# Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network

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## Summary

**Background** Adding ibrutinib to standard immunochemotherapy might improve outcomes and challenge autologous stem-cell transplantation (ASCT) in younger (aged 65 years or younger) mantle cell lymphoma patients. This trial aimed to investigate whether the addition of ibrutinib results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing treatment without ASCT. We also investigated whether standard treatment with ASCT is superior to a treatment adding ibrutinib but without ASCT.

**Methods** The open-label, randomised, three-arm, parallel-group, superiority TRIANGLE trial was performed in 165 secondary or tertiary clinical centres in 13 European countries and Israel. Patients with previously untreated, stage II–IV mantle cell lymphoma, aged 18–65 years and suitable for ASCT were randomly assigned 1:1:1 to control group A or experimental groups A+I or I, stratified by study group and mantle cell lymphoma international prognostic index risk groups. Treatment in group A consisted of six alternating cycles of R-CHOP (intravenous rituximab 375 mg/m² on day 0 or 1, intravenous cyclophosphamide 750 mg/m² on day 1, intravenous doxorubicin 50 mg/m² on day 1, intravenous vincristine 1·4 mg/m² on day 1, and oral prednisone 100 mg on days 1–5) and R-DHAP (or R-DHAOx, intravenous rituximab 375 mg/m² on day 0 or 1, intravenous or oral dexamethasone 40 mg on days 1–4, intravenous cytarabine 2×2 g/m² for 3 h every 12 h on day 2, and intravenous cisplatin 100 mg/m² over 24 h on day 1 or alternatively intravenous oxaliplatin 130 mg/m² on day 1) followed by ASCT. In group A+I, ibrutinib (560 mg orally each day) was added on days 1–19 of R-CHOP cycles and as fixed-duration maintenance (560 mg orally each day for 2 years) after ASCT. In group I, ibrutinib was given the same way as in group A+I, but ASCT was omitted. Three pairwise one-sided log-rank tests for the primary outcome of failure-free survival were statistically monitored. The primary analysis was done by intention-to-treat. Adverse events were evaluated by treatment period among patients who started the respective treatment. This ongoing trial is registered with ClinicalTrials.gov, NCT02858258.

**Findings** Between July 29, 2016 and Dec 28, 2020, 870 patients (662 men, 208 women) were randomly assigned to group A (n=288), group A+I (n=292), and group I (n=290). After 31 months median follow-up, group A+I was superior to group A with 3-year failure-free survival of 88% (95% CI 84–92) versus 72% (67–79; hazard ratio 0·52 [one-sided 98·3% CI 0–0·86]; one-sided p=0·0008). Superiority of group A over group I was not shown with 3-year failure-free survival 72% (67–79) versus 86% (82–91; hazard ratio 1·77 [one-sided 98·3% CI 0–3·76]; one-sided p=0·9979). The comparison of group A+I versus group I is ongoing. There were no relevant differences in grade 3–5 adverse events during induction or ASCT between patients treated with R-CHOP/R-DHAP or ibrutinib combined with R-CHOP/R-DHAP. During maintenance or follow-up, substantially more grade 3–5 haematological adverse events and infections were reported after ASCT plus ibrutinib (group A+I; haematological: 114 [50%] of 231 patients; infections: 58 [25%] of 231; fatal infections: two [1%] of 231) compared with ibrutinib only (group I; haematological: 74 [28%] of 269; infections: 52 [19%] of 269; fatal infections: two [1%] of 269) or after ASCT (group A; haematological: 51 [21%] of 238; infections: 32 [13%] of 238; fatal infections: three [1%] of 238).

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**Interpretation** Adding ibrutinib to first-line treatment resulted in superior efficacy in younger mantle cell lymphoma patients with increased toxicity when given after ASCT. Adding ibrutinib during induction and as maintenance should be part of first-line treatment of younger mantle cell lymphoma patients. Whether ASCT adds to an ibrutinib-containing regimen is not yet determined.

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## Introduction

Mantle cell lymphoma remains a challenging subtype of lymphoma due to the broadly varying clinical course. Clinical course varies from observation only over years to a rapidly progressing, treatment-refractory disease.[1–4] During the last decade, in addition to the clinical mantle cell lymphoma international prognostic index (MIPI), blastoid morphology, high Ki-67, and *TP53* alterations have been identified as the most important high-risk biological features.[5–10] In young (aged ≤65 years), medically fit patients, dose-intensification by adding cytarabine or autologous stem-cell transplantation (ASCT) has led to improved long-term clinical and survival outcomes versus standard immunochemotherapy, although this has mostly been in low-risk patients.[11–12] In addition, rituximab maintenance has resulted in improved survival rates compared with observation.[13] In relapsed mantle cell lymphoma, monotherapies with Bruton's tyrosine-kinase (BTK) inhibitors have become the preferred salvage treatments, based on superior efficacy compared with conventional chemotherapy or other targeted therapies.[14–16] In the front-line setting, the addition of the BTK inhibitor ibrutinib to bendamustine–rituximab has resulted in superior progression-free survival.[17]

In the current TRIANGLE trial of the European Mantle Cell Lymphoma Network, ibrutinib has been added during induction and as maintenance to one of the current immunochemotherapy standards, both in addition to ASCT and instead of ASCT. We aimed to investigate whether the addition of ibrutinib to immunochemotherapy and ASCT results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing immunochemotherapy without ASCT. Furthermore, considering the short-term and long-term toxicity of high-dose treatment, we aimed to investigate whether standard treatment with ASCT is still superior to a treatment adding ibrutinib to induction and maintenance without ASCT.

## Methods

### Study design

TRIANGLE is an investigator-sponsored, multicentre, randomised, open-label, three-arm parallel-group, confirmatory superiority trial (appendix p 5). Patients were recruited from 165 secondary or tertiary university, community, or private hospitals and private clinical centres in Germany, Italy, the Netherlands, Spain, Sweden, Poland, Denmark, Switzerland, Norway, Czech Republic, Belgium, Israel, Portugal, and Finland. Ethical approval was obtained from the ethics committees of all participating centres.

### Patients

Previously untreated male or female (sex recorded by the investigator) adults aged 18–65 years with histologically

### Research in context

#### Evidence before this study

On Aug 3, 2023, we performed a PubMed search without explicit time or language restrictions for randomised phase 3 trials investigating the role of autologous stem cell transplantation (ASCT) or Bruton's tyrosine-kinase inhibitors in younger transplant-eligible patients with mantle cell lymphoma. The only trial fulfilling the search criteria was the first randomised trial of the European Mantle Cell Lymphoma Network, comparing efficacy and safety of autologous stem cell transplantation with a maintenance strategy after induction chemotherapy. During the planning stage of the TRIANGLE trial, ibrutinib had shown promising efficacy in the treatment of relapsed or refractory mantle cell lymphoma. A recently published randomised trial had shown prolonged progression-free but not overall survival by adding ibrutinib to first-line rituximab–bendamustine in older (aged ≥65 years), non-transplant-eligible patients with mantle cell lymphoma.

#### Added value of this study

The results of the TRIANGLE trial confirm superior efficacy by the addition of ibrutinib to pre-trial standard treatment of younger, transplant-eligible patients with mantle cell lymphoma. Autologous stem cell transplantation without ibrutinib does not result in superior efficacy compared with a high-dose cytarabine-containing immunochemotherapy combined with fixed-duration ibrutinib.

#### Implications of all the available evidence

Fixed-duration ibrutinib should become part of the first line treatment of younger mantle cell lymphoma patients. Whether ASCT adds efficacy to an ibrutinib-containing regimen outweighing the considerable toxicity of ASCT is still to be determined.

confirmed mantle cell lymphoma, Ann Arbor stage II–IV, suitable for ASCT, with an Eastern Cooperative Oncology Group performance status of 2 or less, and at least one measurable lesion were enrolled. Patients were excluded if they required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with strong CYP3A4 or CYP3A5 inhibitors, had a history of intracranial haemorrhage within 6 months before randomisation, or known CNS involvement of mantle cell lymphoma. Complete inclusion and exclusion criteria are provided in the trial protocol (appendix pp 38–40). This protocol was performed according to the updated Declaration of Helsinki and all patients provided written informed consent for trial participation.

### Randomisation and masking

Patients were randomly allocated to three treatment groups: immunochemotherapy with ASCT (group A), ibrutinib plus immunochemotherapy with ASCT (group A+I), and ibrutinib plus immunochemotherapy without ASCT (group I), with a ratio of 1:1:1. Randomisation was implemented in the electronic data capture system, was blocked and stratified according to study groups and MIPI risk groups,[5] and used computer-generated random numbers with unpredictable seed. Investigators initiated randomisation through the electronic case report form and were not able to predict the randomisation result. Due to the omission of ASCT and the earlier start of maintenance in group I, blinding of neither ASCT nor ibrutinib was feasible.

### Procedures

Induction immunochemotherapy in all three groups consisted of six alternating cycles of intravenous rituximab 375 mg/m² on day 0 (if given one day before the start of chemotherapy) or day 1 (the first day of chemotherapy), intravenous cyclophosphamide 750 mg/m² on day 1, intravenous doxorubicin 50 mg/m² on day 1, intravenous vincristine 1·4 mg/m² on day 1, and oral prednisone 100 mg on days 1–5 (R-CHOP) and either intravenous rituximab 375 mg/m² on day 0 or 1, intravenous or oral dexamethasone 40 mg on days 1–4, intravenous cytarabine 2×2 g/m² for 3 h every 12 h on day 2, and intravenous cisplatin 100 mg/m² over 24 h on day 1 (R-DHAP) or alternatively intravenous rituximab 375 mg/m² on day 0 or 1, intravenous or oral dexamethasone 40 mg on days 1–4, intravenous cytarabine 2×2 g/m² for 3 h every 12 h on day 2, and intravenous oxaliplatin 130 mg/m² on day 1 (R-DHAOx), with subsequent G-CSF (filgrastim) support (subcutaneous 5 µg/kg daily from day 6) every 21 days. In group A+I and group I, patients additionally received oral ibrutinib 560 mg (Janssen, Beerse, Belgium) on days 1–19 of the R-CHOP cycles, and 2 years of continuous oral ibrutinib 560 mg daily maintenance if patients were failure-free after induction. In groups A and A+I, ASCT was performed with THAM conditioning (total body irradiation 10 Gy on days –7 to –5, intravenous cytarabine 1·5 g/m² over 30 min twice daily on day –4 and –3, and intravenous melphalan 140 mg/m² over 1 h on ay –2) or BEAM/TEAM (intravenous carmustine 300 mg/m² over 1 h on day –7 or intravenous thiotepa 5 mg/kg twice daily on day –7, intravenous etoposide 2×100 mg/m² over 1 h every 12 h on day –6 to –3, cytarabine 2×200 mg/m² over 30 min every 12 h on day –6 to –3, and intravenous melphalan 140 mg/m² over 1 h on day –2), based on investigator's discretion. In all study groups, rituximab maintenance for 3 years could be added according to national guidelines (appendix pp 48–49).

Response assessments were performed by the investigator, based on physical examinations, pre-planned CT scans, laboratory results, and bone marrow examinations applying the Revised Response Criteria for Malignant Lymphoma.[18] Of note, even if PET-CT scans were performed, the results were not incorporated in the response evaluation. If initial bone marrow infiltration was detected, subsequent bone marrow biopsies were mandatory. Response was assessed at midterm induction (after four cycles), at end of induction, 6 weeks after end of induction, and thereafter half-yearly for 2 years and thereafter yearly until progression.

Histopathological markers as assessed centrally by the reference pathology laboratories were used for subgroup analyses according to Ki-67 index (<30% or ≥30%), p53 expression (≤50% or >50%), and high-risk biology. High-risk biology was defined as high-risk combined MIPI (MIPI-c) or high p53 expression.[8,9]

Further details on trial procedures can be found in the trial synopsis (appendix pp 38–49) and the full trial protocol (appendix pp 23–124).

### Outcomes

The primary outcome was investigator-assessed failure-free survival, and was defined as time from randomisation to stable disease at end of induction immunochemotherapy, progressive disease, or death from any cause, whichever occurred first. Failure-free survival represents a modified progression-free survival, additionally counting stable disease at end of induction as event.

Secondary outcomes were overall survival (defined as time from randomisation to death from any cause), progression-free survival (defined as time from randomisation to disease progression or death), duration of remission (time from end of successful induction to disease progression or death), overall and complete remission rates, and conversion rate of partial remission to complete remission after end of induction.

Adverse event reporting was mandatory from randomisation until 30 days after application of the last trial-specific medication. Thus, adverse event reporting was not mandatory in the observation period of group A. Safety outcomes were rates of grade 3 to 5 and grade 5 adverse events according to the Common Terminology Criteria for Adverse Events version 4.03 as well as cumulative incidence

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See **Online** for appendix

rates of secondary primary malignancies. A complete list of all secondary endpoints can be found in the trial protocol (appendix pp 41–42).

### Statistical analysis

Three pairwise one-sided hypothesis tests using log-rank statistics for failure-free survival were planned: group A+I versus group A (null hypothesis: group A+I not superior to group A), group A+I versus group I (null hypothesis: group A+I not superior to group I), and group A versus group I (null hypothesis: group A not superior to group I); the significance level of each pairwise comparison is one-sided 0·01666 (0·05/3; Bonferroni-correction) to maintain a global one-sided significance level of 5%.

Assuming up to 5 years of recruitment and 5 years of additional follow-up, up to 870 patients were planned for the trial to be powered to detect superiority of group A+I versus group A and group A+I versus group I of 12% at 5 years (77·1% *vs* 64·8%, hazard ratio [HR] 0·60) with 90% power each and superiority of group A versus group I of 16% in failure-free survival at 5 years (64·8% *vs* 48·5%, HR 0·60) with statistical power of 95%. For each pairwise comparison, regular interim analyses were planned to be performed twice yearly to allow early stopping for efficacy or futility with truncated sequential probability ratio tests correcting for multiple testing (appendix pp 2–4).[19] The timing of interim analyses was pre-specified in the protocol and the disclosure of results was permitted after formal decision of each statistical test. Following the recommendation of the Data and Safety Monitoring Committee we report here results from the pre-planned interim analysis after formal decisions of two of the three statistically monitored tests. One sequential test (comparing group A+I *vs* group I) is still ongoing and the final analysis is planned to be done with prolonged follow-up at the end of the trial. Overrunning analyses were performed to integrate data accumulating after formal decision of sequential tests,[20] and bias-corrected maximum-likelihood HR estimates along with one-sided 98·3% CIs were reported correcting for the sequential design.[19] Of note, these CIs might have higher coverage probabilities than indicated.[19]

Failure-free survival, overall survival, progression-free survival, and duration of remission were estimated with Kaplan–Meier methods uncorrected for the sequential design. Time-to-event outcomes were censored at the last date showing absence of any event. One-sided 98·3% CIs for HRs were calculated based on Cox regression with Bonferroni-correction for the three pairwise tests. As sensitivity analyses we adjusted for MIPI score without and with Ki-67 index and stratified for the randomisation factors study group and MIPI risk group. Complete remission rates and overall response rates were compared between group A and pooled A+I and I induction groups using Fisher's exact test. Cumulative incidence of treatment failure, next lymphoma treatment, and secondary malignancies were estimated using cumulative incidence function and compared by Gray's test with a one-sided significance level of 0·05/3, treating death without event of interest as the competing event.

Efficacy analyses were performed by intention-to-treat. As sensitivity analyses, the primary hypotheses were evaluated in a modified intention-to-treat analysis cohort, including all randomly assigned patients with confirmed mantle cell lymphoma who started induction chemotherapy according to the randomly allocated treatment group. Adverse events were evaluated according to treatment periods (induction, ASCT, and maintenance or follow-up) and analysed in groups according to the treatment actually given. Induction safety was compared between group A and pooled A+I and I treatment groups. An exploratory analysis was conducted to compare the duration of remission in group I between patients with and without rituximab maintenance. The frequency of adverse events during maintenance or follow-up was compared between patients with ibrutinib maintenance without rituximab maintenance and patients with both ibrutinib and rituximab maintenance. The exploratory analysis was done using Cox regression with two-sided 95% CIs for HR. Calculation of p values and estimation of HRs for primary hypotheses was performed using the PEST3 software (1994, Reading University) correcting for the sequential statistical design. All other analyses were done using R version 4.04.

A Data and Safety Monitoring Committee supervised the progress of the trial and ensured patient safety and trial data and scientific integrity. The trial was registered with ClinicalTrials.gov, NCT02858258.

### Role of the funding source

The funders of the trial had no role in the trial design, data collection, data analysis, data interpretation, or writing of the Article.

## Results

From July 29, 2016 to Dec 28, 2020, 870 patients were randomly assigned to group A (n=288), group A+I (n=292), and group I (n=290), and 866 patients started induction treatment (286 patients in group A, 292 patients in group A+I, and 288 patients in group I; figure 1). Among all 870 randomly assigned patients, the median age was 57 years (range 27–68, IQR 52–61), 662 (76%) were male, and 862 (99%) had histologically confirmed mantle cell lymphoma. Most patients were in low (504 [58%] of 870 patients) or intermediate (236 [27%] of 870 patients) MIPI risk groups (table 1).

By the data cutoff date for primary analysis on May 22, 2022, six cycles of induction treatment were completed in 808 patients (261 in group A, 275 in group A+I, and 272 in group I). ASCT was completed in 242 patients from group A and 250 patients from group A+I, and, deviating from the designated study group, in three patients from group I. Ibrutinib maintenance was started in 238 patients in group A+I and 260 patients in

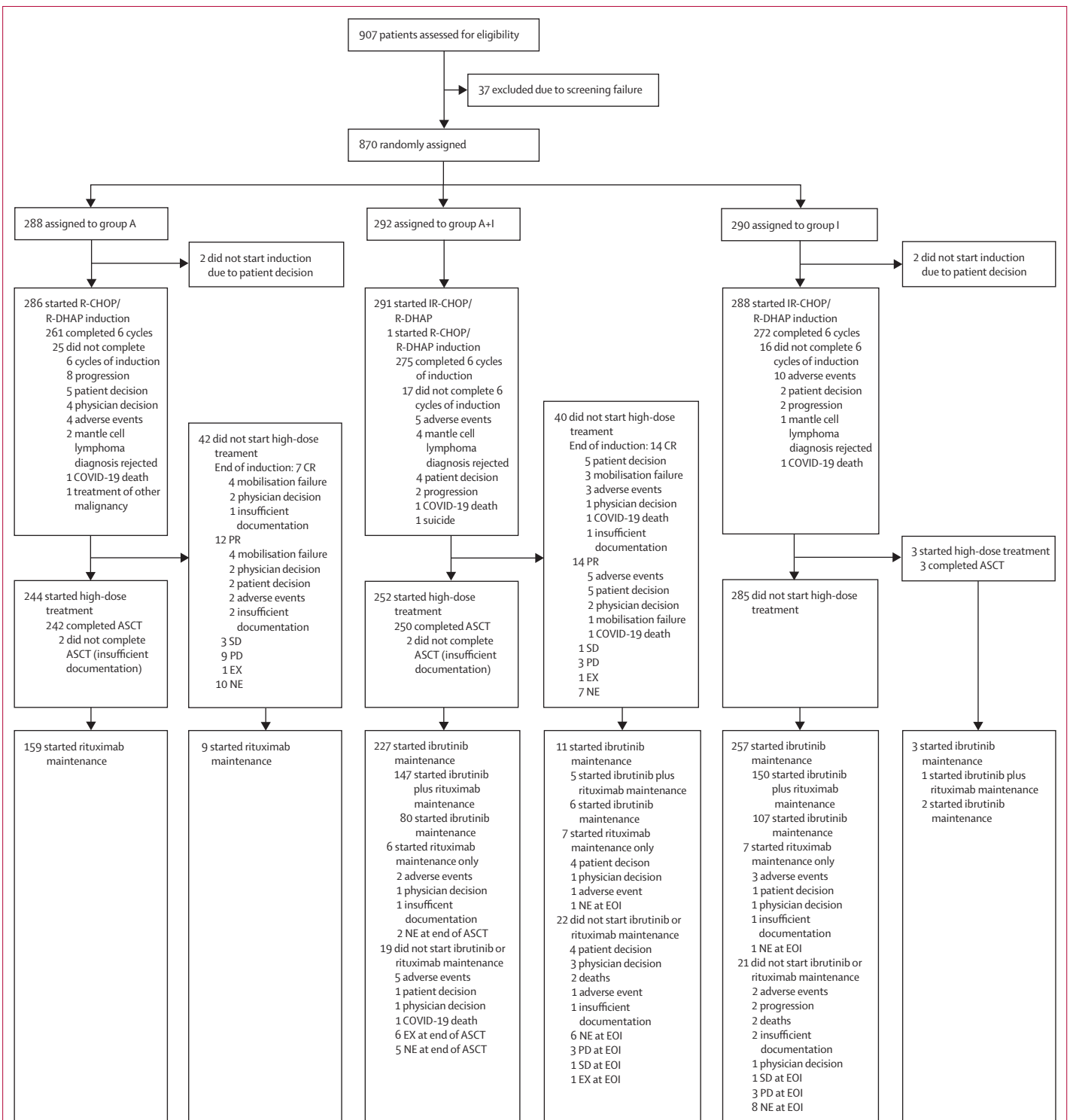


***Figure 1:*** **Trial profile**

ASCT=autologous stem-cell transplantation. CR=complete remission. EOI=end of induction. EX=early death. IR-CHOP=ibrutinib with R-CHOP. NE=not evaluable. PD=progressive disease. PR=partial remission. R-CHOP=intravenous rituximab 375 mg/m², intravenous cyclophosphamide 750 mg/m², intravenous doxorubicin 50 mg/m², intravenous vincristine 1·4 mg/m², and oral prednisone 100 mg. R-DHAP=intravenous rituximab 375 mg/m², intravenous or oral dexamethasone 40 mg, intravenous cytarabine 2 × 2 g/m², and intravenous cisplatin 100 mg/m². SD=stable disease.

| | Group A (N=288) | Group A+I (N=292) | Group I (N=290) |
|---|---|---|---|
| Age (years)* | 57 (52–61) | 57 (52–61) | 57·5 (52– 61) |
| Sex | | | |
| Male | 218 (76%) | 216 (74%) | 228 (79%) |
| Female | 70 (24%) | 76 (26%) | 62 (21%) |
| Race | | | |
| White | 283 (98%) | 283 (97%) | 290 (100%) |
| Other | 5 (2%) | 9 (3%) | 0 (0%) |
| Histology* | | | |
| Mantle cell lymphoma | 286 (99%) | 288 (99%) | 288 (99%) |
| Ann Arbor stage | | | |
| I | 0 | 0 | 0 |
| II | 11/285 (4%) | 12/290 (4%) | 18/289 (6%) |
| III | 24/285 (8%) | 21/290 (7%) | 29/289 (10%) |
| IV | 250/285 (88%) | 257/290 (89%) | 242/289 (84%) |
| B-symptoms | 72/285 (25%) | 78/290 (27%) | 87/285 (31%) |
| Eastern Cooperative Oncology Group performance status | | | |
| 0 | 213 (74%) | 213 (73%) | 208 (72%) |
| 1 | 70 (24%) | 77 (26%) | 77 (27%) |
| 2 | 5 (2%) | 2 (1%) | 5 (2%) |
| LDH/ULN | 0·94 (0·78–1·20) | 0·94 (0·77–1·18) | 0·87 (0·74–1·12) |
| LDH>ULN | 123 (43%) | 120 (41%) | 105 (36%) |
| Leukocytes (white blood cells, G/L) | 7·34 (5·50–10·91) | 7·09 (5·28–11·11) | 7·4 (5·77–11·92) |
| MIPI score | 5·62 (5·40–5·91) | 5·64 (5·35–5·95) | 5·61 (5·39–5·92) |
| Low | 168 (58%) | 168 (58%) | 168 (58%) |
| Intermediate | 79 (27%) | 80 (27%) | 77 (27%) |
| High | 41 (14%) | 44 (15%) | 45 (16%) |
| Ki-67 index (%) | 18 (n=249) (10–38) | 18 (n=262) (12–40) | 18·5 (n=259) (10–35) |
| Ki-67 index ≥30% | 81/249 (33%) | 81/262 (31%) | 82/259 (32%) |
| Cytology blastoid | 28/253 (11%) | 34/261 (13%) | 31/265 (12%) |
| P53 expression >50% | 21/183 (11%) | 25/175 (14%) | 31/189 (16%) |
| High-risk biology | 31/185 (17%) | 37/179 (21%) | 44/192 (23%) |

Data are n (%), or n/N (%), or median (IQR). LDH=lactate dehydrogenase. MIPI=mantle cell lymphoma international prognostic index. ULN=upper limit of normal. *One patient aged 68 years and one patient aged 66 years were randomly assigned in group A+I; histology of non-mantle cell lymphoma patients: one follicular lymphoma and one chronic lymphocytic leukemia in group A, one lymphoma not otherwise specified, one non-Hodgkin lymphoma not otherwise specified, one splenic marginal zone lymphoma, and one marginal zone lymphoma in group A+I, and one diffuse large B-cell lymphoma and one hairy cell leukemia in group I.

***Table 1:*** **Baseline characteristics**

group I, among whom 98 (41%) of 238 patients in group A+I and 82 (32%) of 260 patients in group I stopped ibrutinib maintenance more than 2 weeks before the completion of 2 years. Median duration of completed ibrutinib maintenance was 22·3 months (range 0·1–29·7, IQR 7·4–24·0) for group A+I (n=168) and 23·9 months (range 0·2–28·3, IQR 15·4–24·0) for group I (n=181). Among 229 patients who completed ASCT and started ibrutinib maintenance, the median time between end of ASCT (stem-cell re-transfusion) and start of ibrutinib maintenance was 49 days (range 20–351, IQR 39–75). 70 patients in group A+I and 78 patients in group I were still on ibrutinib maintenance by the data cutoff date. Rituximab maintenance was added for 168 (58%) of 288 patients in group A, 165 (57%) of 292 patients in group A+I, and 158 (54%) of 290 patients in group I. Treatment had ended in 546 patients (210 in group A, 168 in group A+I, and 168 in group I), among whom 340 (69 in group A, 127 in group A+I, and 144 in group I) ended ibrutinib or rituximab maintenance, and 206 (141 in group A, 41 in group A+I, and 24 in group I) did not start maintenance or progressed or died during maintenance. 324 patients (78 in group A, 124 in group A+I, and 122 in group I) were still on ibrutinib or rituximab maintenance (without documentation of end of maintenance or progression or death).

After a median follow-up of 31 months (95% CI 30·1–33·0, reversed Kaplan–Meier, appendix p 5), failure-free survival at 3 years was 72% (67–79) for group A and 88% (84–92) for group A+I (HR 0·52 [one-sided 98·3% CI 0·00–0·86]; one-sided p=0·0008; figure 2, appendix p 14). The effect was similar within MIPI, cytology, Ki-67, and rituximab maintenance subgroups (figure 3A, appendix pp 6–8), whereas a greater benefit for group A+I was observed in patients with high p53 expression versus group A (HR 0·14 [one-sided 98·3% CI 0·00–0·57]) and high-risk biology (high combined MIPI or p53 immunohistochemistry expression >50%; HR 0·31 [one-sided 98·3% CI 0·00–0·78]; figure 3A, figure 4).

Furthermore, group A failed to show superiority over group I with a 3-year failure-free survival of 72% (95% CI 67–79) for group A compared with 86% (82–91) for group I (HR 1·77 [one-sided 98·3% CI 0·00–3·76]; one-sided p=0·9979; figure 2). The lack of failure-free survival superiority of group A versus group I was observed in all analysed subgroups, and especially in the rituximab maintenance groups (figure 3B, appendix p 7). The pairwise comparison for the superiority test of group A+I versus group I is still ongoing and will be reported later.

Overall survival at 3 years was 86% in group A (95% CI 82–91), 91% in group A+I (88–95), and 92% in group I (88–95; figure 2). Causes of death were progressive lymphoma in 16 (6%) of 288 patients in group A, four (1%) of 292 patients in group A+I, and 11 (4%) of 290 patients in group I (appendix p 15), and comorbidities in 11 (4%) of 288 patients in group A, seven (2%) of 292 patients in group A+I, and five patients (2%) of 290 patients in group I. Treatment-related deaths occurred in four (1%) of 288 patients in group A and three (1%) of 292 patients in group A+I, and no therapy-associated deaths were observed in group I. Due to the limited power, formal statistical tests of overall survival were only pre-planned for the final analysis at the end of the trial. For all time-to-event outcomes, adjusted and stratified analyses yielded effect estimates similar to the unadjusted (appendix p 14). For the primary hypotheses of failure-free survival, modified intention-to-treat analyses excluding 13 patients (four in group A, five in group A+I, and four in group I) did not change the results (appendix p 14).

More patients had disease progression or died in group A (n=67) than in group A+I (n=34) or in group I (n=35). The 3-year progression-free survival was 73% (95% CI 67–79) for group A, 88% (84–93) for group A+I, and 87% (83–92) for group I (appendix p 9). The uncorrected HRs for progression-free survival were 0·46 (one-sided 98·3% CI 0·00–0·72; one-sided p=0·00012) comparing group A+I with group A, and 2·10 (0·00–3·28; p>0·99) comparing group A with group I.

Among patients who had partial response or complete response at end of induction, 52 patients in group A, 30 patients in group A+I, and 32 patients in group I had disease progression or died. The 3-year duration of remission was 76% (95% CI 70–83) in group A, 88% (84–93) in group A+I, and 87% (82–92) in group I (appendix p 9). The HR of duration of remission was 0·52 (one-sided 98·3% CI 0·00–0·84; p=0·0021) for group A+I versus group A and 1·80 (0·00–2·91; p>0·99) for group A versus group I.

Complete response rates (249 [45%] of 559 patients [95% CI 41–49] in groups A+I and I combined *vs* 98 [36%] of 272 patients [30–42] in group A; p=0·020) and overall response rates (549 [98%] of 559 patients [97–99] *vs* 256 [94%] of 272 patients [91–97]; p=0·0025) were higher at end of induction in groups A+I and I combined versus group A. Among patients with partial response, 98 (62%) of 158 (95% CI 54–70) patients in group A, 100 (66%) of 152 (58–74) patients in group A+I, and 85 (57%) of 148 (49–65) patients in group I achieved complete remission during follow-up. Results on the remaining secondary efficacy outcomes, progression-free survival from 4 to 6 weeks after end of induction, midterm response rates, and response rates 4–6 weeks after end of induction are reported in the appendix (p 19). Relevant protocol deviations are summarised in the appendix (p 20).

During induction treatment, the most common grade 3–5 adverse events were blood and lymphatic system disorders (203 [71%] of 287 patients treated with R-CHOP/R-DHAP and 438 [76%] of 579 patients treated with ibrutinib and R-CHOP [IR-CHOP]/R-DHAP; table 2, appendix p 10). Decreased platelets (169 [59%] of 287 patients treated with R-CHOP/R-DHAP *vs* 351 [61%] of 579 patients treated with IR-CHOP/R-DHAP), decreased neutrophil count (135 [47%] of 287 *vs* 288 [50%] of 579), and anaemia (62 [22%] of 287 *vs* 140 [24%] of 579) were the most frequent blood and lymphatic system disorders. Similarly, during ASCT (in patients treated with R-CHOP/R-DHAP *vs* patients treated with IR-CHOP/R-DHAP), blood and lymphatic system disorders remained the most common grade 3–5 adverse events (145 [59%] of 245 *vs* 150 [59%] of 254), followed by general disorders and administration site conditions (49 [20%] of 245 *vs* 54 [21%] of 254), gastrointestinal disorders (51 [21%] of 245 *vs* 51 [20%] of 254), and infections and infestations (41 [17%] of 245 *vs* 52 [20%] of 254), with similar frequencies in both study groups (table 2, appendix p 10). During maintenance or follow-up, more

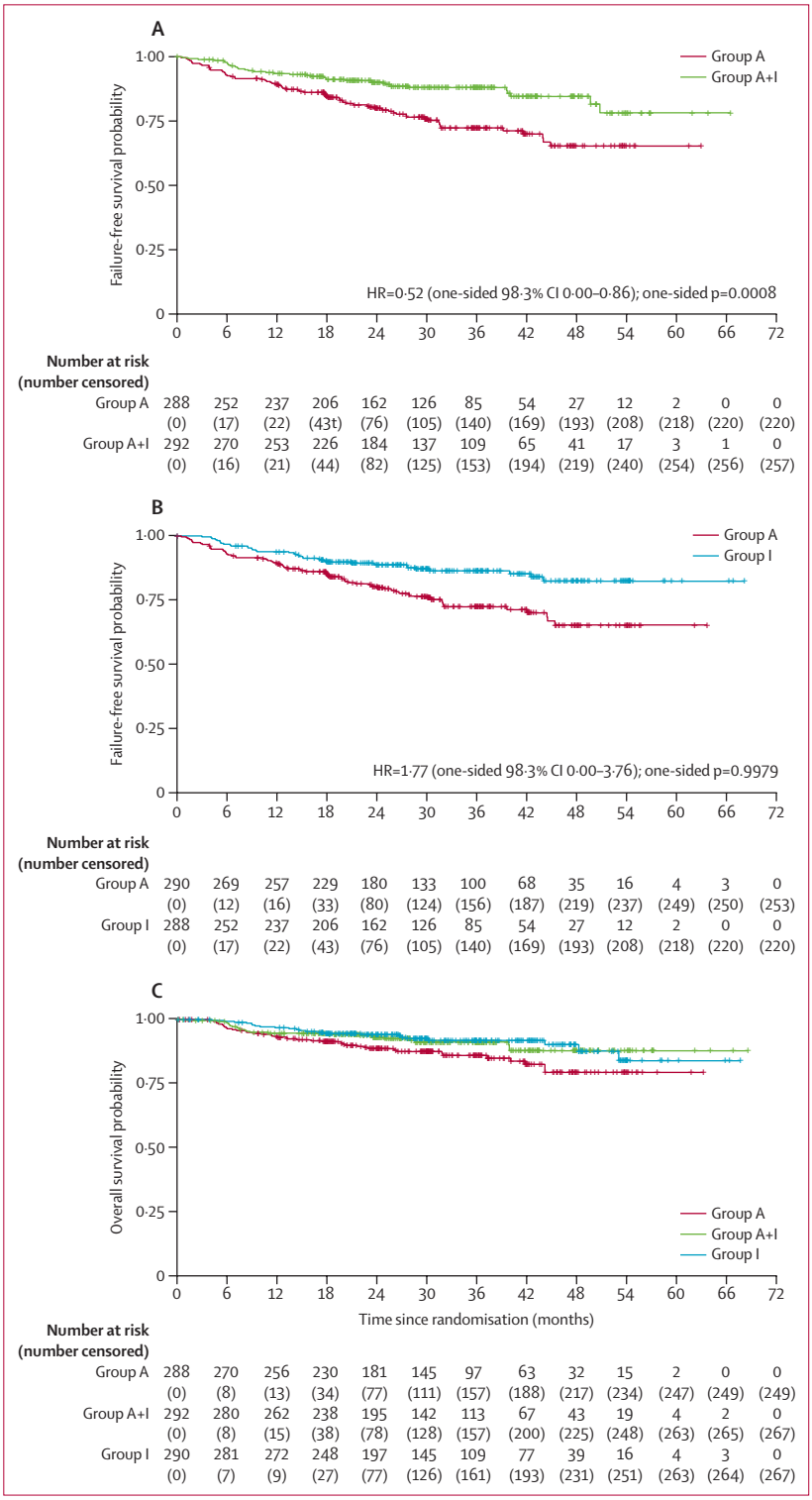


***Figure 2:*** **Failure-free survival for group A+I *vs* group A (A), group A *vs* group I (B), and overall survival for all treatment groups (C)**
HR=hazard ratio.

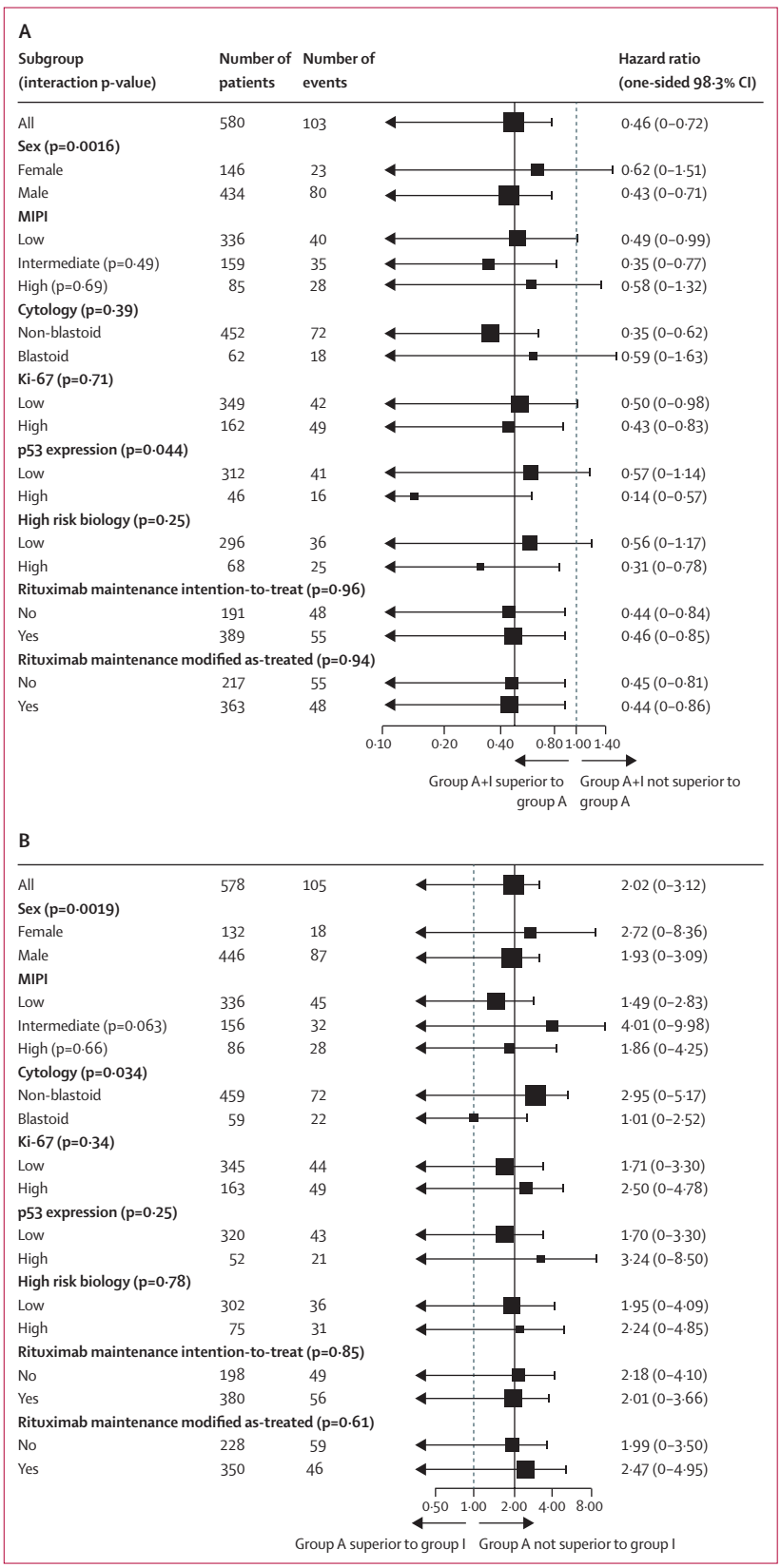


***Figure 3:*** **Forest plot of failure-free survival in subgroups for group A+I *vs* group A (A) and group A *vs* group I (B)**

p values are for interactions. Ki-67 was classified as low (<30%) or high (≥30%); p53 expression was classified as low (≤50%) or high (>50%); high-risk biology was classified as low (low, low intermediate, or high intermediate MIPI-c and low p53 expression) or high (high MIPI-c or high p53 expression). Rituximab maintenance intention-to-treat was defined as rituximab maintenance by centre decision and included patients who started maintenance after the first recorded start date of rituximab maintenance of a trial patient in the same centre, or patients without a documentation of maintenance from a centre where all other patients with documentation of maintenance received rituximab, irrespective of whether rituximab maintenance was actually received. Rituximab maintenance modified as-treated was defined as patients who actually received rituximab maintenance, or if not (eg, patient did not respond), the classification was the same as rituximab maintenance intention-to-treat. All results are uncorrected for the sequential design and hazard ratios are unadjusted. Hazard ratios are shown with one-sided 98·3% CIs corresponding to the primary one-sided hypotheses. No lower confidence limits for the treatment efficacy estimates are given. Superiority of group A+I versus group A was confirmed by an upper confidence limit smaller than 1·0 (A) and superiority of group A versus group I would have been confirmed by an upper confidence limit smaller than 1·0 (B). Due to reduced statistical power in the subgroups, CIs are only hypothesis generating.MIPI=mantle cell lymphoma international prognostic index.

grade 3–5 adverse events were reported in patients receiving ibrutinib either after ASCT (group A+I) or without preceding ASCT (group I), compared with patients without ibrutinib maintenance (group A; table 3, appendix p 11). Blood and lymphatic system disorders occurred in 114 (50%) of 231 patients (group A+I), 74 (28%) of 269 patients (group I), and 51 (21%) of 238 patients (group A), with decreased neutrophil count being most frequent (101 [44%] of 231 *vs* 62 [23%] of 269 *vs* 40 [17%] of 238). Infections and infestations were observed in 58 (25%) of 231 patients (group A+I), 52 (19%) of 269 patients (group I), and 32 (13%) of 238 patients (group A).

Infections were the most common fatal adverse events during ASCT (five [2%] of 254 patients in group A+I and four [2%] of 245 patients in group A) and maintenance or follow-up (two [1%] of 231 patients in group A+I, two [1%] of 269 patients in group I, and three [1%] of 238 patients in group A) for all treatment groups (appendix pp 17–18). Comparing grade 3–5 adverse events during the 4-month period around ASCT (starting 1 month before ASCT) in transplanted patients and the first 4 months of ibrutinib maintenance in patients treated without ASCT confirmed a substantially higher acute toxicity of ASCT (appendix p 16). Up to now, secondary haematological malignancies (appendix p 13) were observed in two patients treated in group A (one acute myeloid leukaemia and one myelodysplastic syndrome) and one patient treated in group I (multiple myeloma). Secondary non-haematological malignancies occurred in 14 (5%) of 292 patients (group A+I), ten (3%) of 290 patients (group I), and five (2%) of 288 patients (group A), with 3-year cumulative incidences of 5·5%, 3·5%, and 2·0% (appendix p 13).

The 3-year cumulative incidence of treatment failure was 21·9% (95% CI 16·3–27·5) in group A, 6% (3–9) in

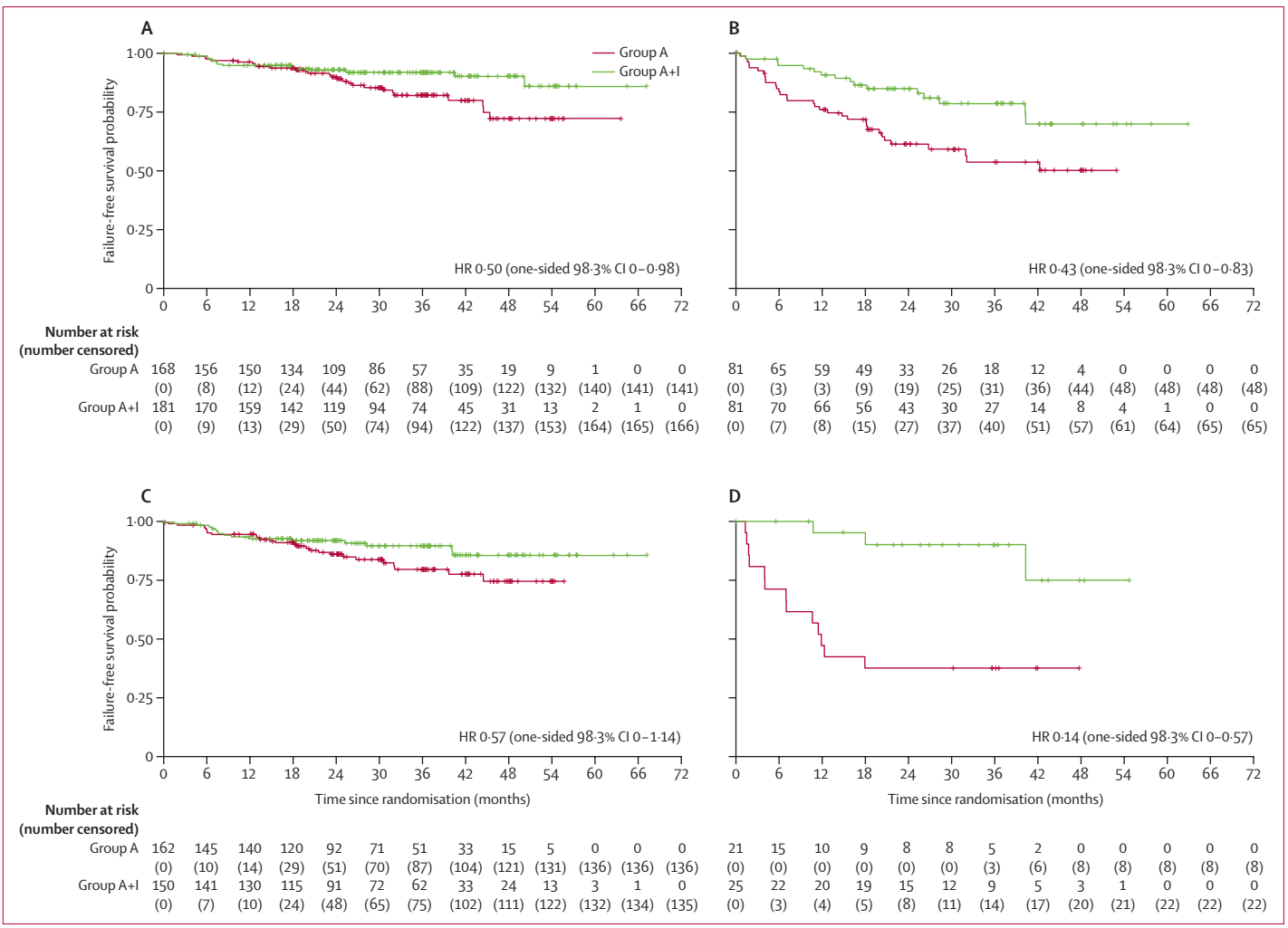


***Figure 4:*** **Failure-free survival for group A+I *vs* group A in selected subgroups of patients with low (<30%) Ki-67 (A), high (≥30%) Ki-67 (B), low (≤50%) p53 (C), and high (>50%) p53 (D)**
HR=hazard ratio.

group A+I, and 10·8% (6·9–14·8) in group I (group A+I *vs* group A: one-sided p<0·0001; group A *vs* group I: one-sided p>0·99; appendix p 12). The cumulative incidence of salvage treatment at 3 years was 18·2% (13·1–23·3) in group A, 5·8% (2·9–8·7) in group A+I, and 10·1% (6·3–13·9) in group I (appendix p 12). Among patients with first-line failure, 43 (63%) of 68 patients in group A, 17 (49%) of 35 patients in group A+I, and 27 (73%) of 37 patients in group I received a salvage therapy, with more patients receiving ibrutinib in group A (34 [79%] of 43) versus group A+I (four [24%] of 17) and group I (three [11%] of 27).

In group I, an exploratory analysis showed improved duration of remission when rituximab was added to maintenance (HR 0·35 [95% CI 0·17–0·72]; p=0·0044). In patients with ibrutinib maintenance without rituximab maintenance (82 in group A+I and 114 in group I), 40 (49%; group A+I) and 38 (33%; group I) had at least one adverse event of infections and infestations of any grade, and 12 (15%) and 13 (11%) patients had at least one grade 3–5 adverse event of infections and infestations. In patients with both ibrutinib and rituximab maintenance (149 in group A+I and 155 in group I), 107 (72%) and 100 (65%) patients experienced at least one adverse event of infections and infestations of any grade, and 46 (31%) and 39 (25%) patients experienced at least one grade 3–5 adverse event of infections and infestations.

The failure-free survival comparison of group A versus group I was pre-planned as one-sided superiority test of the null hypothesis "group A not superior to group I" on a one-sided 1·667% significance level. An exploratory post hoc calculation of a two-sided p value fulfilling a two-sided significance level of 3·333%—corresponding to trial-wise two-sided 10% significance level after Bonferroni-correction—yielded a two-sided p=0·004 correcting for the sequential design. The two-sided 96·667% CI for the group A versus group I failure-free survival comparison, uncorrected for the sequential design, was 1·30–3·10.

| | R-CHOP/ R-DHAP (n=287) | IR-CHOP/ R-DHAP (n=579) | R-CHOP/ R-DHAP+ASCT (n=245) | IR-CHOP/ R-DHAP+ASCT (n=254) |
|---|---|---|---|---|
| **During induction** | | | | |
| Blood and lymphatic system disorders | 203 (71%) | 438 (76%) | .. | .. |
| Platelet count decreased | 169 (59%) | 351 (61%) | .. | .. |
| Neutrophil count decreased | 135 (47%) | 288 (50%) | .. | .. |
| Anaemia | 62 (22%) | 140 (24%) | .. | .. |
| White blood cell decreased | 44 (15%) | 88 (15%) | .. | .. |
| Febrile neutropenia | 25 (9%) | 70 (12%) | .. | .. |
| Lymphocyte count decreased | 15 (5%) | 38 (7%) | .. | .. |
| Gastrointestinal disorders | 36 (13%) | 70 (12%) | .. | .. |
| Nausea | 13 (5%) | 17 (3%) | .. | .. |
| Vomiting | 10 (3%) | 18 (3%) | .. | .. |
| Diarrhoea | 7 (2%) | 21 (4%) | .. | .. |
| Infections and infestations | 26 (9%) | 72 (12%) | .. | .. |
| Metabolism and nutrition disorders | 19 (7%) | 75 (13%) | .. | .. |
| Hypokalaemia | 4 (1%) | 34 (6%) | .. | .. |
| General disorders and administration site conditions | 16 (6%) | 37 (6%) | .. | .. |
| Fatigue | 6 (2%) | 15 (3%) | .. | .. |
| Investigations | 11 (4%) | 42 (7%) | .. | .. |
| Renal and urinary disorders | 14 (5%) | 38 (7%) | .. | .. |
| Acute kidney injury | 12 (4%) | 35 (6%) | .. | .. |
| Vascular disorders | 13 (5%) | 32 (6%) | .. | .. |
| Hypertension | 8 (3%) | 24 (4%) | .. | .. |
| Nervous system disorders | 9 (3%) | 28 (5%) | .. | .. |
| Cardiac disorders | 6 (2%) | 19 (3%) | .. | .. |
| Respiratory, thoracic, and mediastinal disorders | 8 (3%) | 17 (3%) | .. | .. |
| **During ASCT** | | | | |
| Blood and lymphatic system disorders | .. | .. | 145 (59%) | 150 (59%) |
| Platelet count decreased | .. | .. | 119 (49%) | 111 (44%) |
| Neutrophil count decreased | .. | .. | 89 (36%) | 85 (33%) |
| Anaemia | .. | .. | 50 (20%) | 56 (22%) |
| Febrile neutropenia | .. | .. | 49 (20%) | 56 (22%) |
| White blood cell decreased | .. | .. | 42 (17%) | 42 (17%) |
| Lymphocyte count decreased | .. | .. | 9 (4%) | 7 (3%) |
| General disorders and administration site conditions | .. | .. | 49 (20%) | 54 (21%) |
| Mucosal inflammation | .. | .. | 39 (16%) | 45 (18%) |
| Fever | .. | .. | 10 (4%) | 8 (3%) |
| Gastrointestinal disorders | .. | .. | 51 (21%) | 51 (20%) |
| Mucositis oral | .. | .. | 21 (9%) | 21 (8%) |
| Nausea | .. | .. | 11 (4%) | 16 (6%) |
| Diarrhoea | .. | .. | 13 (5%) | 6 (2%) |
| Infections and infestations | .. | .. | 41 (17%) | 52 (20%) |
| Sepsis | .. | .. | 7 (3%) | 17 (7%) |
| Lung infection | .. | .. | 8 (3%) | 11 (4%) |
| Other | .. | .. | 5 (2%) | 12 (5%) |
| Device-related infection | .. | .. | 6 (2%) | 7 (3%) |

(Table 2 continues on next page)

## Discussion

In this large, randomised, phase 3 trial, the pre-trial standard of immunochemotherapy followed by ASCT in younger patients was challenged by ibrutinib, either in combination or instead of ASCT. Both experimental ibrutinib-containing groups showed a relevant improvement in response rates as well as failure-free survival. In line with previous reports on immunochemotherapy-only based regimens, especially in the biological high-risk subset with p53 overexpression, the addition of ibrutinib led to a major improvement in efficacy.[6,7]

According to the predefined statistical design, the superiority of ibrutinib in addition to standard treatment has been statistically confirmed, whereas the superiority of the previous ASCT-containing standard (group A) over the experimental ibrutinib-containing group without ASCT (group I) was not confirmed. In this trial, we reconsidered the efficacy of ASCT-containing treatment in the setting of today's clinical standard approaches including cytarabine-containing induction, rituximab maintenance, and ibrutinib, which were not established when the randomised trial confirming the superiority of ASCT was performed.[11] The rationale for the one-sided superiority test for group A versus group I relied on the judgement of an ASCT-related death rate of approximately 3%, considering the application of ASCT only acceptable if a significantly improved long-term outcome was proven. At the planning stage, we did not anticipate a potential for group I to be superior to group A, but assumed comparable efficacy. A two-sided design was neither considered reasonable or feasible. Thus, the calculated two-sided p values and CIs are only exploratory. Of note, the retrospectively calculated two-sided p value on a trial-wise two-sided significance level of 10% and the uncorrected 98·3% CIs are consistent with and suggestive for a superiority of ibrutinib plus immunochemotherapy standard without ASCT over immunochemotherapy standard with ASCT.

So far, Kaplan–Meier plots of both ibrutinib-containing groups are overlapping, and the statistical monitoring is still ongoing. Thus, further follow-up is required to determine whether ASCT adds any benefit to the ibrutinib-only group. In contrast, the observed toxicity during ASCT and maintenance clearly favours the ibrutinib-only group.

Importantly, the results of the immunochemotherapy standard with ASCT group are almost superimposable to our previously reported outcome of this regimen.[12] We chose failure-free survival as the primary outcome because in mantle cell lymphoma stable disease is associated with poor prognosis and usually represents an indication for salvage treatment. Of note, due to the high efficacy of induction treatment, progression-free survival and failure-free survival only differed in seven patients and results for failure-free survival and progression-free survival were almost identical.

In accordance with the Data and Safety Monitoring Committee we decided to display the overall survival rates along with the failure-free survival results, but to postpone the statistical overall survival evaluation until longer follow-up is available. So far, the separation of the two ibrutinib failure-free survival curves from the ASCT only group seems to translate in corresponding overall survival trends.

At the trial planning stage, results from the LYSA-LYMA trial became available, showing that rituximab maintenance prolongs progression-free survival and overall survival after cytarabine-containing induction and ASCT.[13] Therefore, the TRIANGLE trial allowed rituximab maintenance be added to all three trial groups from the beginning according to national guidelines. During the trial, the results were fully published, and rituximab maintenance became standard of care in most European countries. However, the implementation of rituximab maintenance into routine care was heterogeneous in different countries. Therefore, among all randomly assigned patients (including those not responding to treatment), rituximab maintenance was given to 56% of patients comparably in all three trial groups. An exploratory analysis confirmed the benefit of rituximab maintenance in this setting, resulting in improved progression-free survival rates (HR 0·35). The benefit of ibrutinib was also independent of rituximab maintenance (ie, both patient subsets, with and without rituximab maintenance, showed comparable results). The observed toxicity rates for the combined ibrutinib and rituximab maintenance were slightly increased in comparison with ibrutinib monotherapy. However, feasibility seems to be comparable, based on a similar median duration of completed maintenance.

Mainly driven by younger age, the trial population was generally of lower risk as reflected by only 15% of patients being clinically high-risk according to MIPI. Interaction analyses did not reveal significant differences in treatment efficacy by MIPI risk groups.

These results are somewhat in contrast to a similar study in older patients.[17] In that study, after a prolonged follow-up the addition of unlimited ibrutinib to a bendamustine–rituximab induction with rituximab maintenance resulted in a slightly improved progression-free, but almost identical overall survival. The detailed analysis of toxicities did not identify a unique reason for the increased non-lymphoma mortality, but overall, increased rates of side-effects were detected especially during the maintenance phase. Likewise, in diffuse large B-cell lymphoma the combination of ibrutinib with R-CHOP also led to a superior progression-free survival, whereas in older patients a significantly increased toxicity of the combined regimen hampered the survival rates.[21]

Recently, ibrutinib has been withdrawn from the US market for relapsed mantle cell lymphoma due to formal reasons but two additional second generation BTK inhibitors are still registered for relapsed mantle cell

| | R-CHOP/ R-DHAP (n=287) | IR-CHOP/ R-DHAP (n=579) | R-CHOP/ R-DHAP+ASCT (n=245) | IR-CHOP/ R-DHAP+ASCT (n=254) |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Metabolism and nutrition disorders | .. | .. | 27 (11%) | 21 (8%) |
| Hypokalaemia | .. | .. | 9 (4%) | 13 (5%) |
| Decreased appetite | .. | .. | 10 (4%) | 6 (2%) |
| Investigations | .. | .. | 12 (5%) | 13 (5%) |
| Respiratory, thoracic, and mediastinal disorders | .. | .. | 9 (4%) | 12 (5%) |
| Vascular disorders | .. | .. | 7 (3%) | 9 (4%) |
| Skin and subcutaneous tissue disorders | .. | .. | 3 (1%) | 10 (4%) |
| Cardiac disorders | .. | .. | 6 (2%) | 2 (1%) |

Grade 3–5 adverse events and preferred terms occurring in at least 3% of patients in any treatment group shown. MedDRA coded preferred terms and system organ class were reclassified to match Common Terminology Criteria for Adverse Events version 4·03 for all preferred terms that had occurred in more than ten patients. ASCT=autologous stem-cell transplantation. IR-CHOP=ibrutinib with R-CHOP. R-CHOP=intravenous rituximab 375 mg/m², intravenous cyclophosphamide 750 mg/m², intravenous doxorubicin 50 mg/m², intravenous vincristine 1·4 mg/m², and oral prednisone 100 mg. R-DHAP=intravenous rituximab 375 mg/m², intravenous or oral dexamethasone 40 mg, intravenous cytarabine 2 × 2 g/m², and intravenous cisplatin 100 mg/m².

***Table 2:*** **Frequency of patients with at least one grade 3–5 adverse event by system organ class and preferred terms during induction and ASCT**

| | Group A (N=238) | Group A+I (N=231) | Group I (N=269) |
|---|---|---|---|
| Blood and lymphatic system disorders | 51 (21%) | 114 (50%) | 74 (28%) |
| Neutrophil count decreased | 40 (17%) | 101 (44%) | 62 (23%) |
| Febrile neutropenia | 6 (3%) | 14 (6%) | 7 (3%) |
| Platelet count decreased | 5 (2%) | 13 (6%) | 8 (3%) |
| White blood cell decreased | 4 (2%) | 10 (4%) | 6 (2%) |
| Anaemia | 4 (2%) | 6 (3%) | 4 (1%) |
| Infections and infestations | 32 (13%) | 58 (25%) | 52 (19%) |
| Lung infection | 13 (5%) | 22 (10%) | 18 (7%) |
| Coronavirus infection | 4 (2%) | 7 (3%) | 15 (6%) |
| Shingles | 1 (<1%) | 10 (4%) | 1 (<1%) |
| Gastrointestinal disorders | 7 (3%) | 14 (6%) | 12 (4%) |
| Diarrhoea | 2 (1%) | 7 (3%) | 5 (2%) |
| Nervous system disorders | 3 (1%) | 12 (5%) | 12 (4%) |
| Cardiac disorders | 3 (1%) | 7 (3%) | 12 (4%) |
| General disorders and administration site conditions | 5 (2%) | 6 (3%) | 11 (4%) |
| Musculoskeletal and connective tissue disorders | 4 (2%) | 6 (3%) | 9 (3%) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | 6 (3%) | 6 (3%) | 7 (3%) |
| Investigations | 2 (1%) | 12 (5%) | 2 (1%) |
| Gamma-glutamyl transferase increased | 2 (1%) | 6 (3%) | 0 |
| Injury, poisoning, and procedural complications | 1 (<1%) | 4 (2%) | 9 (3%) |
| Respiratory, thoracic, and mediastinal disorders | 2 (1%) | 7 (3%) | 4 (1%) |
| Vascular disorders | 2 (1%) | 3 (1%) | 7 (3%) |
| Metabolism and nutrition disorders | 0 | 4 (2%) | 7 (3%) |
| Skin and subcutaneous tissue disorders | 1 (<1%) | 8 (3%) | 1 (<1%) |

Grade 3–5 adverse events and preferred terms occurring in at least 3% of patients in any treatment group shown. MedDRA coded preferred terms and system organ class were reclassified to match Common Terminology Criteria for Adverse Events version 4.03 for all preferred terms that had occurred in more than ten patients.

***Table 3:*** **Frequency of patients with at least one grade 3–5 adverse events by system organ class and preferred terms during maintenance or follow-up**

lymphoma.[22,23] Although these compounds seem to have quite comparable efficacy, no phase 3 data on combinations with chemotherapy are currently available.

Based on this potentially new standard of an ibrutinib-containing regimen, salvage treatment in patients might be more challenging. Historically, patients progressing under ibrutinib showed a poor outcome independent of conventional salvage treatment.[24] Therefore, it is important to emphasise that the ibrutinib maintenance in the current trial was applied for a fixed duration (2 years), and the majority of patients were still in remission after completion of maintenance. Thus, re-exposure with BTK inhibitors might be worthwhile, but only scarce data on salvage after a time-limited ibrutinib treatment are currently available in mantle cell lymphoma.[25] In addition, immunological approaches including CAR T cells and bispecific antibodies as well as BTK protein degraders or non-covalent BTK inhibitors might at least partially overcome the poor outcome of relapses after covalent BTK inhibitors.[26–28]

Limitations of our study include the still limited follow-up, and the outstanding comparison of the two experimental groups and overall survival as discussed. Unfortunately, no patient-reported outcomes were collected in this complex academic trial.

Based on our results, it is possible immunochemotherapy could be omitted in first-line treatment similar to chronic lymphocytic leukaemia. So far, two phase 2 studies have reported an excellent outcome in mostly low-risk patients.[29,30] However, this question has to be explored in future trials.

In conclusion, our phase 3 trial demonstrates the superior efficacy of ibrutinib-containing immunochemotherapy compared with the pre-trial standard approach with ASCT consolidation and defines a new standard of care in front-line treatment of young, medically fit mantle cell lymphoma patients. Whether ASCT, with additional toxicity, still adds benefit to ibrutinib-based treatment in subsets of patients is not yet determined.

#### Contributors

MD, JDo, EG, MJ, JW, MHu, UM, JR, MT, VV, OS, MGdS, SL, StS, AK, RJ, MC, GH, LA, CV, TvM, SW, PLZ, UN, PH, FB, KS, CH, MHa, JDi, CP, WK, CS, and ML were involved in the investigation. MD, JDo, EG, MJ, JW, UM, MT, OS, GH, DG, CS, ML, and EH were involved in providing resources. MD, JDo, EG, MJ, JW, MHu, UM, JR, MT, VV, OS, MGdS, SL, LJ, StS, AK, RJ, MC, GH, LA, CV, TvM, SW, PLZ, UN, PH, FB, KS, CH, MHa, JDi, CP, WK, CS, MU, ML, and EH were involved in writing (review and editing). MD, JDo, EG, MJ, JW, UM, MT, OS, GH, CS, MU, ML, and EH were involved in conceptualisation. MD, LJ, CS, and EH were involved in methodology. MD, JDo, EG, MJ, JW, UM, OS, DG, CS, MU, and ML were involved in project administration. MD, JDo, EG, MJ, JW, UM, JR, VV, OS, MGdS, SL, AK, RJ, MC, LA, CV, TvM, PLZ, UN, PH, FB, KS, CH, MHa, JDi, CP, WK, DG, MU, ML, and EH were involved in supervision. MD and DG were involved in funding acquisition. LJ, MU, and EH were involved in software. MD, MT, and MU were involved in data curation. MD, JDo, EG, MJ, JW, UM, JR, VV, OS, MGdS, SL, LJ, AK, RJ, MC, LA, CV, TvM, PLZ, UN, PH, FB, KS, CH, MHa, JDi, WK, MU, ML, and EH were involved in validation. MD, LJ, MU, and EH were involved in formal analysis. MD, LJ, and EH were involved in writing the original manuscript draft. LJ and EH were involved in visualisation. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. LJ, MU, and EH directly assessed and verified the underlying data reported in the manuscript.

#### Declaration of interests

MD reports research grants for clinical studies from AbbVie, Bayer, Bristol-Myers Squibb/Celgene, Gilead/Kite, Janssen, and Roche; speakers' honoraria from AstraZeneca, BeiGene, Gilead/Kite, Janssen, Lilly, Novartis, and Roche; travel support from Janssen and Roche; and participation on a Data Safety Monitoring Board or Advisory Board for AbbVie, AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Gilead/Kite, Janssen, Lilly/Loxo Oncology, Novartis, and Roche. JDo reports payment for expert testimony (once Advisory Board) from Lilly. EG reports grants from Janssen; honoraria (educational lecture) from Genmab, Gilead, Janssen, and Lilly; support for attending meetings or travel from Janssen and Roche; and participation on a Data Safety Monitoring Board or Advisory Board for Gilead/Kite and Miltenyi Biotec. MJ reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie, Gilead/Kite, and Roche; participation on a Data Safety Monitoring Board or Advisory Board for AbbVie, Gilead/Kite, Janssen, and Pierre Fabre. JW reports grants to his institution from GlaxoSmithKline/Novartis and Roche; honoraria for lectures from AbbVie, Amgen, Gilead, Novartis, Roche, Servier, and Takeda; participation on an Advisory Board from AbbVie, Gilead, Novartis, Roche, and Takeda. MHu reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie, AstraZeneca, Celgene, Genmab, Janssen, Merck, Roche, and Takeda; participation on a Data Safety Monitoring Board or Advisory Board for AbbVie, AstraZeneca, Celgene, Genmab, Janssen, Merck, Roche, and Takeda. UM reports travel support from Amgen, Bristol-Myers Squibb/Celgene, Gilead, Janssen-Cilag, and Roche; Advisory Board role for Amgen, AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Gilead, Incyte, Janssen-Cilag, Novartis, Pfizer, Roche, Sanofi, and Takeda; participation in national Guideline committee for the German-Swiss-Austrian Guideline for Mantle Cell Lymphoma. JR reports participation on an Advisory Board for AstraZeneca. VV reports consulting fees from AbbVie, BeiGene, Gilead, Lilly, and Roche; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Janssen; payment for expert testimony from Gilead and Roche; support for attending meetings or travel from AbbVie and Gilead. MGdS reports a research grant from AstraZeneca; payment for Advisory Boards from AbbVie, Gilead, Janssen-Cilag, Roche, and Takeda; payment or honoraria for educational events from Gilead and Janssen-Cilag; support for attending meetings or travel from AbbVie, Janssen-Cilag, Roche, and Takeda; participation on a Data Safety Monitoring Board or Advisory Board for Roche; leadership in a scientific society (Sociedade Portuguesa de Hematologia); administration board on a patient advocacy group (Associação Portuguesa Contra a Leucemia). SL reports grants or contracts to her institution from Bristol-Myers Squibb/Celgene, Genmab, HUTCHMED, Novartis, and Roche; consulting fees from AbbVie, Genmab, Gilead, Novartis, ORION Pharma, Roche, and Swedish Orphan Biovitrum (sobi); payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Gilead, Incyte, and Novartis; participation on a Data Safety Monitoring Board or Advisory Board for Incyte. StS reports grants or contracts from any entity from AbbVie, Acerta Pharma, Amgen, AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Roche, Gilead, GlaxoSmithKline, Infinity Pharmaceuticals, Janssen, Novartis, Sunesis Pharmaceuticals, and Verastem; consulting fees from AbbVie, Acerta Pharma, Amgen, AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Roche, Gilead, GlaxoSmithKline, Infinity Pharmaceuticals, Janssen, Novartis, Sunesis Pharmaceuticals, and Verastem; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie, Acerta Pharma, Amgen, AstraZeneca, BeiGene, Bristol-Myers Squibb/Celgene, Roche, Gilead, GlaxoSmithKline, Infinity Pharmaceuticals, Janssen, Novartis, Sunesis Pharmaceuticals, and Verastem; participation on a Data

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### Data sharing

Clinical data along with annotated case report form can be provided on the basis of a scientific collaboration within the European Mantle Cell Lymphoma Network after approval of a proposal by the scientific committee of the European Mantle Cell Lymphoma Network (www.european-mcl.net).

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