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Treatment patterns and outcomes of unfit and elderly patients with Mantle cell lymphoma unfit for standard immunochemotherapy: A UK and Ireland analysis

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Abstract 200 words

Mantle cell lymphoma (MCL) presenting in elderly, unfit patients represents a clinical challenge. Front-line 'attenuated' or low-intensity immunochemotherapy is often employed, although outcomes are relatively unexplored. We report outcomes of attenuated immunochemotherapy in 95 MCL patients across 19 centres in UK and Ireland considered unfit for full-dose Rituximab-Bendamustine or R-CHOP. Regimens examined were

Rituximab-CVP (n=19), dose attenuated R-CHOP (n=22), dose attenuated Rituximab-Bendamustine (n=24) and Rituximab-Chlorambucil (n=30). Primary outcome was progression-free survival (PFS). Secondary outcomes included overall response, overall survival (OS) and toxicity. Median age was 79 years (range:58-89). 50% were ≥80 years and median CIRS-G score was 6 (range:0-24). Median PFS for all patients was 15 months (95% CI:8.7-21.2) and median OS was 31.4 months (95% CI:19.7-43.2). By multivariable analysis (MVA), the only clinical factor associated with an inferior PFS was blastoid morphology (HR:2.90, p=0.01). Notably, higher treatment intensity (R-CHOP/R-Bendamustine composite) provided an independently superior PFS compared with RCVP/R-Chlorambucil (MVA HR:0.49, p=0.02). Factors associated with inferior OS by MVA were ECOG performance status (HR:2.14, p=0.04), blastoid morphology (HR:4.08, p=0.001) and POD24 status (HR:5.68, p<0.001). Overall, survival following front-line dose-attenuated immunochemotherapy is unsatisfactory. Clinical trials investigating novel agents such as BTK and BCL2 inhibitors in this specific clinical setting are warranted.

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Introduction

Mantle cell lymphoma (MCL) represents 3-10% of non-Hodgkin B-cell lymphoma (NHL) with an incidence of 0.8/100,000 in Europe and North America[1]. One third of new diagnoses affect patients aged >75 years[2-4]. Disease behaviour is heterogeneous, varying from indolent to aggressive but commonly follows a multiply relapsing course. Diagnosis is established by identifying translocation t(11;14) (q13;32), leading to aberrant Cyclin D1 overexpression[5]. SOX11 expression, high Ki67%, and TP53 mutations are associated with worse prognosis[6], while the MIPI score (age, performance stage, LDH level and white cell count (WCC)) is a validated prognostic system[7].

The therapeutic landscape has evolved substantially over recent years, initially with the introduction of anti-CD20 antibodies[8, 9] and then with Bruton's kinase inhibitors (BTKi)[10-12]. A standard of care approach for young, fit patients typically <65 years involves high dose cytarabine (HDAC) and anti-CD20 antibody-based induction followed by an autologous stem-cell transplant (autoSCT) in first remission[13]. Excess toxicity with this approach limits its broader utility in older patients.

For older patients unfit for autoSCT, practice varies with standard induction regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) followed by R-maintenance[14], VR-CAP (rituximab, bortezomib, cyclophosphamide, doxorubicin, prednisolone)[15], R-Bendamustine[16], R-BAC (rituximab, bendamustine, cytarabine)[17] used with broadly comparable outcomes. Results of the NCRI ENRICH front-line MCL trial (R-Bendamustine/R-maintenance or R-CHOP/R-maintenance versus R-ibrutinib (CRUK/14/026)) are awaited with interest. Similarly, other prominent industry-sponsored randomised trials have used R-Bendamustine as the control arm in older patients (NCT01776840, NCT04002297).

A NORDIC study of 1389 older MCL patients found no difference in the efficacy of any regimens commonly used. Survival for patients receiving chlorambucil (n=132, median 78 years) and CVP (cyclophosphamide, vincristine, prednisolone) (n=35, median 77 years) were reported, although only a minority received rituximab (23%)(3). Three-year overall survival (OS) for chlorambucil-treated patients was 39.3% and 22.9% for CVP-treated patients. Age was independently associated with poor prognosis and when adjusting for MIPI, gender, and rituximab, CVP patients had a worse OS[3].

Optimising therapy for patients deemed unfit for standard induction regimens described above remains a significant clinical challenge. Attenuation of aforementioned regimens with tailored dose reductions depending on comorbidities and frailty may be considered[18]. Despite this, there are little data in terms of the efficacy and safety of attenuated immunochemotherapy when used in an elderly or unfit population and the optimum approach remains unknown[18, 19]. Prospective trials in this population are rare given the relatively small numbers and patient frailty. Given all these factors, we performed a UK and Ireland retrospective analysis of 95 unfit MCL patients who have received active front-line therapy over the last decade to address these questions. We aimed to assess survival, treatment toxicity and factors associated with outcome.

Methodology

Data were retrospectively collected from 95 patients across 19 participating hospitals (UK and Ireland). Patient selection is described in Figure S1. All patients had a histological confirmed stage I-IV MCL from 01/2010 to 01/2020. Patients with central nervous system involvement with MCL at baseline were excluded. All patients included were transplant ineligible and deemed too frail to tolerate full dose R-CHOP or R-Bendamustine induction due to either age, frailty or comorbidities. Dose attenuated R-CHOP was defined as any dose reduction of doxorubicin < 50mg/m^2 and/or cyclophosphamide <750mg/m^2 respectively. Dose attenuated R-Bendamustine was defined as any dose reduction <90mg/m^2. Cycle 1 doses were specifically collected for R-Bendamustine and R-CHOP patients. Patients who received attenuated R-CHOP, attenuated R-Bendamustine, R-CVP or R-Chlorambucil were included. Patients were only included if the attenuated regimen was intended to be used from cycle 1 rather than reduced later following toxicity or poor tolerance. Patients treated with purely palliative intent (e.g. steroids only) were excluded. R-maintenance post-induction was permitted and initial palliative local radiotherapy pre-induction could also be used.

Patients' electronic and paper records were systematically reviewed to produce baseline characteristics, treatment characteristics and toxicity. Baseline characteristics included age, stage, Eastern Cooperative Oncology Group performance status (ECOG PS), LDH, WCC, MCL International Prognostic Index (MIPI), albumin, haemoglobin, B-symptoms, histopathology subtype, Ki67%, cyclin D1 expression, bulk (defined ≥10cm) and Cumulative Illness Rating Scale-Geriatric (CIRS-G) score. MIPIb (biological MIPI) was calculated in cases where

Ki67% was available. MCL diagnosis was not included when calculating CIRS-G. Intended number of induction cycles, maintenance treatment and radiotherapy were collected along with actual cycles given. Date of earliest response, date of progression or last follow up and further treatment lines were collected. For toxicity assessment, we collected key outcomes: inpatient admissions and grade 3-4 adverse events as defined by the CTCAE version 4.02 grading system. Cause of death was determined by examining patient records. Treatment-related mortality (TRM) as cause of death was described according to the treating clinician's discretion. Patients must have completed induction and received ≥1 cycle (including patients stopping early due to toxicity/progression) to be included.

Statistical analysis

Clinicians provided best overall response rate (ORR), earliest ORR and progression outcomes according to Lugano criteria[20]. Use of computed topography (CT) and positron emission topography (PET)/CT varied between centres. As bone marrow biopsy was not routinely performed in all response assessment, complete response was defined as CR/CRu (complete response unconfirmed). Progression-free survival (PFS) was defined as the time from the start of induction until relapse, progression, death, or censored at last follow-up. OS was defined as the time from start of induction to time of death from any cause or censored at the last follow-up. Duration of response (DoR) was measured from the date of earliest response until relapse, progression, death, or censored at the last follow-up. Survival analyses were calculated in standard fashion by Kaplan-Meier analysis[21]. Univariable and multivariable Cox regression was used to examine the associations between baseline factors, regimens, PFS and OS[22] with the proportional hazard assumption confirmed for all variables. A stepwise forward selection technique was used for multivariable analyses, with a p-value of <0.05 set as the limit for inclusion in the final model. Progression of disease <24 months (POD24) calculated from start of induction was included in OS Cox regression. Statistical analyses were performed using IBM SPSS Statistics for Windows, v27 (IBM Corp., Armonk, N.Y., USA) with 95% confidence intervals presented and p<0.05 considered significant. Follow-up was censored at the most recent hospital visit or death. The data was censored, and the database locked in 11/2020 for analysis. All authors had full access to the data in the study and the corresponding author had final responsibility for the decision to submit the manuscript for publication. All patient data were anonymised at source and treated according to the principles of the Declaration of Helsinki and the UK Data Protection Act (1998). The study received service evaluation approval at each participating site.

Results

Baseline characteristics

Patient and disease characteristics of 95 consecutive patients are included in **Table 1**. The median age was 79 years (range:58-89). The median follow-up was 19.0 months. Two-thirds were male. Twenty-two percent had a baseline

ECOG PS of 0, 41% an ECOG PS of 1 and 37% an ECOG ≥2. The median CIRS-G score was 6 (range 0-24) and 47% had a CIRS-G >6. The majority (93%) had stage III-IV disease with 91% presenting with a high MIPI or MIPIb score. MIPIb was available in 85%, while for the remaining patients MIPI was calculated. Blastoid histology was seen in 15%. Median time from initial MCL diagnosis to front-line treatment was 1.1 months (range:0-113.0). Few patients were observed for >6 months (n=15 >6 months including n=13 >12 months). Table 1 divides the baseline characteristics according to the regimen administered and displays a summary of the regimens used. Participating centres and treatment approaches are listed in Table S1. The 30 patients receiving R-Chlorambucil were older (median 83 years, p=0.03), had a worse ECOG PS (ECOG ≥2 in 52% vs 29% across other 3 combined treatment groups, p=0.04). Patients receiving R-CVP or R-Chlorambucil had a numerically greater comorbidity burden (CIRS-G >6 55% vs 41% for dose attenuated R-CHOP/R-bendamustine patients). MIPI scores, bulk, Ki67% and staging were similar across all groups.

There was an approximately even split across regimens examined: R-CVP (n=19), dose attenuated R-CHOP (n=22), dose attenuated R-Bendamustine (n=24) and R-Chlorambucil (n=30). All regimens were given with the intention to administer 6 cycles. Median intended dose intensity at cycle 1 for bendamustine was 45mg/m^2 (IQR 45-70), cyclophosphamide was 400mg/m^2 (IQR 393.75-400) and doxorubicin 25mg/m^2 (IQR 25-25).

Adjunctive radiotherapy was given in 7%. R-maintenance (375 mg/m2 8-weekly) was administered to 35 patients (38%) with only half (19% of whole cohort) receiving ≥6 doses. R-maintenance was most commonly used following attenuated R-CHOP (n=12, 55%) and dose attenuated R-Bendamustine (n=12, 50%). Table 2 summarises response data. ORR for the whole cohort was 72% (CR/CRu 31%). Numerically higher responses (ORR 82-83%, CR/CRu 32-42%) was observed in patients treated with attenuated R-Bendamustine or attenuated R-CHOP compared to R-Chlorambucil (ORR 63%) and R-CVP (ORR 58%). Despite these initial, relatively high responses seen with attenuated R-Bendamustine and R-CHOP, response duration was relatively limited. The median DoR for the whole cohort was 19.1 months (95% CI 12.9-25.4). Regimens with numerically longest DoR were attenuated R-Bendamustine (33.8 months (95% CI 10.9-56.7)) and attenuated R-CHOP (22.0 months (95% CI 4.8-39.2)). Out of 60 patients that progressed, 47 received further treatment including 36 receiving Ibrutinib.

Survival analysis

The median PFS across all patients was 15.0 months (95% CI 8.7-21.2). Two-year PFS was 37.3% (95% CI 26.4-47.7) and 3-year PFS was 22.1% (95% CI 12.3-31.9) (**Figure 1A**). The median OS across all patients was 31.4 months (95% CI 19.7-43.2). Two-year OS was 56.2% (95% CI 45.4-67.0) and 3-year OS was 43.8% (95% CI 32.0-55.6) (**Figure 1B**). **Figure 2A-B** displays PFS and OS according to regimen. The median PFS and OS for attenuated R-CHOP patients was 16.7 months (95% CI 9.8-23.7) and 55.2 months (95% CI 1.9-108.4), attenuated R-Bendamustine patients was

21.9 months (95% CI 0-46.3) and 48.1 months (95% CI 0-109.5), R-CVP patients was 7.4 months (95% CI 0.3-14.5) and 26.1 months (95% CI 2.7-49.4), and R-Chlorambucil patients was 12.0 months (95% CI 5.4-18.7) and 31.4 months (95% CI 17.9-45.0) respectively. For the 15 patients observed initially for >6 months, the median PFS was 24.0 months (95% CI 5.0-43.1).

Given the nature of this retrospective analysis, limited and focused toxicity data were intentionally collected. Major AEs including grade 3-4 AEs, total admission number and causes of admissions are described in Table S2. Attenuated R-CHOP and R-Bendamustine lead to numerically high cumulative inpatient number of days per patient (10.3 and 11.2 days/patient respectively) compared to R-CVP (9.3 days/patient) and R-Chlorambucil (6.6 days/patient). R-Chlorambucil resulted in the lowest number of admissions during induction. R-Bendamustine resulted in the highest number of total grade 3-4 AEs per patient (21 grade 3-4 AEs).

Given the availability in the latter course of the data collection of both bendamustine and ibrutinib, PFS and OS was also analysed according to the time period of data collection (2010-2014 versus 2015-2020). Interestingly, we observed an inferior OS but not PFS in the later time period (2015-2020) (Figure S3A-B). We noted considerable differences in higher risk baseline characteristics that are likely to have influenced this finding (ECOG ≥2 (6/29 (20.7%) vs 28/65 (43.1%)), p=0.04) and blastoid morphology ((12/58 (20.7%) vs 0/25 (0%)), p=0.01)).

Univariable analysis

Baseline parameters that were statistically significant univariable predictors of inferior PFS (Table 3) included blastoid histology (hazard ratio (HR) 2.70 (95% CI 1.38-5.26)), Ki67% ≥30% (HR 1.72, 95% CI 1.03-2.86), and bulk (HR 2.28 (95% CI 1.26-4.16). Univariable predictors of OS included the same factors but also age (HR 1.05, 95% CI 1.01-1.10), male gender (HR 1.84, 95% CI 1.02-3.30), ECOG 3-4 (HR 1.85, 95% CI 1.07-3.20) and high CIRS-G (HR 1.06, 95% CI 1.01-1.12) (Table 4). POD24 was a strong predictor of inferior OS (HR 3.17, 95% CI 1.80-5.60, p<0.001) (Figure 3). Treatment approach was compared in the univariable and multivariable analysis. When analysed as groups of more intensive regimens (composite: R-CHOP plus R-Bendamustine) compared to others (R-CVP plus R-Chlorambucil), a superior PFS (HR 0.53, p=0.01) but not OS was observed (Figure 4A-B). When each individual regimen was compared to the composite of the other three regimens as the reference, patients receiving R-CVP had an inferior PFS (HR 2.07, 95% CI 1.21-3.56, p=0.008) and a trend to worse OS (HR 1.66, 95% CI 0.92-3.00, p=0.09). No differences with other combinations examined in this fashion for PFS or OS were noted.

Multivariable analysis (MVA)

By multivariable analysis, the only clinical factor associated was blastoid morphology (HR 2.90, 95% CI 1.34-6.31, p=0.02) (Table 3). Higher treatment intensity (i.e., R-CHOP plus R-Bendamustine composite) resulted in a superior PFS compared with those receiving R-CVP/R-Chlorambucil (HR 0.49, 95% CI 0.27-0.90, p=0.02). Factors associated with inferior OS by multivariable analysis were ECOG 3-4 (HR 2.14, 95% CI 1.04-4.44, p=0.04), blastoid morphology

(HR 4.08, 95% CI 1.74-9.58, p=0.001) and POD24 (HR 5.68, 95% 2.61-12.39, p<0.001) (Table 4).

Ibrutinib-treated patients

Thirty-six patients received ibrutinib at relapse including 30 at second line, 6 at third line or greater. The median PFS for the patients that received ibrutinib was only PFS 6.9 months. This compared indirectly to the same 36 patients who obtained a median PFS of 32.0 months following front-line therapy (**Figure S2**).

Causes of Death

Overall, there were 58 deaths. The included systemic progressive disease (n=36), bowel perforation (n=1), frailty (n=1), multifactorial (n=1), infection (n=8), secondary malignancies (n=2), cardiac event (n=1) and not known (n=8). TRM was documented in only 2 patients (R-CVP n=1, R-Chlorambucil n=1).

Discussion

To our knowledge, we report the largest contemporary series of patients receiving therapeutic intervention for MCL in a cohort considered by their treating physician to be unfit for standard immunochemotherapy (namely full dose R-CHOP, full dose R-Bendamustine, VR-CAP, R-BAC) in routine clinical practice in the literature. The age of our cohort (median 79 years), comorbidity burden (CIRS-G >6 in 48%) and impaired performance status (37% ECOG ≥2) reflects this. Although this cohort represents only 10% of MCL patients, it remains a poorly investigated field with little prospective or retrospective evidence to guide therapeutic decisions. Despite attenuated or 'mini' R-CHOP being an established front-line approach in elderly diffuse large B-cell lymphoma patients considered unfit for full dose immunochemotherapy[23, 24], to our knowledge no data exists describing outcomes in MCL receiving this approach.

Our findings corroborate the limited available data and show survival outcomes in this patient group remain unsatisfactory with a median PFS of only 15 months. We investigated survival outcomes with four of the most commonly used regimens: attenuated R-CHOP, attenuated R-Bendamustine, R-CVP and R-Chlorambucil. Although it is difficult to compare across small subgroups, we noted a broadly similar median PFS across most groups in the 12-22 month range. Survival is potentially confounded by imbalanced baseline characteristics. It was notable and unsurprising that patients receiving R-Chlorambucil were frailer and older. Despite this, none of the regimens used provided clear benefit over another in univariable analysis for both PFS and OS. Overall, these results compare unfavourably with clinical trial results for R-CHOP/R-maintenance, R-Bendamustine and VR-CAP treated patients where the median PFS ranges between 24-64 months[8, 15, 16, 25]. We also show for the first time in this specific patient cohort that POD24 patients have an inferior OS, corroborating other recent series in younger patients[26].

Although it is challenging to compare across groups, we analysed patients by relative intensity of therapy. Patients receiving either attenuated R-CHOP or R-Bendamustine had an improved PFS (HR 0.49, p=0.02) compared to R-CVP/R-Chlorambucil treated patients on adjusted multivariable analysis. These results may suggest attenuation of standard immunochemotherapy (R-CHOP, R-Bendamustine) result in improved disease control in the very elderly, however these results should be treated as hypothesis-generating only and require validation.

We note R-Bendamustine only became available for widespread use in 2014, 4 years after the start of data collection, however the number of patients who received this treatment were comparable to the others. Additionally, Ibrutinib was not available until 2015 and therefore the survival results seen following Ibrutinib use at relapse only represents a proportion of the cohort in the R/R setting. In 55 patients for whom ibrutinib were available at relapse, 36 (65%) received Ibrutinib.

Given the poor outcomes described, novel non-chemotherapeutic approaches such as BTK or BCL2 inhibitors may improve outcomes. Outcomes of 50 low risk younger MCL patients receiving front-line ibrutinib-R is recently reported[27]. ORR was 90% (CR 62%) and 5-year PFS was 88%. Despite this impressive activity, notable AEs occurred (grade 3-4 AF 22%, grade 3-4 diarrhoea 14%, grade 3-4 fatigue 18%, grade 3-4 myalgia 14%). Whether second or next generation BTK inhibitors such as acalabrutinib[28], zanubrutinib[12], LOXO-305[29, 30] or BCL2 inhibitors such as venetoclax - which is active in R/R MCL[31, 32] and very elderly chronic lymphocytic leukaemia patients[33] - will improve tolerability and survival remains unanswered. An update of 38 patients receiving R-lenalidomide (R2) noted an estimated at 7-year PFS of 60.3% and 7-year OS of 73.2%. Although R2 is not licensed in this setting, these outcomes with this combination also provide rationale for further investigation in elderly patients unfit for full dose immunochemotherapy[34].

A strength of our data lies in its consecutive, unselected nature of a representative population across a wide range of clinical practice settings. We believe these outcomes are generalisable to daily practice. Limitations include the retrospective non-randomised nature, relatively small overall and subgroup sample size, potential physician frailty assessment and treatment selection bias, the possibility of unmeasured confounding factors and potential for medical chart misinterpretation. Recognising this, we attempted where possible to mitigate biases by applying established criteria and focusing on objective parameters. We did not centrally review histopathological tissue and recognise there is some risk for misinterpretation of histological MCL subtypes. We mitigated for this risk by dividing simply by blastoid versus non-blastoid histology within the analysis. We also recognise the potential for non-uniform follow-up and lack of scheduled, protocol-derived radiological reassessment. This is not unique to this data, although we acknowledge the theoretical potential to affect PFS and influence indirect comparison with PFS from trials.

We recognise our analysis did not focus on the group of patients receiving palliative therapy only or no active therapy. We recognise the importance of managing this patient cohort well with expert communication with family members and early palliative care expertise. Further work to understand the proportion of patients managed with this approach and their outcomes is warranted.

In conclusion, we present a comprehensive analysis of the survival of elderly, frail MCL patients considered unsuitable for standard front-line immunochemotherapy. Attenuated R-Bendamustine or R-CHOP may improve disease control compared to R-CVP or R-Chlorambucil. However, overall survival outcomes are unsatisfactory and elderly patients requiring treatment remain with a clear unmet need. Novel agents such as next generation BTK inhibitors, immunomodulatory agents (e.g. lenalidomide-rituximab) and BCL2 inhibitors may help improve survival whilst inducing less toxicity and subsequently a better quality of life in this setting and prospective data are warranted.

Conflicts of interest

TAE Roche: Honorarium, Advisory Board Honorarium, Gilead: Honorarium; Research support; Travel to scientific conferences, KITE: Advisory Board Honorarium, Takeda: Travel to scientific conferences, Janssen: Honorarium, Abbvie: Honorarium; Travel to scientific conferences, AstraZeneca: Honorarium, Research funding, Loxo Oncology: Advisory Board Honorarium, Trial steering committee, Beigene: Advisory Board Honorarium, Incyte: Advisory Board Honorarium. **AR:** Gilead: Support for registration and travel to conferences, **HM:** AbbVie: Support for registration and travel to conferences**,** Roche: Speaker meetings**,** Takeda: Speaker meetings**. AG:** Takeda: Advisory board honoraria**,** Celgene Support for registration and travel to conferences, **MB:** Takeda: Research funding and support for registration and travel to conferences**,** Gilead: Research funding and support for registration and travel to conferences**,** Roche: Research funding and support for registration and travel to conferences Abbvie: Research funding**,** Celtrion: Support for registration and travel to conferences Tevapharma: Honoraria**, JL:** Kite: Consultancy fees, advisory board honorarium**,** Takeda: Support for registration and travel to conferences**, NS:** Abbvie: Speaker fees and advisory board**,** Janssen: Speaker fees and advisory board, Roche: Speaker fees and advisory board. **GF**: Research funding, Abbvie. **NMC**: Honoraria, AstraZeneca, support for registration and travel to conferences, Abbvie.

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Author contributions

TE designed the study. AR co-ordinated the data collection and co-wrote the manuscript with TE, which all authors critically reviewed. AR and GF collected the majority of the data. MW performed the statistical analysis. TE, AR, RC managed many patients in the study.

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Figure 1A: Progression free survival of all patients

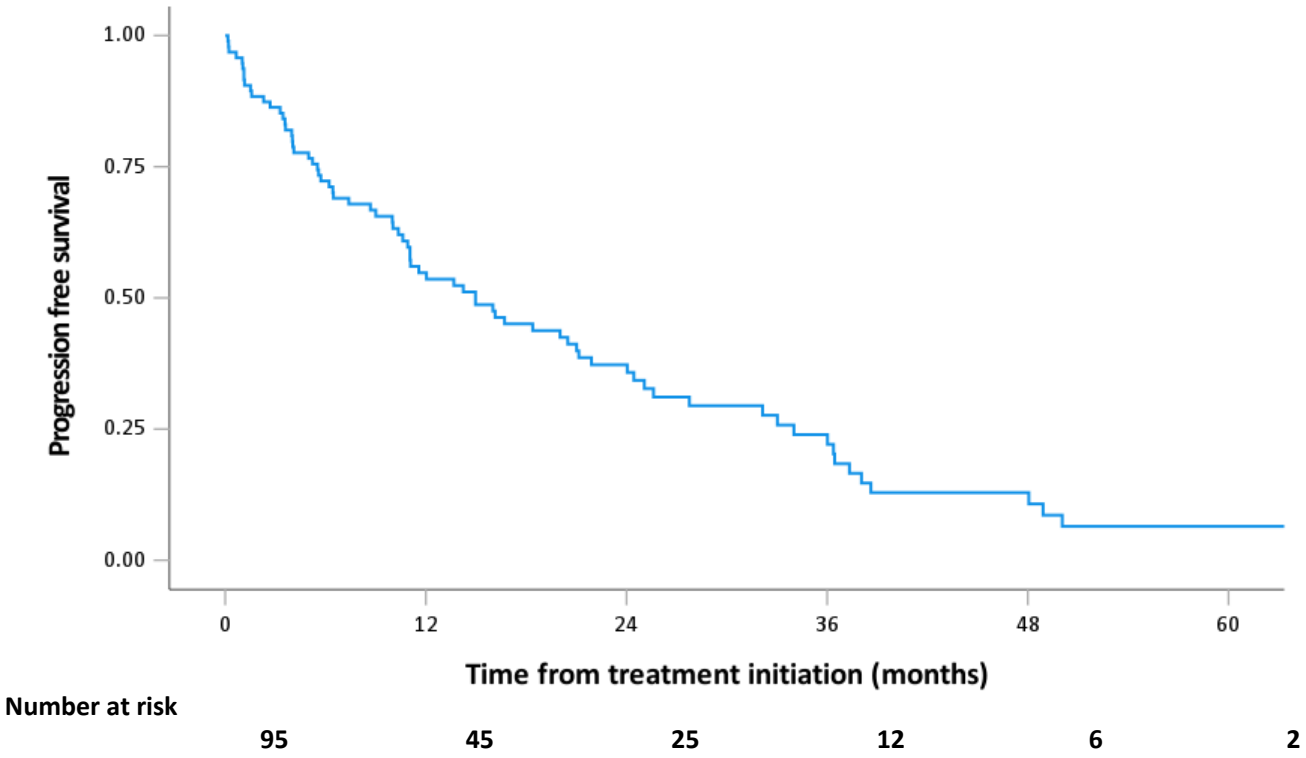


Figure 1B: Overall survival of all patients

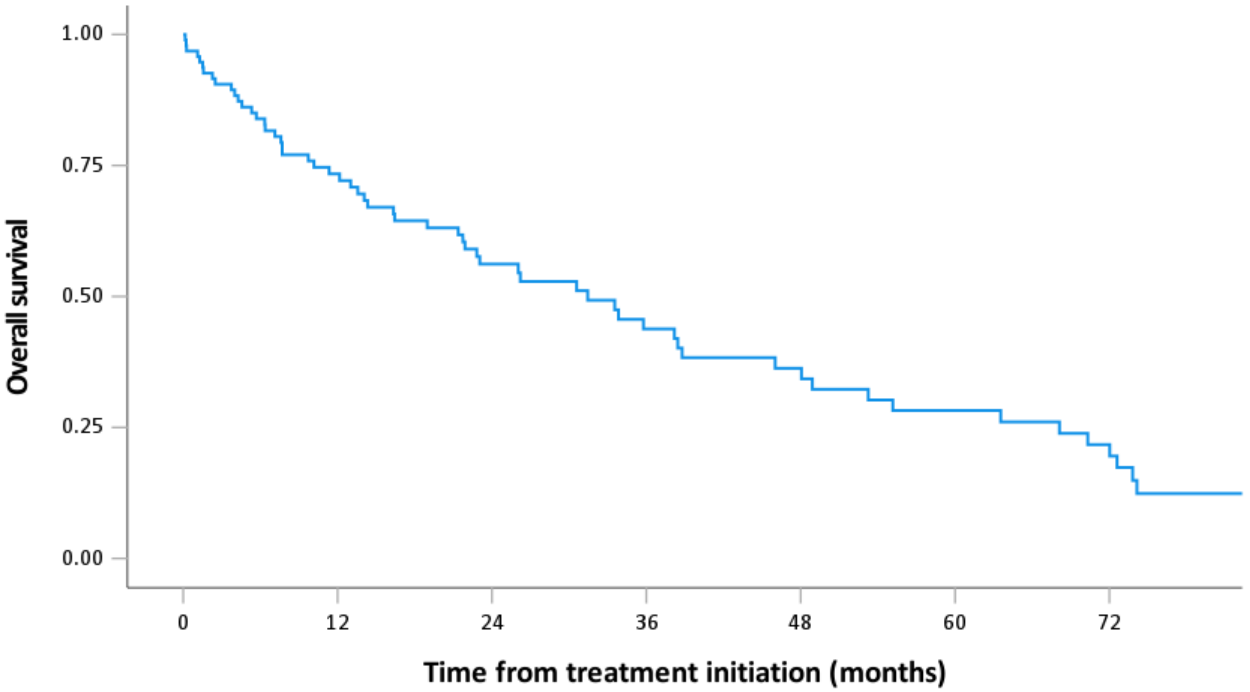
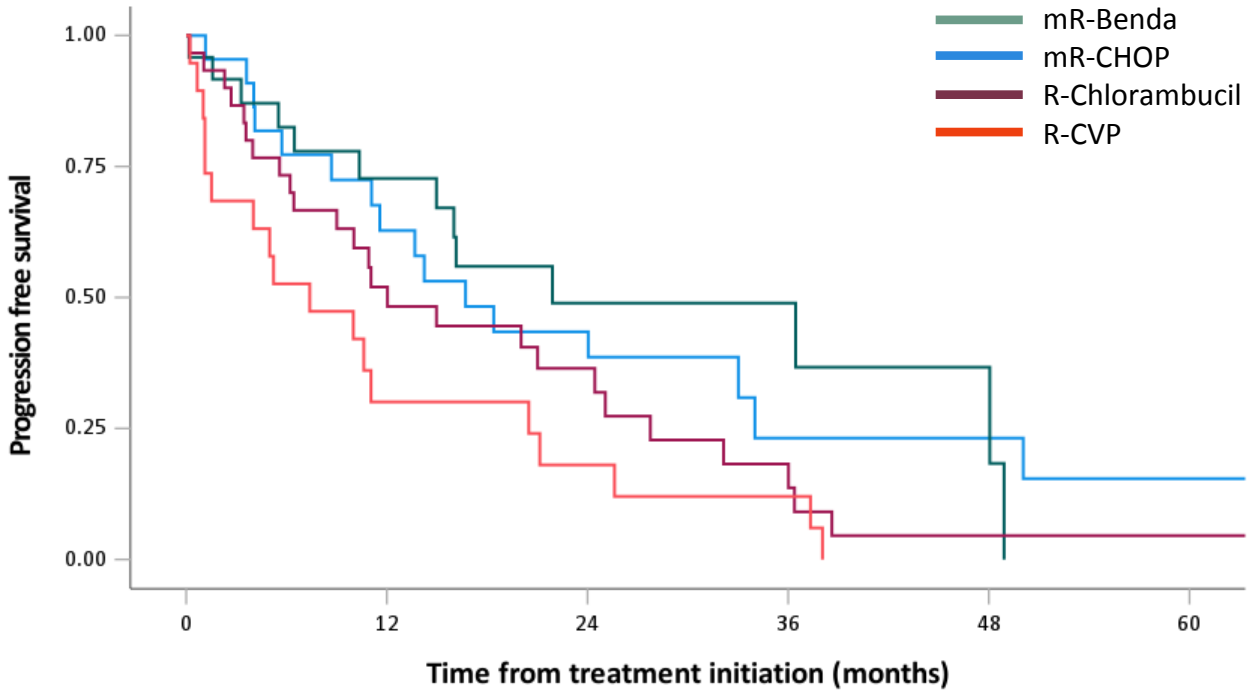
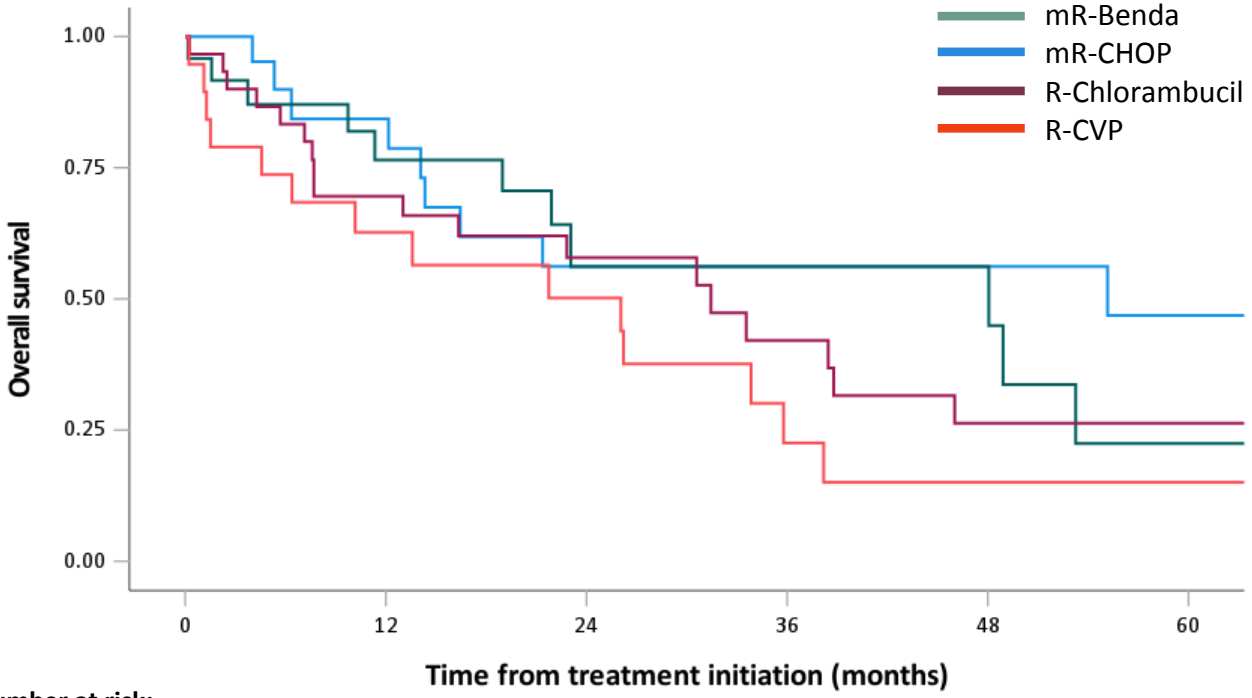


Figure 2A: Progression free survival by frontline chemotherapy regimen



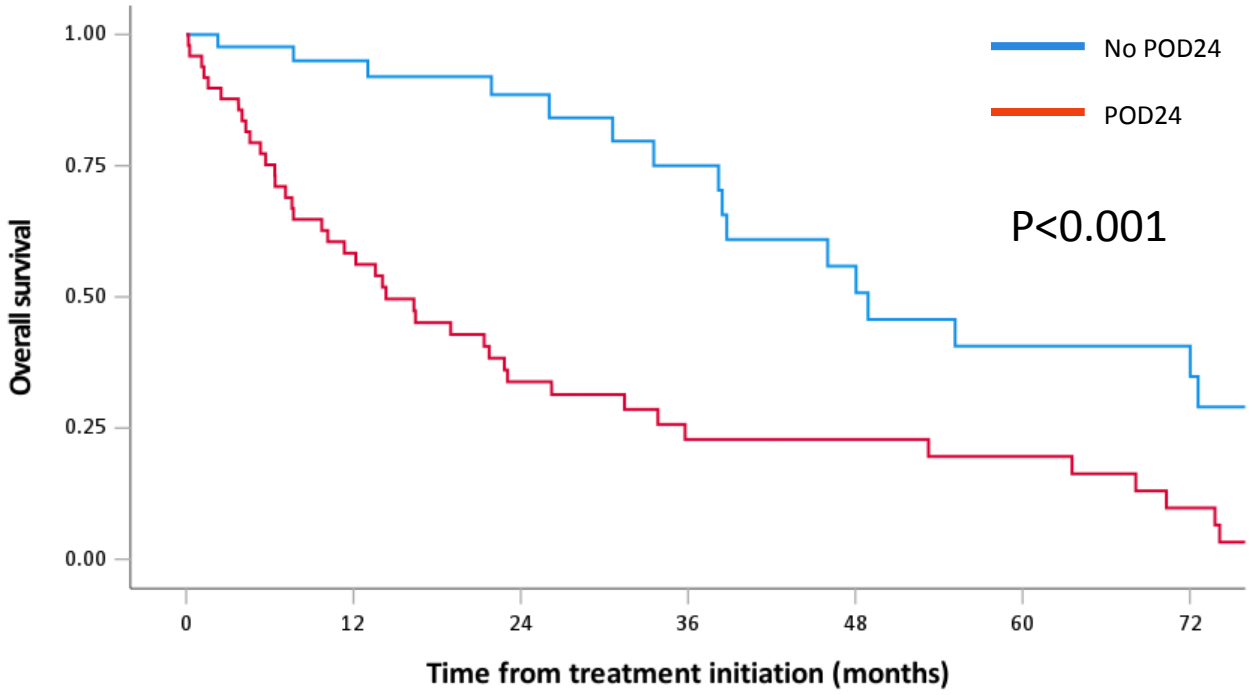
Number at risk:						
mR-Benda	24	13	5	4	2	0
mR-CHOP	22	13	9	3	3	1
R-Chlorambucil	30	14	8	3	1	1
R-CVP	19	5	3	2	1	0

Figure 2B: Overall survival by frontline chemotherapy regimen



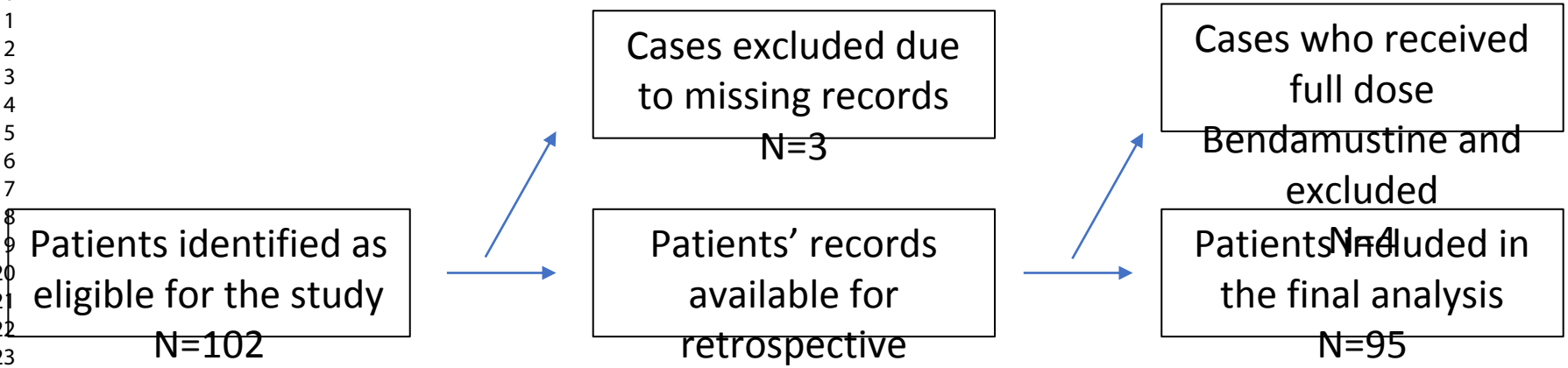
Number at risk:						
mR-Benda	24	14	7	6	4	2
mR-CHOP	22	15	10	7	6	4
R-Chlorambucil	30	19	12	8	5	5
R-CVP	19	10	8	3	2	2

Figure 3: Overall survival according to POD24 status



Number at risk:							
No POD24:	43	31	23	16	10	7	6
POD24:	49	27	14	8	7	6	3

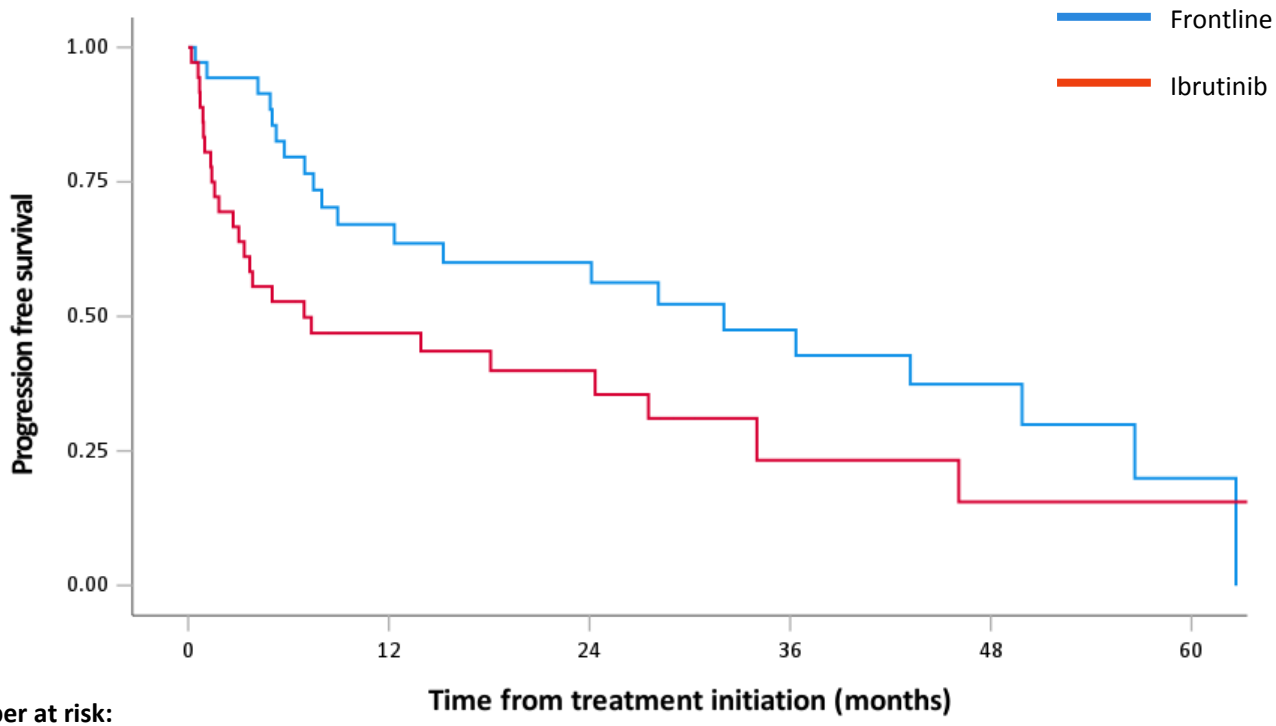
Figure S1. Patient selection



Eligibility Criteria

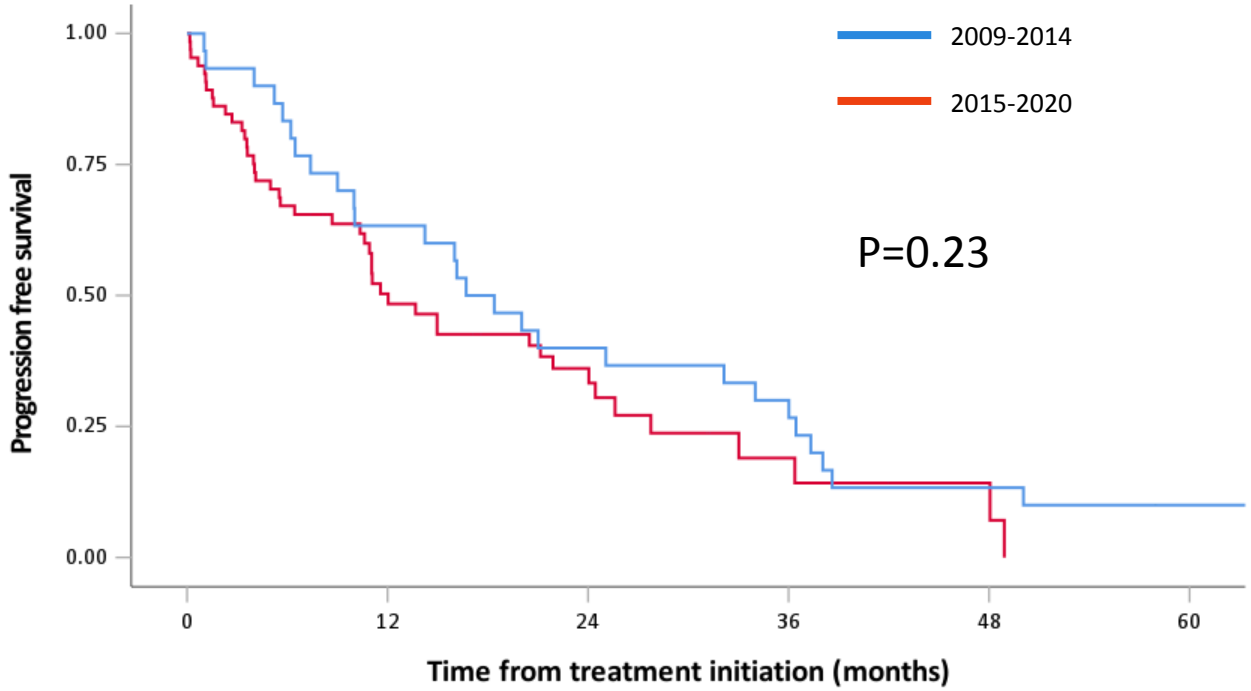
- Histopathological diagnosis of Mantle Cell Lymphoma from 01/2010 to 01/2020
- No Central Nervous System involvement at baseline
- Transplant ineligible and deemed unfit to have full dose R-CHOP or R-Bendamustine
- Intention to treat with attenuated R-CHOP, attenuated R-Bendamustine, R-Chlorambucil or R-CVP
- Received at least one dose of the above regimens

Figure S2: Indirect PFS comparison for 36 ibrutinib-treated patients



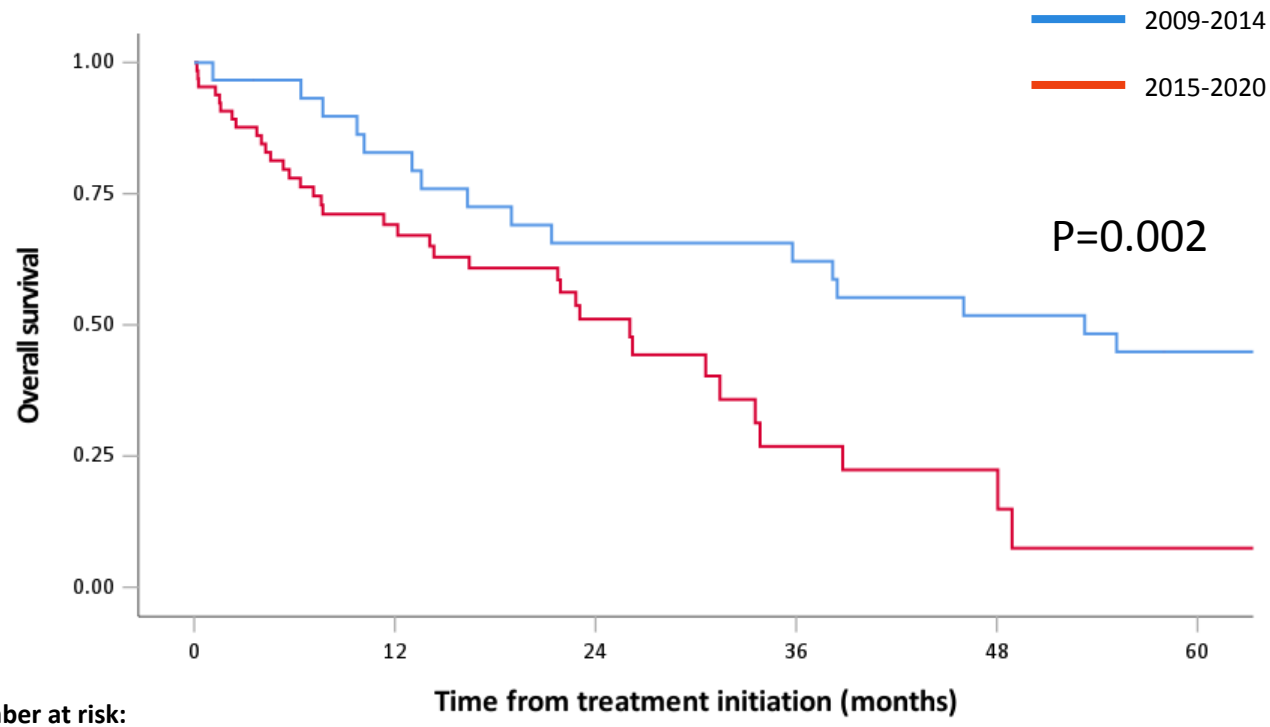
Number at risk:						
Frontline therapy	36	19	16	10	6	2
Ibrutinib	36	14	9	3	2	1

Figure S3A. Pre and post 2015 PFS



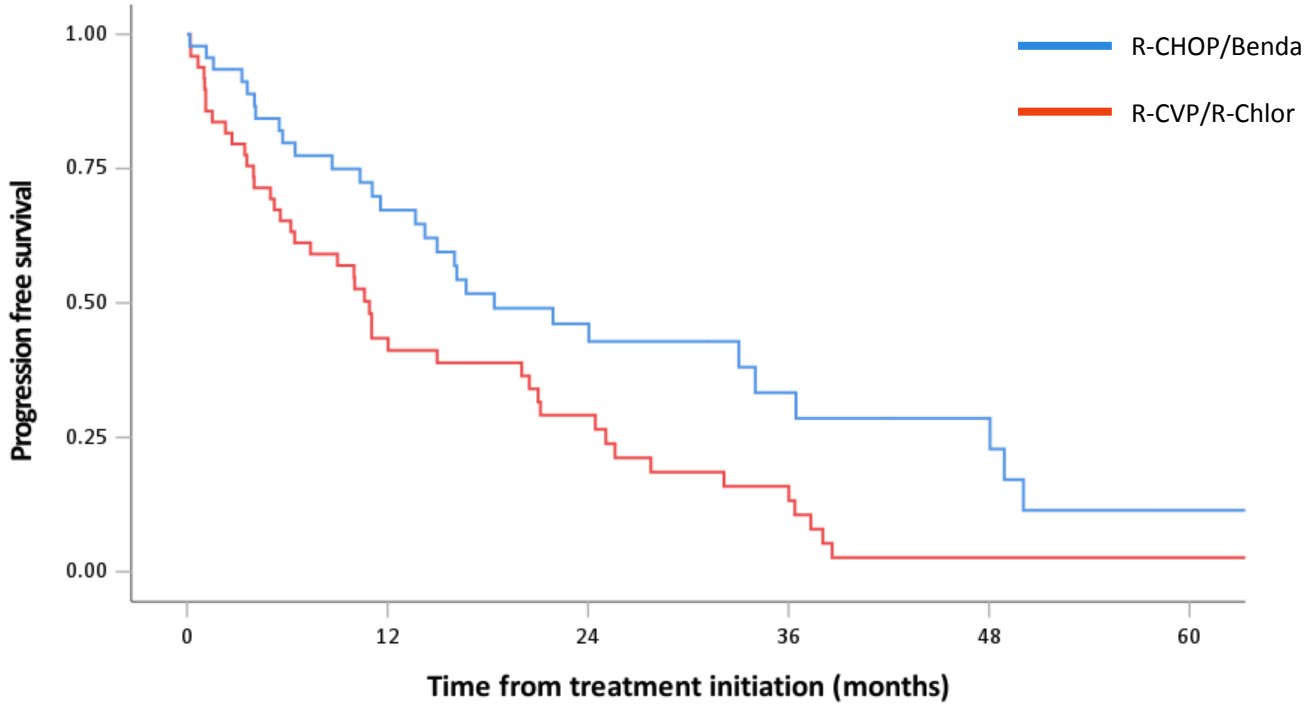
Number at risk:						
2009-2014	30	19	12	8	4	2
2015-2020	65	26	13	4	1	1

Figure S3B. Pre and post 2015 OS



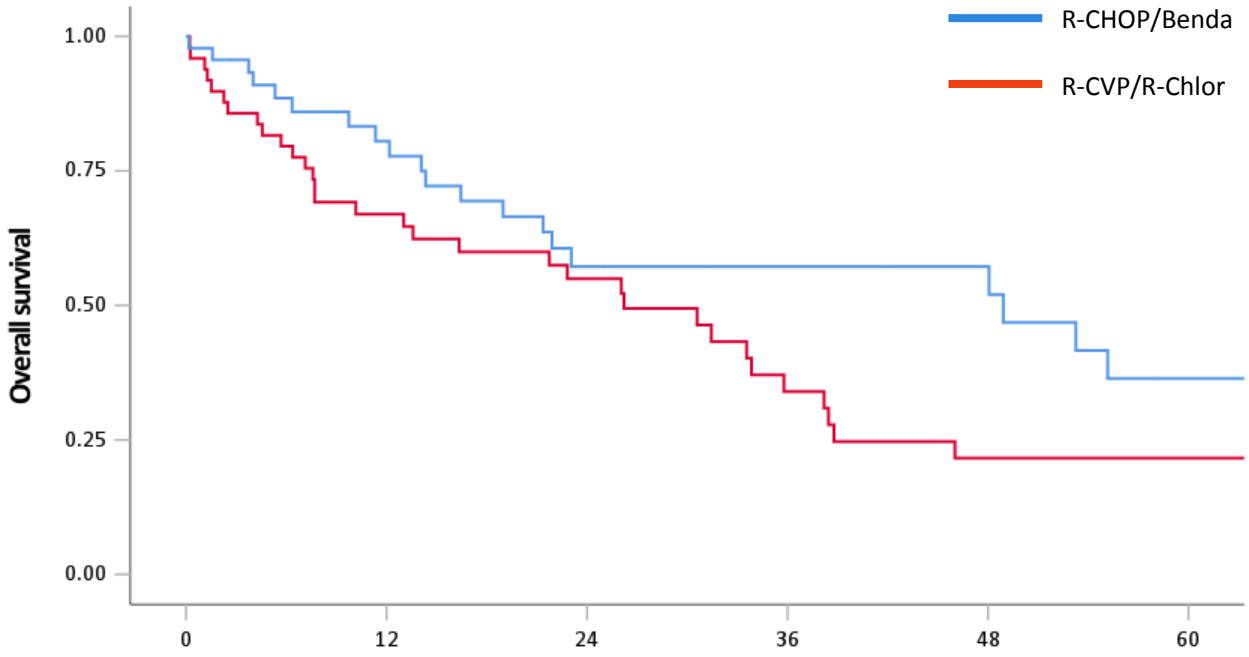
Number at risk:						
2009-2014	30	24	19	18	15	12
2015-2020	65	34	18	6	2	1

Figure S4A. PFS – RB/RCHOP vs R-CVP/Chlor



Number at risk:						
R-CHOP/Benda	46	26	14	7	4	1
R-CVP/Chlor	49	19	11	5	1	1

Figure S4B. OS - RB/RCHOP vs R-CVP/Chlor



Number at risk:						
R-CHOP/Benda	46	29	17	12	11	6
R-CVP/Chlor	49	29	20	11	7	6

Table 1: Baseline and Treatment Characteristics

Baseline characteristics and treatment summary			Total cohort [n=95]	Attenuated R-CHOP [n=22]	Attenuated R-Bendamustine [n=24]	R-Chlorambucil [n=30]	R-CVP [n=19]
Patient	Age (years)	(median, range)	79 (58-89, IQR: 75-84)	78 (58-85, IQR: 75.5-82.25)	78 (59-89, IQR: 74-83.25)	83 (60-89, IQR: 75-86)	78 (61-89, IQR: 75-81)
		≥80	47/95 (50%)	9/22 (41%)	10/24 (42%)	20/30 (67%)	8/19 (42%)
	Sex	Male	64/95 (67%)	12/22 (55%)	18/24 (75%)	18/30 (60%)	16/19 (84%)
	ECOG PS	0	21/95 (22%)	4/22 (18%)	6/24 (25%)	5/29 (17%)	6/19 (32%)
		1	39/95 (41%)	13/22 (59%)	9/24 (38%)	9/29 (31%)	8/19 (42%)
		2-3	35/95 (37%)	5/22 (23%)	9/24 (38%)	15/29 (52%)	5/19 (26%)
	CIRS-G	Median (range)	6 (0-24, IQR: 4-9)	5 (0-16, IQR: 3-8.25)	6 (2-15, IQR: 4-9)	6 (0-24, IQR: 5-9)	8 (1-18, IQR: 4-14)
		>6	45/95 (47%)	8/22 (36%)	11/24 (46%)	14/30 (47%)	12/19 (63%)
		Score/Categories* (Median)	2 (0-4.33, IQR: 1.66-2.5)	2.38 (0-4.33, IQR: 1.62-3)	2 (1.5-3.0, IQR: 1.75-2.25)	2.0 (0-4, IQR: 1.68-2.5)	2 (1-3.5, IQR: 1.62-2.37)
	LDH >ULN*	Yes	50/90 (56%)	13/19 (68%)	16/24 (67%)	14/28 (50%)	7/19 (37%)
	Albumin <LLN*	Yes	44/95 (46%)	11/22 (50%)	12/24 (50%)	15/30 (50%)	6/19 (32%)
	Hb <LLN*	Yes	67/95 (71%)	13/22 (59%)	16/24 (67%)	22/30 (73%)	16/19 (84%)
	B-symptoms*	Yes	37/85 (44%)	9/19 (47%)	12/24 (50%)	9/27 (33%)	7/15 (47%)
	Stage* **	1	4/94 (4%)	2/22 (9%)	0/24 (0%)	2/30 (7%)	0 (0%)
		2	3/94 (3%)	0/22 (0%)	0/24 (0%)	1/30 (3%)	2/19 (11%)
		3	20/94 (21%)	7/22 (32%)	3/23 (13%)	8/30 (27%)	2/19 (11%)

Disease		4	67/94 (71%)	13/22 (59%)	20/23 (87%)	19/30 (63%)	15/19 (79%)
	Histopathology subtype*	Non-blastoid	71/83 (86%)	20/22 (91%)	17/20 (85%)	21/26 (81%)	13/15 (87%)
		Blastoid	12/83 (15%)	2/22 (9%)	3/20 (15%)	5/26 (19%)	2/15 (13%)
	Ki67%*	≥30	40/81 (49%)	10/20 (50%)	10/22 (46%)	10/22 (46%)	10/17 (59%)
		<30	41/81 (51%)	10/20 (50%)	12/22 (55%)	12/22 (55%)	7/17 (42%)
	Cyclin D1*	Positive	89/93 (96%)	22/22 (100%)	23/24 (96%)	25/28 (89%)	19/19 (100%)
		Negative	4/93 (4%)	0/22 (0%)	1/24 (4%)	3/28 (11%)	0 (0%)
	Bulk Disease (>10cm)	Yes	16/95 (17%)	2/22 (9%)	4/24 (17%)	4/30 (13%)	6/19 (16%)
		No	79/95 (83%)	20/22 (91%)	20/24 (83%)	26/30 (87%)	13/19 (84%)
	MIPI	Score (median, range)	7.45 (5.7-10.7, IQR: 6.9-8.1)	7.4 (6.6-9.6, IQR: 6.9-8.1)	7.3 (6.4-9.6, IQR: 6.825-8.025)	7.6 (6.1-10.7, IQR: 6.83-8.08)	7.4 (5.7-8.7, IQR: 7-8.4)
		Low	0/90 (0%)	0/19 (0%)	0/24 (0%)	0/28 (0%)	0/19 (0%)
		Intermediate	8/90 (9%)	0/19 (0%)	5/24 (21%)	2/28 (7%)	1/19 (5%)
		High	82/90 (91%)	19/19 (100%)	19/24 (79%)	26/28 (93%)	18/19 (95%)
Treatment summary	Intended no. of cycles given (median, range)		6 (1-8)	6 (4-8)	6 (6)	6 (1-8)	6 (4-6)
	No. of cycles given (median, range)		6 (1-8)	6 (2-8)	6 (1-6)	5 (1-8)	4 (1-6)
	Radiotherapy		7	1	0	4	2
	Maintenance rituximab (any doses)		35	12	12	5	6
	Maintenance rituximab (6+ doses)		18	7	8	1	2

Progressed	60	14	9	21	16
Further Lines of treatment***	47	13	7	18	9
Ibrutinib	36	10	7	12	7

*Number of patients with unknown data in the total cohort were: CIRS-G score/categories n=4, elevated LDH n=5, B-symptoms n=10, stage n=1, Histopathology subtype n=12, Ki67% n=14, Cyclin D1 n=2, MIPI n=5. **Modalities for staging used: CT n=38, CT and Bone Marrow Biopsy n=44, PET-CT n=9, PET-CT and bone marrow n=4. High LDH was defined as higher than the upper normal limit of the value that each laboratory has. Low albumin was defined as lower than the lower normal limit that each laboratory has. Anaemia was defined as haemoglobin being less than the lower normal limit for the relevant sex that each laboratory has. Non-blastoid histopathology type includes: Classic type n=61, Pleomorphic n=7 and small cell n=3. ECOG: Eastern Cooperative Oncology Group. CIRS-G: Cumulative Illness Rating Scale-Geriatrics. LDH: Lactate dehydrogenase. Hb: Haemoglobin. ULN: Upper limit of normal range. LLN: Lower limit of normal range. MIPI: Mantle cell lymphoma Prognostic Index. ****4 Patients that received further lines of treatment had stable disease and hadn't progressed at that time. 37 patients received 1 further line, 6 patients 2 further lines, 3 patients 3 further lines and 1 patient 4 further lines.

Table 2: Best Overall response rate to induction regimens

Best response to induction	ORR (CR+PR)	CR/CRu	PR	SD	PD	NK	Median DOR* (months) (95% CI)
Total cohort (n=95)	**68/95 (72%)**	29/95 (31%)	39/98 (40%)	7/95 (7%)	17/95 (18%)	3/95 (4%)	19.1 (12.9-25.4)
R-CVP (n=19)	**11/19 (58%)**	3/19 (16%)	8/19 (42%)	1/19 (5%)	5/19 (26%)	2/19 (10%)	17.0 (2.5-31.5)
Attenuated R-CHOP (n=22)	**18/22 (82%)**	7/22 (32%)	11/22 (50%)	1/22 (5%)	3/22 (14%)	0/22 (0%)	22.0 (4.8-39.2)
Attenuated R-Bendamustine (n=24)	**20/24 (83%)**	10/24 (42%)	10/24 (42%)	0/24 (0%)	3/24 (13%)	1/24 (4%)	33.8 (10.9-56.7)
R-Chlorambucil (n=30)	**19/30 (63%)**	9/30 (30%)	10/30 (33%)	5/30 (17%)	6/30 (20%)	0/30 (0%)	16.0 (3.9-28.1)

Table 3: Univariable and multivariable analysis for progression-free survival

				Univariable analysis		*Multivariable analysis*	
Characteristic		**2 year PFS (95% CI)**	**Events/N**	**PFS HR (95% CI)**	**P**	**PFS HR (95%CI)**	**P**
Age*			72/95	1.02 (0.99-1.06)	0.27		
Sex	**Female**	45.4 (27.2-63.6)	21/31	1			
	Male	30.6 (18.3-42.9)	51/64	1.55 (0.93-2.59)	0.09		
Stage	**I/II**	42.9 (6.2-79.5)	5/7	1			
	III/IV	35.5 (24.6-46.4)	66/87	1.82 (0.72-4.62)	0.21		
ECOG	**1-2**	38.5 (27.6-49.4)	46/59	1			
	3-4	33.6 (16.6-50.6)	25/35	1.20 (0.73-1.95)	0.47		
LDH (ratio to upper limit normal)*			69/90	1.07 (0.97-1.18)	0.17		
log(WCC)*			72/95	1.01 (0.61-1.67)	0.97		
Albumin*			72/95	1.00 (0.96-1.03)	0.77		
Haemoglobin*			72/95	1.00 (0.99-1.01)	0.86		
B-symptoms	**No**	38.3 (23.4-53.2)	36/48	1			
	Yes	38.4 (21.8-55.0)	26/37	0.92 (0.55-1.53)	0.74		
Histology	**Non-blastoid**	40.1 (28.0-52.2)	53/71	1		1	
	Blastoid	9.5 (0-27.1)	11/12	2.70 (1.38-5.26)	**0.004**	2.90 (1.34-6.31)	**0.01**
Ki67	**<30%**	54.0 (37.5-70.5)	26/41	1			
	≥30%	23.4 (9.7-37.1)	35/40	1.72 (1.03-2.86)	**0.04**		
MIPI	**Low-Int**	48.6 (12.0-85.2)	7/9	1			
	High	35.6 (24.7-46.5)	62/81	1.27 (0.57-2.83)	0.57		
Bulk >10cm	**No**	42.9 (31.3-54.5)	58/79	1			
	Yes	7.8 (0-22.3)	14/16	2.28 (1.26-4.16)	**0.007**		
CIRS-G*			72/95	1.04 (0.99-1.09)	0.1		
Chemo intensity	**CVP/Chlor**	29.2 (15.9-42.5)	43/49	1		1	
	CHOP/Bend a	46.1 (30.4-61.8)	29/46	0.53 (0.33-0.85)	**0.01**	0.49 (0.27-0.90)	**0.02**

*continuous variables. Abbreviations: CIRS-G: Cumulative Illness Rating Scale-Geriatric, ECOG PS: Eastern Cooperative Oncology Group performance status, MIPI: MCL international prognostic index, WCC: white cell count, LDH, lactate dehydrogenase. Rx: treatment. Missing data: Stage n=1, ECOG n=1, LDH n=5, B-symptoms n=10, Histology n=12, Ki67 n=15, MIPI n=5, Early POD n=3. N=65 patients with full data available included in multivariable analysis (MVA), 49 PFS events in total. A stepwise forward selection technique was used for multivariable analyses, with a p-value of <0.05 set as the limit for inclusion in the final model.

Table 4: Univariable and multivariable analysis for overall survival

				Univariable analysis		*Multivariable analysis*	
Characteristic		**2 yr OS (95% CI)**	**Events/ N**	**OS HR (95% CI)**	**OS P value**	**OS HR (95% CI)**	**OS P value**
*Age**			60/95	1.05 (1.01-1.10)	**0.02**		
Sex	**Female**	68.2 (51.0-85.4)	17/31	1			
	Male	49.7 (36.2-63.2)	43/64	1.84 (1.02-3.30)	**0.04**		
Stage	**I/II**	68.6 (32.2-104.6)	4/7	1			
	III/IV	55.6 (44.3-66.9)	55/87	1.40 (0.51-3.89)	0.52		
ECOG	**1-2**	62.4 (49.3-75.5)	37/59	1		1	
	3-4	42.9 (24.0-61.7)	22/35	1.85 (1.07-3.20)	**0.03**	2.14 (1.04-4.44)	**0.04**
*LDH (ratio to upper limit normal)**			58/90	1.08 (0.97-1.20)	0.17		
*log(WCC)**			60/95	1.34 (0.78-2.30)	0.28		
*Albumin**			60/95	1.00 (0.96-1.05)	0.95		
*Haemoglobin**			60/95	1.00 (0.99-1.01)	0.75		
B-symptoms	**No**	58.6 (43.2-74.0)	30/48	1			
	Yes	53.4 (36.3-70.5)	22/37	1.01 (0.58-1.75)	0.97		
Histology	**Non-blastoid**	63.0 (50.9-75.1)	43/71	1		1	
	Blastoid	14.3 (0-38.2)	10/12	4.30 (2.01-8.90)	**<0.001**	4.08 (1.74-9.58)	**0.001**
Ki67	**<30%**	66.8 (50.1-83.5)	20/41	1			
	≥30%	40.9 (33.1-48.7)	31/40	1.93 (1.08-3.42)	**0.03**		
MIPI	**Low-Int**	88.9 (68.3-109.5)	6/9	1			
	High	50.5 (38.7-62.3)	52/81	1.42 (0.60-3.35)	0.43		
Bulk >10cm	**No**	62.3 (50.9-73.6)	49/79	1			

	Yes	20.2 (0-44.5)	11/16	2.11 (1.08-4.13)	**0.03**		
CIRS-G (continuous)			60/95	1.06 (1.00-1.12)	**0.04**		
Early POD <24m	**No early POD**	88.6 (77.8-99.4)	17/43	1		1	
	Early POD	33.8 (20.1-47.5)	41/49	3.17 (1.80-5.60)	**<0.001**	5.68 (2.61-12.39)	**<0.001**
Chemo intensity	**CVP/Chlor**	55.0 (40.5-69.5)	36/49	1			
	CHOP/Benda	57.2 (41.5-72.9)	24/46	0.70 (0.42-1.19)	0.19		

*continuous variables. Abbreviations: CIRS-G: Cumulative Illness Rating Scale-Geriatric, ECOG PS: Eastern Cooperative Oncology Group performance status, MIPI: MCL international prognostic index, WCC: white cell count, LDH, lactate dehydrogenase. Rx: treatment. Missing data: Stage n=1, ECOG n=1, LDH n=5, B-symptoms n=10, Histology n=12, Ki67 n=15, MIPI n=5, Early POD n=3. N=63 patients with full data available included in multivariable analysis (MVA), 40 OS events in total. A stepwise forward selection technique was used for multivariable analyses, with a p-value of <0.05 set as the limit for inclusion in the final model.

Participating Centres	Number of patients	R-CVP	Attenuated RCHOP	Attenuated R-Benda	R-Chlorambucil
Ireland Cancer Network					
University Hospital Galway	2	2			
University Hospital Limerick	3			2	1
St Vincent's University Hospital	4	1		3	
University Hospital of Waterford	4	1		1	2
Mercy University Hospital	3	2	1		
West of Scotland Hospitals					
Beatson West of Scotland Cancer Centre	19	10	3	1	5
Wales					
Cardiff University Hospital	4			3	1
England					
Royal Cornwall Hospital	6				6
University College London Hospital	3				3
Norfolk and Norwich University Hospitals	6		1		5
Newcastle Hospitals	5			4	1
Nottingham University Hospitals	6				6
University Hospital of Southampton	5			4	1
The Christie, Manchester	6	1		5	
Thames Valley Cancer Network					

Oxford University Hospitals	4		4		
Buckinghamshire Healthcare	7	1	6		
Great Western Hospitals	4		4		
Royal Berkshire Hospital	2	1	1		
Milton Keynes University Hospitals	2		2		

Table S22: Toxicity of regimens

Toxicity Outcomes	R-CHOP N=22	R-Benda N=24	R-Chlorambucil N=30	R-CVP N=19	Total Cohort N=95
Admissions in induction	12/22	16/23	12/28	13/19	54/95
Admissions in maintenance	2/12	3/12	1/5	1/6	7/35
Cycle 1 as inpatient	4/22	10/23	8/28	9/19	31/92
Total N admissions Total, median (range)	16 (1, 0-4, IQR 0-1)	30 (1, 0-3, IQR 0-2.75)	25 (0, 0-4, IQR 0-2)	25 (1, 0-4, IQR 0-2)	96, 1 (0-4, IRQ 0-2)
Cumulative inpatient days. Total, median (range)	226 (1, 0-90, IQR 0-10.75)	268 (4.5, 0-54, IQR 0-19.25)	198 (5, 0-54, IQR 0-5)	176 (6, 0-33, IQR 0-14)	868, 2 (0-90, IQR 0-9.25)
Cumulative inpatient days per patient	10.3	11.2	6.6	9.3	9.1
Causes of admission (All grades)					
Chest Infection	3	5	5	3	16
Febrile neutropenia	0	1	4	6	11
Cytopenias	0	4	4	1	9
UTI	2	2	1	1	6
GI infection	0	1	0	4	5
Bleeding	0	1	2	0	3
VTE	1	0	0	1	2
Renal Impairment	0	3	0	0	3
Other	10	13	9	8	41
Grade 3-4 AEs	14	21	18	15	69