective of the trial arm. For the primary outcome, failure-free survival (FFS), stable disease at the end of induction, any progression, or death were counted as events. Three pairwise log-rank tests for FFS were monitored with regular pre-planned interim analyses maintaining each a one-sided 0.0167 significance level. A pre-defined decision criterion based on the statistical significance of the treatment comparisons was established to determine the future treatment recommendation. Secondary outcomes were overall response (OR), complete remission (CR), overall survival (OS), and grade 3-5 AEs.

**RESULTS:** Between July 2016 and December 2020, 870 patients were randomized to A (n=288), A+I (n=292), and I (n=290). Median age was 57 years (range 27-68), 76% of the patients were male, 87% had stage IV, and 58%/27%/15% had low/intermediate/high risk MIPI. OR and CR rates were 94% and 36% of 272 evaluable patients in arm A (R-CHOP/R-DHAP) as compared to 98% and 45% of 559 evaluable patients in the combined A+I/I arms (ibrutinib-R-CHOP/R-DHAP). After a median follow-up of 31 months, A failed to show superiority over I in terms of FFS with 3-year FFS 72% (A) vs. 86% (I; p=0.9979, hazard ratio: 1.77, Figure 1A). A+I was superior to A in terms of FFS with 3-year FFS 88% (A+I) vs. 72% (A; p=0.0008, hazard ratio: 0.52). Subgroup analyses by the intention to apply rituximab maintenance did not change the main results on the lack of superiority of A vs. I and the superiority of A+I vs. A. Statistical monitoring for the FFS comparison of A+I vs. I is still ongoing. Three-year OS was 86% in A, 91% in A+I, and 92% in I (Figure 1B). There were no substantial differences in the occurrence of grade 3-5 AEs during induction with R-CHOP/R-DHAP vs ibrutinib-R-CHOP/R-DHAP (neutropenia: 47%/49% of patients, leukopenia: 15%/15%, febrile neutropenia: 9%/12%, infections and infestations: 9%/12%, cardiac disorders: 2%/3%). The two ASCT-containing arms did not substantially differ in grade 3-5 AEs (A/A+I: neutropenia: 36%/33%, febrile neutropenia: 20%/22%, leukopenia: 17%/17%, infections and infestations: 17%/20%). In contrast, during maintenance, there were substantially more grade 3-5 AEs in A+I as compared to A and I (A+I/A/I: neutropenia: 44%/17%/23%, leukopenia: 4%/2%/2%, febrile neutropenia: 6%/3%/3%, infections and infestations: 25%/13%/19%, cardiac disorders: 3%/1%/4%).

**CONCLUSIONS:** The addition of ibrutinib during induction and as maintenance with or without ASCT showed strong efficacy with acceptable toxicity. It has been clearly demonstrated that the current standard high-dose regimen is not superior to the new ibrutinib-containing regimen without ASCT. More follow-up is needed to clarify the role of ASCT in the context of ibrutinib-containing treatment. However, the current results already support the use of ibrutinib in the first-line treatment of younger MCL patients.

Figure 1A: FFS (primary outcome) and B: OS according to randomized trial arm A (R-CHOP/R-DHAP followed by ASCT), A+I (ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance) and I (ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance)

