Stem Cell Transplant for Mantle Cell Lymphoma in Taiwan

Yu-Hung Wang
National Taiwan University Hospital
Ching-Yun Hsieh
China Medical University Hospital
Liang-Tsai Hsiao
Taipei Veterans General Hospital
Tung-Liang Lin
Linkou Chang Gung Memorial Hospital
Yi-Chang Liu
Kaohsiung Medical University
Ming Yao
National Taiwan University Hospital
Tran-Der Tan
Koo Foundation Sun Yat-Sen Cancer Center
Bor-Sheng Ko (bskomd@ntu.edu.tw)
National Taiwan University Cancer Centre

Research Article

Keywords: mantle cell lymphoma, stem cell transplant, Taiwan, ibrutinib

Posted Date: November 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1031902/v1

Version of Record: A version of this preprint was published at Scientific Reports on April 5th, 2022. See the published version at https://doi.org/10.1038/s41598-022-09539-5.

Abstract

Mantle cell lymphoma (MCL) is a B-cell lymphoma featuring an aggressive course and a progressive relapsing pattern. International guidelines recommend early consolidative autologous stem cell transplant (auto-SCT) for eligible patients while reserving allogeneic SCT (allo-SCT) as second-line therapy for refractory cases. Since data describing the implementation of transplants in the Asian population with MCL are limited, we aimed to analyze post-SCT outcomes of 99 MCL patients from the Taiwan Bone Marrow Transplant Registry database. The median age was 56 years, and 11% of the patients had blastoid variant MCL. Ninety-four patients received auto-SCT, while 13 patients received allo-SCT, eight of which received allo-SCT after failing auto-SCT. Before auto-SCT, 52% of the patients were in their first complete remission (CR1). Overall, 37 patients (39%) relapsed after auto-SCT. The median post-auto-SCT progression-free survival and overall survival (OS) were 43.6 months and not reached, respectively. Blastoid variant MCL, transplant not received in CR1, and disease progression within 12 months post-auto-SCT independently predicted inferior OS in multivariate analysis. The median post-allo-SCT OS was 74 months. Two patients (15%) died of MCL recurrence post-allo-SCT. Three patients with refractory diseases were salvaged with ibrutinib or venetoclax to allo-SCT. Treatment strategies incorporating novel agents warrant further optimization.

Introduction

Mantle cell lymphoma (MCL) is a B-cell lymphoma that mostly presents with an advanced stage and frequent extranodal involvement, including bone marrow and gastrointestinal tract involvement[1-5]. The clinical course is typically aggressive, with a progressive shortening of response duration and disease-free survival after each relapse[6,7]. High-dose chemotherapy with autologous stem cell transplant (auto-SCT) has become the standard of care for eligible patients[8-10]. Nevertheless, the high chance of disease recurrence within 3–5 years, particularly in high-risk populations (i.e., patients with blastoid variant MCL or *TP53* mutation), often affects the post-SCT course and makes long-term survival challenging[11-15]. Allogeneic SCT (allo-SCT), which is often reserved as a second-line treatment, remains an option for those who fail auto-SCT or have refractory disease[16,17]. Recently, in line with the promising responses to small molecule targeted agents, such as BTK and BCL-2 inhibitors, treatment strategies combining conventional therapy, auto-SCT or allo-SCT, and targeted therapies may be warranted[18-23].

The current risk stratification and global treatment guidelines were primarily developed based on Western studies[24-27]. Data that describe the epidemiology, use of transplantation, and outcomes in Asian populations are relatively scarce[28-34]. Herein, we present a registry-based study and delineate the post-SCT outcome of 99 MCL patients in Taiwan. Pre-SCT parameters and therapy modalities were also analyzed for risk stratification and survival prediction.

Results

Patient characteristics

In total, 94 patients received auto-SCT, while 13 patients received allo-SCT (8 of which received the allo-SCT after relapsing after auto-SCT). The median age of the 94 MCL patients who received only auto-SCT was 55 years (Table 1). There were 77 male patients and 17 female patients. The Ann Arbor stage at diagnosis in most patients was stage 4 (79.8%). Approximately three-fourths of patients (74.5%) had bone marrow involvement at diagnosis. Regarding morphology subtypes, 76 patients (87.2%) had a classic type, 10 (10.6%) had blastoid variant MCL, and 2 (2.2%) had pleomorphic variant MCL. In terms of MIPI classification, patients were stratified into low (40.7%), intermediate (39.5%), and high (19.8%) risk groups. In 18 patients with available Ki-67% data from the registry, eight patients (44.4%) had a Ki-67% equal to or higher than 30%.

The characteristics of the 13 patients who received allo-SCT are presented in Table 2. The median age was 49.6 years. Three of the 13 (23%) patients had blastoid variant MCL, whereas 11 of the 13 (85%) patients had bone marrow involvement of MCL at diagnosis. Overall, 7 (54%), 2 (15%), and 4 (31%) patients had low-, intermediate-, and high-risk disease according to the MIPI classification.

Stem cell harvest and transplantation procedures

In Taiwan, the most commonly used regimen for stem cell harvest is etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) with or without rituximab, followed by granulocyte colony-stimulating factor (G-CSF) administration[35]. A minority of patients received high-dose cytarabine in combination with dexamethasone and cisplatin (DHAP) or other cytarabine-based regimens before harvest[36]. All except for ten patients received BCNU, etoposide, cytarabine, and melphalan (BEAM) as the conditioning chemotherapy regimen before auto-SCT[37]. Ten patients received the Benda-EAM regimen (which substitutes the BCNU in the BEAM regimen with bendamustine) as the conditioning regimen[38,39]. The most commonly used conditioning regimens for allo-SCT in Taiwan are generally categorized into myeloablative and reduced-intensity regimens. The myeloablative regimens are usually backboned with busulfan IV 3.2 mg/kg/day consecutively from day -8 to day -5 and cyclophosphamide IV 60 mg/kg/day on day -3 and day -2. In contrast, the reduced-intensity regimens are based on the following scheme: fludarabine 30 mg/m2/day consecutively from day -8 to day -4, busulfan IV 3.2 mg/kg/day on day -5 and day -4, and cyclophosphamide IV 60 mg/kg/day on day -2. Anti-thymocyte globulin (ATG) 4-6 mg/kg can be added as a part of the conditioning regimen in HLA-mismatched allo-SCT scenarios. Usually, cyclosporin with methotrexate is used

for graft-versus-host disease (GVHD) prevention in myeloablative allo-SCT, and cyclosporin with mycophenolate mofetil is used for reduced-intensity protocols.

Stem cell transplantation

Before auto-SCT, 49 patients (52.1%) were in their first complete remission (CR1), 16 (17%) were in their second complete remission (CR2), and 29 (30.9) were in partial remission (PR). Overall, 37 patients (39.4%) had recurrence of disease after auto-SCT. Among them, eighteen (48.6%) patients experienced relapse within 12 months after auto-SCT. The median time to post-auto-SCT relapse was 13.1 months (range: 0.7-84).

Among the 13 patients who received allo-SCT, 8 experienced relapses after prior auto-SCT (Table 2). Five patients had primary refractory diseases and were salvaged with various regimens to receive frontline allo-SCT. Only two (15.4%) patients had recurrence of MCL after allo-SCT and eventually succumbed to the disease. However, three patients died of infections after allo-SCT. Patient unlinked patient number (UPN) 13 had disease progression before the scheduled auto-SCT, and he was salvaged with ibrutinib and achieved PR prior to subsequent allo-SCT. Patient UPN 14 had a primary disease that was refractory to multiple lines of therapy and finally achieved PR after treatment with a combination of asparaginase, paclitaxel, and gemcitabine. He then received allo-SCT and was disease-free and alive until the last follow-up. Patient UPN 36 experienced relapse one month after her auto-SCT. Allo-SCT was used as salvage due to the rapid progression of the disease. She had acute GVHD and ensuing infection and died of uncontrolled infection; imaging and bone marrow examinations before death showed no evidence of disease recurrence. Patient UPN 41 had blastoid variant MCL and relapsed eight months after auto-SCT. Her lymphoma was refractory to ibrutinib; rituximab, BCNU, vincristine, methotrexate etoposide, and methylprednisolone (R-BOMES); and rituximab, bendamustine, and cytarabine (R-BAC). She finally attained PR with venetoclax and underwent allo-SCT. Patient UPN 46 had primary refractory disease, although we confirmed that he had nonblastoid MCL. He received ibrutinib with bendamustine and rituximab and was bridged to allo-SCT. Other details are shown in Table 2.

Infections

Within 180 days of auto-SCT, 46 infection episodes were documented. Seven (15.2%) patients experienced gram-negative bacilli bacteremia, and five had gram-positive cocci bacteremia. Three patients had invasive fungal infection, and one had *Pneumocystis jiroveci* pneumonia. Notably, 12 (26.1%) patients had cytomegalovirus antigenemia, while another two patients had cytomegalovirus colitis after auto-SCT. Approximately one-tenth of patients experienced a flare-up of herpes simplex virus and subsequent varicella-zoster virus infection. Other details are provided in Supplementary Table 1.

Maintenance therapy

After proceeding with auto-SCT or allo-SCT, 22 (22.2%) patients received maintenance therapy. Twelve (54.5%) patients received rituximab, two of whom received rituximab and alternating bortezomib; six (27.3%) patients used bortezomib for maintenance therapy; and four used ibrutinib.

Ibrutinib

Ibrutinib was used at a dose of 560 mg/day in twelve patients as a salvage therapy: in ten patients, ibrutinib was administered because of relapse after prior auto-SCT, and in two patients, ibrutinib was administered as salvage and bridging therapy to allo-SCT. The median treatment line of ibrutinib was 3.5 (range: 2-6). The median duration of ibrutinib use was 4.6 months (range: 0.5-64). Of the ten evaluable patients, the overall response rate was 70%. Four (40%) patients achieved PR, whereas 3 (30%) patients attained complete remission. Two patients (20%) maintained stable disease, while one patient (10%) had disease progression despite treatment. The median time to response and the response duration were 2.1 months (range: 0.6-4.4) and 6.6 months (range: 1.3-59), respectively. Two patients (20%) lost their response after three months and 18 months. The most frequently encountered adverse events were bleeding (30%) and pulmonary infection (30%), including *Pneumocystis jiroveci* pneumonia in two patients (20%) and pulmonary nontuberculous mycobacterial infection in one patient (10%), followed by cytopenia (20%) and general fatigue (10%).

Survival

The median post-auto-SCT PFS and OS, censored at allo-SCT if performed, of the 94 patients receiving auto-SCT were 43.6 months and not reached (NR), respectively (Figure 1a). Furthermore, the median post-allo-SCT PFS and OS of the 13 patients receiving allo-SCT were 36 months and 48.9 months, respectively (Figure 1b).

Specifically, for auto-SCT, patients with blastoid variant MCL had significantly shorter PFS and OS than those without blastoid variant MCL (median PFS, 7.9 months vs. 43.6 months, $p<0.001$, Figure 2a; and median OS, 25.5 months vs. NR, $p=0.015$, Figure 2b). Furthermore, disease status before auto-SCT also had an impact on survival, as expected. Patients who underwent auto-SCT in CR1 (n=49, 52.1%) had more prolonged survival than those who underwent auto-SCT in CR2 or PR (PFS, 50.8 vs. 31.3 months, $p=0.084$; and OS, NR vs. 66.8 months, $p=0.013$, Figures 3a and 3b, respectively). After auto-SCT, patients who had progression of disease within 12 months post-auto-SCT (POD12)[14] had a significantly inferior OS compared with those who did not have POD12 (median: 23.3 months vs. NR, $p=0.002$, Figure 4). In the multivariate analysis, blastoid variant MCL, transplant not received in CR1, and POD12 independently predicted worse post-auto-SCT survival (Table 3).

Discussion

International guidelines recommend various induction regimens, mainly cytarabine-containing regimens, for transplant-eligible MCL patients and underscore the importance of frontline auto-SCT[26,27]. The survival benefit of early consolidation followed by auto-SCT was first reported in a prospective randomized trial of the European MCL Network, notwithstanding that there was only a PFS, but not an OS, benefit[10]. In Asia, Miura et al. analyzed the outcomes of 64 newly diagnosed Japanese patients with MCL[40]. Sixteen patients in the study received various intensive chemotherapies and ensuing auto-SCT. Before auto-SCT, nine patients were in CR1, one was in CR2, and six were refractory. The survival was quite promising, with a 5-year OS of 93%, compared to the 5-year OS of less than 50% in their counterparts. In another retrospective study, 16% of 501 Japanese patients received auto-SCT following induction chemotherapy with a rituximab-high-dose cytarabine combination[41]. This strategy yielded HRs of 0.24 and 0.43 for PFS and OS, respectively, compared to R-CHOP treatment. A survival benefit of frontline auto-SCT was also observed in 97 transplant-eligible patients in a recently published Taiwanese study[30]. This multi-institutional study identified auto-SCT, gastric MCL involvement, blastoid variant MCL, and POD12 as independent prognostic factors. Patients who underwent auto-SCT in CR1 also had a better OS than those who underwent auto-SCT in CR2 or PR (median OS: NR vs. 71 months, p=0.027). In line with previously mentioned studies, approximately half of the patients in the present study received auto-SCT in CR1 and had a superior post-SCT survival than those who received auto-SCT in CR2 or PR. In addition, while transplant received in CR1 and POD12 both had prognostic significance in the multivariate analysis, there seemed to be a lower incidence of POD12 in patients transplanted in CR1 than in those transplanted in CR2 or PR (12.2% vs. 28.9%, p=0.07).

The role of maintenance therapy with rituximab after auto-SCT has been established in the randomized, phase III LyMA trial, in which the rituximab group had superior event-free survival, PFS, and OS at 4 years post randomization[42]. A systematic review and meta-analysis also indicated that rituximab maintenance therapy improved post-auto-SCT PFS and OS in MCL patients[43]. However, post-SCT maintenance therapy in our analysis did not seem to affect post-SCT survival as much as it did in the previous studies. Admittedly, since the Taiwan National Health Insurance does not reimburse maintenance rituximab for MCL, the rate of patients receiving post-auto-SCT maintenance rituximab in this study was limited, thereby precluding a sound comparison.

While real-world data have potentially demonstrated the benefit of upfront auto-SCT in some patients, a high recurrence rate, even after consolidation treatment, has been observed in patients harboring high-risk factors, including blastoid variant MCL or *TP53* mutation[15,44,45]. Hence, an approach with intensified chemotherapy followed by frontline auto-SCT for young and fit patients might be justified, particularly in the era of novel agents and improved safety and accessibility of allo-SCT.

Although current data supporting allo-SCT as upfront therapy are lacking, earlier studies suggested at least some benefits for patients with chemorefractory MCL. Hamadani et al. investigated the outcomes of 202 patients from the Center for International Blood and Marrow Transplant Research (CIBMTR) database and found that approximately 25% of patients with refractory MCL could attain durable remission after allo-HCT[16]. In a study by Fenske et al., 519 chemotherapy-sensitive MCL patients received auto-SCT or allo-SCT with reduced-intensity conditioning at different time points during the disease course[46]. Auto-SCT and allo-SCT resulted in comparable 5-year OS rates (61% vs. 62%, p=0.951). Both auto-SCT and allo-SCT in frontline settings were demonstrated to be beneficial for survival in multivariate analysis. In a recent prospective and multicenter study, 24 of 25 patients received upfront allo-SCT and were engrafted without therapy-related mortality by day 100[47]. With a median follow-up of 60.5 months, there were only three deaths from MCL. The PFS and OS were 56% and 76% at five years, implying that frontline allo-SCT is feasible and should be considered for selected patients, such as those with refractory disease or a high risk of progression. In our cohort, only two patients had a relapse after allo-SCT, and only one out of five patients receiving upfront allo-SCT had died by the end of follow-up, yet too few patients in this cohort received allo-SCT, hindering the results regarding the impact of allo-SCT. Larger-scale, prospective, and randomized controlled trials are warranted to support this approach.

In our cohort, the overall response rate of patients receiving ibrutinib for relapsed/refractory MCL was 70%, in agreement with that in trial settings[48-50]. Two patients were salvaged with ibrutinib and successfully bridged to upfront allo-SCT, while one patient's recurrent disease after auto-SCT was refractory to ibrutinib but responsive to venetoclax. There were no unexpected adverse events, and all events were controlled by tapering of doses. As novel agents have become more broadly used in real-world practice, a treatment strategy that incorporates conventional chemotherapies, stem cell transplants, and targeted therapies needs to be optimized for this heterogeneous disease. For example, whether novel agents should be used in induction, salvage, or maintenance remains to be determined, and consideration of the evidence supporting chemo-free treatment, disease refractoriness following relapse after treatment with novel agents, and, importantly, cost-effectiveness will be required.

This study's limitations lie in its registry-based nature and, crucially, its lack of *TP53* genotyping data. The study could also be improved with more data, including data regarding the regimens and responses of each line therapy. Furthermore, this study enrolled patients over 20 years, thereby introducing various inherent confounding factors into our analysis, for example, the increased use of transplantation with time (52% of patients were transplanted after 2015) despite the trend of increasing age at transplant (before vs. after 2015: 55 years vs. 57 years, p=0.07), which partly reflects the evolution of MCL management.

In summary, this study depicted the implementation of transplantation for MCL patients in an Asian population, emphasizing the OS benefit conferred by early consolidative auto-SCT and the prognostic impact of blastoid variant MCL and POD12. In addition, novel agents such as ibrutinib

or venetoclax may play a role in bridging high-risk patients to subsequent allo-SCT, which was also demonstrated to be feasible in the frontline setting for selected patients. While the results presented are mainly confirmational, these data simultaneously convey the need for additional Asian population-based registry and clinical trials to understand this currently incurable disease and improve patient outcomes.

Patients And Methods

Data source

This retrospective observational study reviewed and analyzed data from the Taiwan Blood and Marrow Transplantation Registry (TBMTR). The TBMTR is maintained by the Taiwan Society of Blood and Marrow Transplantation (TSBMT), which has been tasked with registering clinical information of blood and bone marrow transplant recipients in Taiwan since 2009. Currently, 17 hospitals contribute to the registry, and the collection and analysis of data from the TBMTR is approved by the institutional review board of each participating hospital. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved TSBMT. Informed consent was provided according to the Declaration of Helsinki.

Patient selection

We recruited MCL patients from the TBMTR aged > 20 years who received one or more auto-SCT or allo-SCT for MCL between September 1999 and August 2020. A total of 99 MCL patients were identified. Data on prognosis-relevant variables, such as age, Mantle Cell Lymphoma International Prognostic Index (MIPI) classification, stage at diagnosis, morphologic type of MCL, disease status before SCT, preparation regimens, and post-SCT outcome, were extracted. Treatment response was evaluated per Response evaluation criteria in solid tumors (RECIST)[51,52].

Statistical analysis

We utilized the Mann-Whitney U test to compare the medians and distributions of continuous variables. Fisher's exact test or the $\chi 2$ test was performed to examine the differences between discrete variables. Progression-free survival (PFS) was the duration from the date of reinfusion of autologous stem cells to the date of first documented disease progression, last follow-up, allo-SCT, or death from any cause, whichever occurred first. Overall survival (OS) was the duration from the date of reinfusion of autologous stem cells to the date of last follow-up, allo-SCT, or death from any cause, whichever occurred first. We plotted the survival curves with Kaplan-Meier analysis and calculated the statistical significance with the log-rank test. The Cox proportional hazards model was used in the univariate and multivariate regression analyses. *P* values <0.05 were considered statistically significant. We considered biologically relevant factors (MIPI classification) and parameters with $p<0.1$ in the univariate Cox regression analysis as covariates in the multivariate analysis. All statistical analyses and imaging were performed with IBM SPSS Statistics 23 for Windows and R software.

Declarations

Acknowledgments

We would like to acknowledge the service provided by the Taiwan Blood and Marrow Transplantation Registry (TBMTR). We also thank additional colleagues who provide patient information to TBMTR in this study: Dr. Yeu-Chin Chen of Tri-Service General Hospital, Taipei, Taiwan, R.O.C.; Dr. Chieh-Lin Jerry Teng of Taichung Veterans General Hospital, Taichung, Taiwan, R.O.C.; Dr. Tsai-Yun Chen of National Cheng Kung University Hospital, Tainan, Taiwan, R.O.C.; Dr. Shih-Chiang Lin of Far Eastern Memorial Hospital, New Taipei City, Taiwan, R.O.C.; Dr. Tso-Fu Wang of Buddhist Tzu-Chi General Hospital, Hualien, Taiwan, R.O.C.; Dr. Ming-Chun Ma of Kaohsiung Chang-Gung Memorial Hospital, Kaohsiung, Taiwan, R.O.C; Dr. Shyh-Jer Lin of Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, R.O.C.; Dr. Chih-Cheng Chen of Chang Gung Memorial Hospital, Chiayi, Taiwan, R.O.C.; and Dr. Tsu-Yi Chao of Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan, R.O.C..

Author contributions

YHW contributed to research design, data collection and management, statistical analysis and interpretation, literature research, and manuscript writing. CYH, LTH, TLL, YCL and MY contributed to data collection and management, statistical analysis and interpretation. TDT and BSK contributed to research design and supervision, data collection and management, statistical analysis and interpretation and manuscript writing.

Conflict of interest disclosure

The authors declare that they have no competing interests.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1 Swerdlow, S. H. *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* **127**, 2375-2390, doi:10.1182/blood-2016-01-643569 (2016).

2 Romaguera, J. E. *et al.* Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer* **97**, 586-591, doi:10.1002/cncr.11096 (2003).

3 Cheah, C. Y., Seymour, J. F. & Wang, M. L. Mantle Cell Lymphoma. *J Clin Oncol* **34**, 1256-1269, doi:10.1200/jco.2015.63.5904 (2016).

4 Vose, J. M. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol* **92**, 806-813, doi:10.1002/ajh.24797 (2017).

5 Maddocks, K. Update on mantle cell lymphoma. *Blood* **132**, 1647-1656, doi:10.1182/blood-2018-03-791392 (2018).

6 Kumar, A. *et al.* Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. *Blood Cancer J* **9**, 50, doi:10.1038/s41408-019-0209-5 (2019).

7 Jo, J. C. *et al.* Clinical features and treatment outcomes of limited-stage mantle cell lymphoma: Consortium for Improving Survival of Lymphoma report. *Ann Hematol* **99**, 223-228, doi:10.1007/s00277-019-03803-x (2020).

8 Delarue, R. *et al.* CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. *Blood* **121**, 48-53, doi:10.1182/blood-2011-09-370320 (2013).

9 Eskelund, C. W. *et al.* 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. *Br J Haematol* **175**, 410-418, doi:10.1111/bjh.14241 (2016).

10 Dreyling, M. *et al.* Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. *Blood* **105**, 2677-2684, doi:10.1182/blood-2004-10-3883 (2005).

11 Budde, L. E. *et al.* Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. *J Clin Oncol* **29**, 3023-3029, doi:10.1200/jco.2010.33.7055 (2011).

12 Kumar, S. K. *et al.* Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia* **26**, 149-157, doi:10.1038/leu.2011.196 (2012).

13 Geisler, C. H. *et al.* Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. *Br J Haematol* **158**, 355-362, doi:10.1111/j.1365-2141.2012.09174.x (2012).

14 Dietrich, S. *et al.* Outcome and prognostic factors in patients with mantle-cell lymphoma relapsing after autologous stem-cell transplantation: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT). *Ann Oncol* **25**, 1053-1058, doi:10.1093/annonc/mdu097 (2014).

15 Dreyling, M., Klapper, W. & Rule, S. Blastoid and pleomorphic mantle cell lymphoma: still a diagnostic and therapeutic challenge! *Blood* **132**, 2722-2729, doi:10.1182/blood-2017-08-737502 (2018).

16 Hamadani, M. *et al.* Allogeneic hematopoietic cell transplantation for chemotherapy-unresponsive mantle cell lymphoma: a cohort analysis from the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant* **19**, 625-631, doi:10.1016/j.bbmt.2013.01.009 (2013).

17 Lin, R. J. *et al.* Allogeneic haematopoietic cell transplantation impacts on outcomes of mantle cell lymphoma with TP53 alterations. *Br J Haematol* **184**, 1006-1010, doi:10.1111/bjh.15721 (2019).

18 Davids, M. S. *et al.* Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. *J Clin Oncol* **35**, 826-833, doi:10.1200/jco.2016.70.4320 (2017).

19 Tam, C. S. *et al.* Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. *N Engl J Med* **378**, 1211-1223, doi:10.1056/NEJMoa1715519 (2018).

20 Wang, M. *et al.* Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet* **391**, 659-667, doi:10.1016/s0140-6736(17)33108-2 (2018).

21 Portell, C. A. *et al.* Bendamustine and Rituximab Plus Venetoclax in Untreated Mantle Cell Lymphoma over 60 Years of Age (PrE0405): A Phase II Study. *Blood* **134**, 5243-5243, doi:10.1182/blood-2019-122759 (2019).

22 Wang, M. L. *et al.* Frontline Treatment with Ibrutinib Plus Rituximab (IR) Followed By Short Course R-Hypercvad/MTX Is Extremely Potent and Safe in Patients (age ≤ 65 years) with Mantle Cell Lymphoma (MCL) - Results of Phase-II Window-1 Clinical Trial. *Blood* **134**, 3987-3987, doi:10.1182/blood-2019-126044 (2019).

23 Reem Karmali, J. S. A., Deborah Marie Stephens, Jeffrey A. Barnes, Jason B. Kaplan, Jane N. Winter, Shuo Ma, Adam Matthew Petrich, Ephraim P. Hochberg, Tak Takvorian, Valerie Nelson, Leo I. Gordon, Barbara Pro. Ibrutinib maintenance following induction for untreated mantle cell lymphoma (MCL): Initial safety report. *Journal of Clinical Oncology* **37**, doi:10.1200/JCO.2019.37.15_suppl.7542 (2019).

24 Hoster, E. *et al.* A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood* **111**, 558-565, doi:10.1182/blood-2007-06-095331 (2008).

25 Hoster, E. *et al.* Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network. *J Clin Oncol* **34**, 1386-1394, doi:10.1200/jco.2015.63.8387 (2016).

26 Dreyling, M. *et al.* Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **28**, iv62-iv71, doi:10.1093/annonc/mdx223 (2017).

27 McKay, P., Leach, M., Jackson, B., Robinson, S. & Rule, S. Guideline for the management of mantle cell lymphoma. *Br J Haematol* **182**, 46-62, doi:10.1111/bjh.15283 (2018).

28 Lee, M. Y., Tan, T. D., Feng, A. C. & Liu, M. C. Clinicopathological analysis of 598 malignant lymphomas in Taiwan: seven-year experience in a single institution. *Am J Hematol* **81**, 568-575, doi:10.1002/ajh.20649 (2006).

29 Chuang, S. S., Huang, W. T., Hsieh, P. P., Tseng, H. H. & Chang, H. M. Striking male predominance of mantle cell lymphoma in Taiwan. *J Clin Pathol* **59**, 780, doi:10.1136/jcp.2005.035071 (2006).

30 Wang, Y. H. *et al.* Correlative analysis of overall survival with clinical characteristics in 127 patients with mantle cell lymphoma: a multi-institutional cohort in Taiwan. *Int J Hematol* **112**, 385-394, doi:10.1007/s12185-020-02903-z (2020).

31 Miyoshi, H. & Ohshima, K. Epidemiology of malignant lymphoma and recent progress in research on adult T-cell leukemia/lymphoma in Japan. *Int J Hematol* **107**, 420-427, doi:10.1007/s12185-018-2430-6 (2018).

32 Lee, H. *et al.* Nationwide Statistical Analysis of Lymphoid Malignancies in Korea. *Cancer Res Treat* **50**, 222-238, doi:10.4143/crt.2017.093 (2018).

33 Chim, C. S. *et al.* Mantle cell lymphoma in the Chinese: clinicopathological features and treatment outcome. *Am J Hematol* **59**, 295-301, doi:10.1002/(sici)1096-8652(199812)59:4<295::aid-ajh5>3.0.co;2-n (1998).

34 Yoon, D. H. *et al.* Treatment of mantle cell lymphoma in Asia: a consensus paper from the Asian Lymphoma Study Group. *Journal of Hematology & Oncology* **13**, 21, doi:10.1186/s13045-020-00855-9 (2020).

35 Watts, M. J. *et al.* ESHAP and G-CSF is a superior blood stem cell mobilizing regimen compared to cyclophosphamide 1.5 g m(-2) and G-CSF for pre-treated lymphoma patients: a matched pairs analysis of 78 patients. *Br J Cancer* **82**, 278-282, doi:10.1054/bjoc.1999.0915 (2000).

36 Lefrere, F. *et al.* Sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation induces a high rate of complete response and improves event-free survival in mantle cell lymphoma: a prospective study. *Leukemia* **16**, 587-593, doi:10.1038/sj.leu.2402406 (2002).

37 Mills, W. *et al.* BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* **13**, 588-595, doi:10.1200/jco.1995.13.3.588 (1995).

38 Visani, G. *et al.* Bendamustine, etoposide, cytarabine, melphalan, and autologous stem cell rescue produce a 72% 3-year PFS in resistant lymphoma. *Blood* **124**, 3029-3031, doi:10.1182/blood-2014-08-596668 (2014).

39 Hueso, T. *et al.* Bendamustine-EAM versus BEAM regimen in patients with mantle cell lymphoma undergoing autologous stem cell transplantation in the frontline setting: a multicenter retrospective study from Lymphoma Study Association (LYSA) centers. *Bone Marrow Transplant* **55**, 1076-1084, doi:10.1038/s41409-020-0783-y (2020).

40 Miura, K. *et al.* Does more intensive therapy have effects on mantle cell lymphoma? A clinical experience from the Lymphoma Treatment Study Group in Japan. *Int J Hematol* **93**, 684-686, doi:10.1007/s12185-011-0845-4 (2011).

41 Chihara, D. *et al.* Prognostic model for mantle cell lymphoma in the rituximab era: a nationwide study in Japan. *Br J Haematol* **170**, 657-668, doi:10.1111/bjh.13486 (2015).

42 Le Gouill, S. *et al.* Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *N Engl J Med* **377**, 1250-1260, doi:10.1056/NEJMoa1701769 (2017).

43 Hilal, T. *et al.* Rituximab maintenance therapy for mantle cell lymphoma: A systematic review and meta-analysis. *Am J Hematol* **93**, 1220-1226, doi:10.1002/ajh.25226 (2018).

44 Cohen, J. B. TP53 mutations in MCL: more therapy is not better. *Blood* **130**, 1876-1877, doi:10.1182/blood-2017-08-803551 (2017).

45 Eskelund, C. W. *et al.* TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood* **130**, 1903-1910, doi:10.1182/blood-2017-04-779736 (2017).

46 Fenske, T. S. *et al.* Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. *J Clin Oncol* **32**, 273-281, doi:10.1200/jco.2013.49.2454 (2014).

47 Rule, S. *et al.* Allogeneic stem cell transplantation as part of front line therapy for Mantle cell lymphoma. *Br J Haematol* **184**, 999-1005, doi:10.1111/bjh.15723 (2019).

48 Wang, M. L. *et al.* Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* **369**, 507-516, doi:10.1056/NEJMoa1306220 (2013).

49 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* **387**, 770-778, doi:10.1016/s0140-6736(15)00667-4 (2016).

50 Rule, S. *et al.* Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol* **179**, 430-438, doi:10.1111/bjh.14870 (2017).

51 Eisenhauer, E. A. *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* **45**, 228-247, doi:10.1016/j.ejca.2008.10.026 (2009).

52 Schwartz, L. H. *et al.* RECIST 1.1-Update and clarification: From the RECIST committee. *Eur J Cancer* **62**, 132-137, doi:10.1016/j.ejca.2016.03.081 (2016).

Tables

Table 1. Clinical and laboratory features of 94 mantle cell lymphoma patients who received autologous stem cell transplant

Clinical parameter	Number* (%)
Age†	55 (25-73)
Sex	
Male	77 (81.9)
Female	17 (18.1)
Advanced stage (III/IV)	87 (92.6)
Bone marrow involvement	70 (74.5)
Laboratory data†	
WBC, X 10^9 /L	10.7 (2 - 19)
LDH, U/L	244 (97 - 4082)
MIPI	
Low	37 (40.7)
Intermediate	36 (39.5)
High	18 (19.8)
Unavailable	3
Blastoid variant	10 (10.6)
Ki-67	
<30%	10 (55.6)
≧30%	8 (44.4)
Unavailable	76

*Eight patients received allogeneic stem cell transplant due to relapse/progression of disease after autologous stem cell transplant.

† Median (range)

Abbreviations: MIPI, Mantle Cell Lymphoma International Prognostic Index; WBC, white blood cell

Table 2. Clinical characteristics of 13 mantle cell lymphoma patients who received allogeneic stem cell transplant

UPN	Sex	Age	Morphology	Stage	BM involvement	MIPI	Relapse After ASCT	Salvage therapy bridging to allo-SCT	State before allo-SCT	Survival at last follow up	Overall survival*
1	Male	44	Classic	IV	Yes	Low	Yes	4 cycles of bortezomib + rituximab + bendamustine	CR	Alive	88
8	Male	61	Classic	IV	Yes	Low	Yes	3 cycles of bortezomib + rituximab + bendamustine	CRu	Death due to infection	26
13	Male	52	Blastoid	IV	Yes	Low	Nil.	ibrutinib	PR	Alive	28
14	Male	49	Classic	III	Nil.	High	Nil.	1 cycle of asparaginase + paclitaxel + gemcitabine	PR	Alive	140
34	Male	48	Classic	IV	Yes	Low	Yes	8 cycles of bortezomib + rituximab + bendamustine	CRu	Alive	82
36	Female	66	Blastoid	IV	Yes	High	Yes	Nil.	Refractory	Death due to infection	18
41	Female	52	Blastoid	IV	Yes	Low	Yes	Venetoclax	PR	Alive	25
46	Male	63	Classic	IV	Yes	High	Nil.	3 cycles of Ibrutinib + rituximab + bendamustine	CR	Alive	11
47	Female	36	Classic	IV	Yes	intermediate	Yes	2 cycles of R-BOMES	CR	Death due to MCL	68
52	Male	52	Classic	IV	Yes	Low	Nil.	Not reported	PR	Alive	61
82	Male	42	Classic	III	Nil.	intermediate	Yes	1 cycle of bortezomib + mitoxantrone + dexamethasone	PR	Death due to infection	132
85	Male	47	Classic	IV	Yes	Low	Nil.	Not reported	PR	Death due to MCL	61
89	Male	50	Classic	IV	Yes	High	Yes	2 cycles of rituximab + bendamustine	CR	Alive	24

*months

Abbreviations: CR, complete remission; CRu, complete remission, unconfirmed; MIPI, Mantle Cell Lymphoma International Prognostic Index; PR, partial remission; PD, progression of disease; R-BOMES, Rituximab, carmustine (BCNU), Vincristine, Methotrexate Etoposide, Methylprednisolone; UPN, unlinked patient number

Table 3. Univariate and multivariable analyses for OS of the 94 MCL patients receiving autologous stem cell transplant

Variable	Progression-free survival				Overall survival			
	Univariate		Multivariable		Univariate		Multivariable	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
MIPI*	1.4 (0.9-2.1)	0.131	1.3 (0.8-2.0)	0.291	1.1 (0.6-2.1)	0.848	0.8 (0.3-1.9)	0.597
Bone marrow involvement	1.5 (0.7-3.2)	0.294			3.1 (0.7-13.6)	0.141		
Blastoid variant	2.4 (1.1-5.5)	0.039	1.7 (0.7-4.2)	0.260	3.7 (1.2-11.2)	0.023	3.8 (1.1-12.8)	0.033
Status before transplant†	0.6 (0.3-1.1)	0.088	0.6 (0.3-1.2)	0.179	0.2 (0.1-0.8)	0.023	0.3 (0.1-0.9)	0.049
Bendamustine in conditioning	0.6 (0.1-4.6)	0.641			0.1 (0-65272)	0.666		
Maintenance therapy	0.9 (0.4-1.9)	0.712			0.2 (0.1-1.4)	0.102		
Progression within 12 months					14.3 (4.6-44.9)	<0.001	12.7 (3.9-40.9)	<0.001

P values < .05 are considered statistically significant.

Abbreviations: CI, confidence interval; HR, hazard ratios; MIPI, Mantle Cell Lymphoma International Prognostic Index

*MIPI: stratified into low-, intermediate-, and high-risk groups

†Transplant at first complete remission versus others.

[Note:] Only variables with *P* value less than 0.10 in univariate analysis were incorporated into the multivariable Cox proportional hazard regression analysis.

Figures

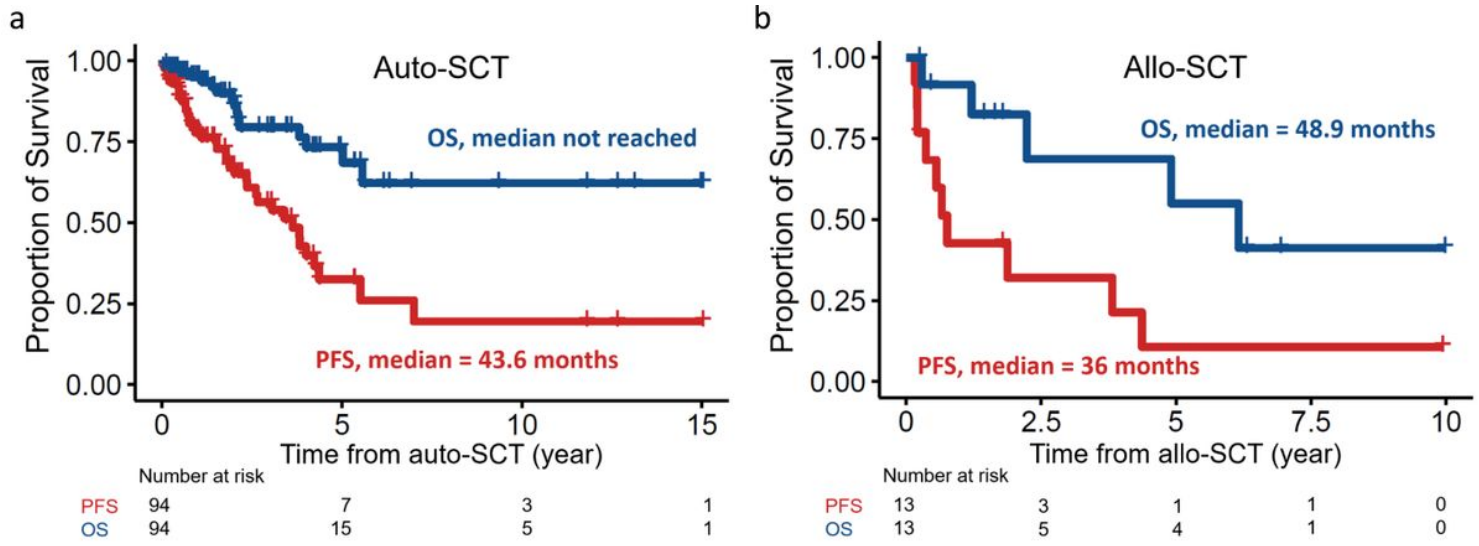

Figure 1

Kaplan-Meier plots of MCL patients receiving autologous (auto-) or allogeneic stem cell transplant (allo-SCT). (a) Progression-free survival (PFS) and overall survival (OS), censored at allo-SCT if performed, of 94 MCL patients receiving auto-SCT. (b) PFS and OS of 13 MCL patients receiving allo-SCT.

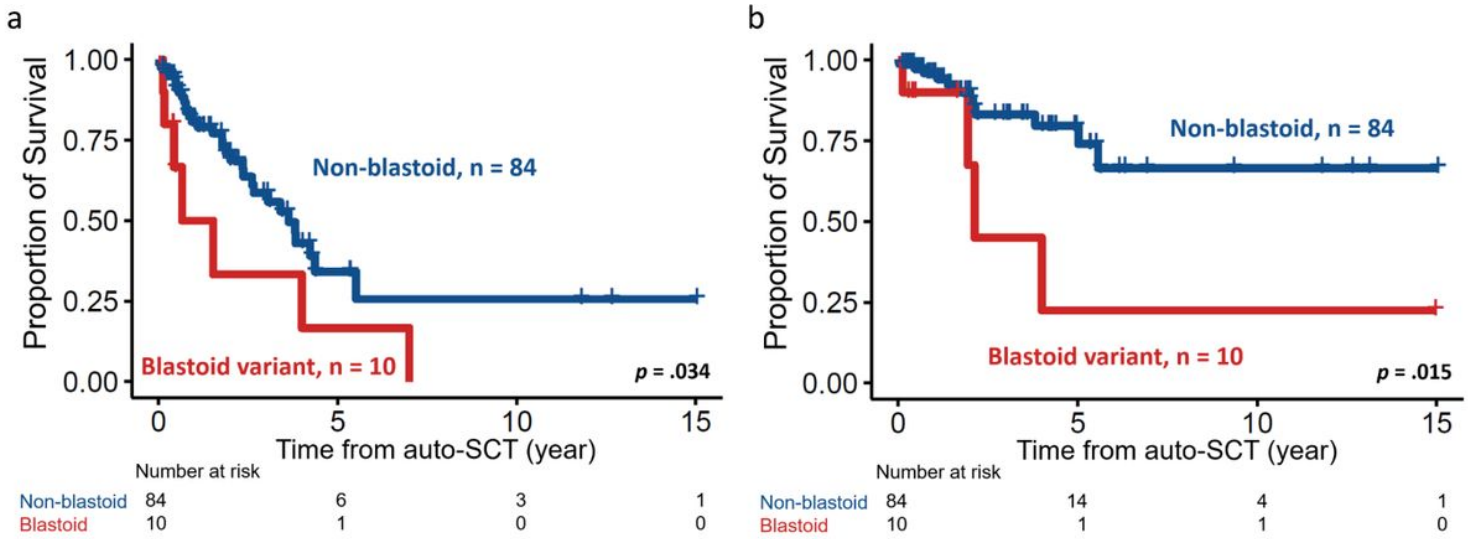

Figure 2

Kaplan-Meier plots stratified by morphologic variant of MCL. (a) PFS and (b) OS of 94 MCL patients with blastoid or non-blastoid variant. Patients with blastoid variant had significantly inferior PFS and OS.

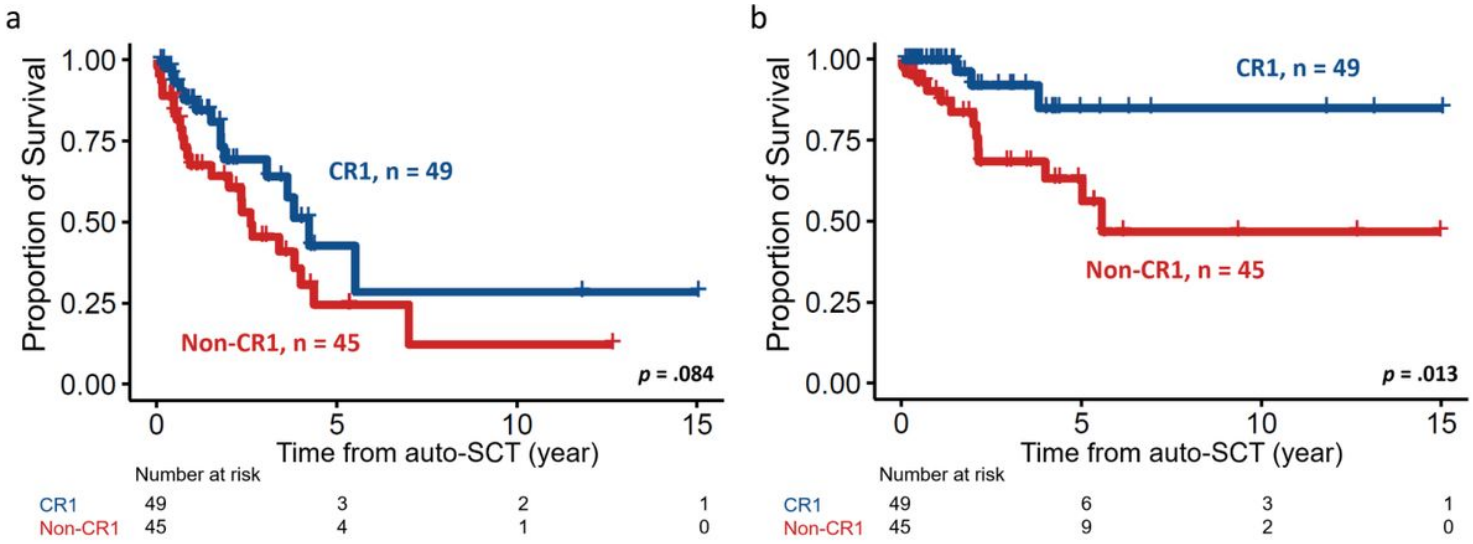

Figure 3

Kaplan-Meier plots stratified by disease status before autologous stem cell transplant. (a) PFS and (b) OS of patients with different disease status before receiving transplant. Patients receiving transplant at their CR1 state had better PFS and OS.

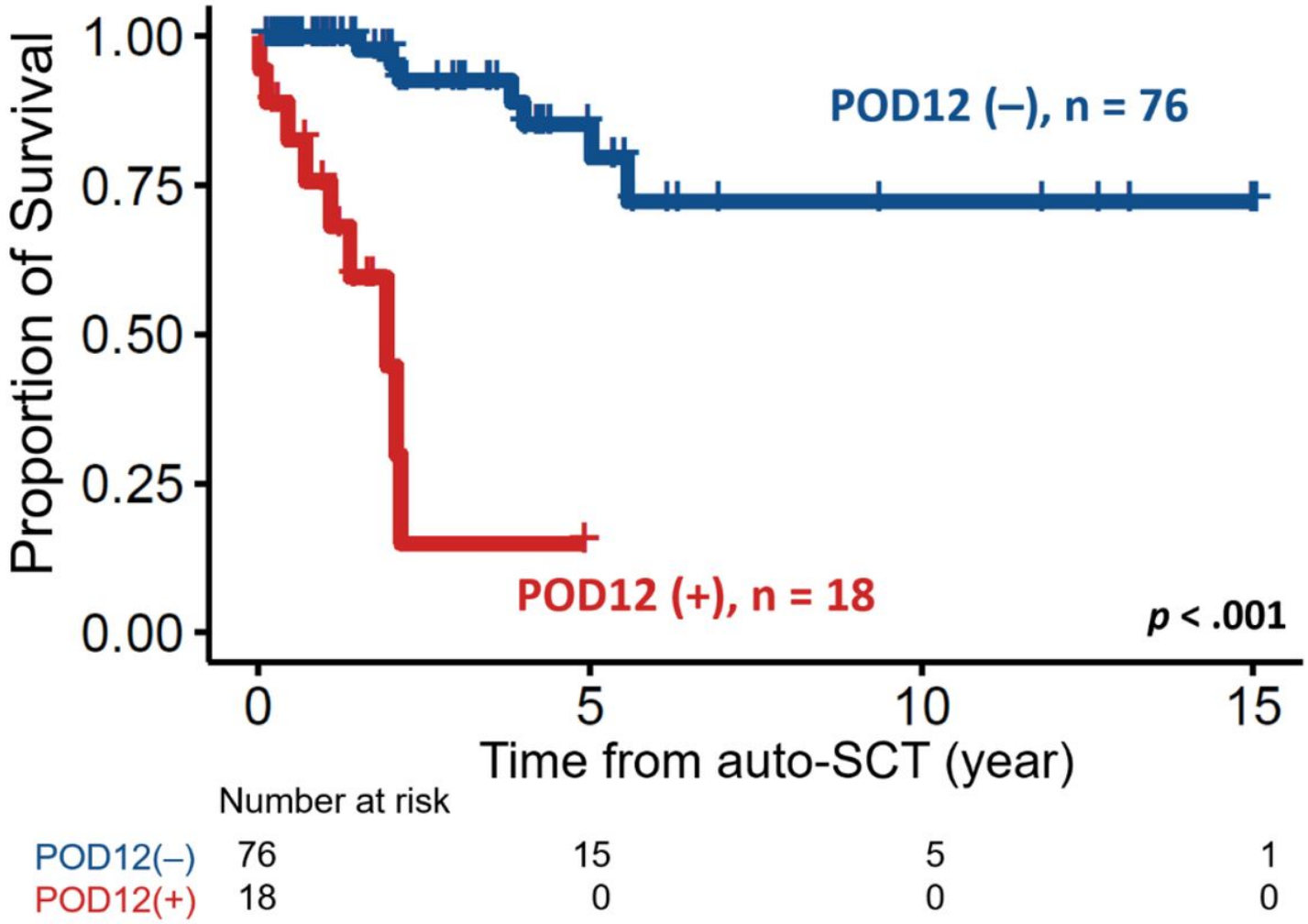

Figure 4

Kaplan-Meier plots stratified by progression of disease within 12 months post-auto-SCT or not. Patients who had progression of disease within 12 months post-auto-SCT (POD 12) had a significantly shortened survival.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarydata.pdf