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A Systematic Review of Treatments for Relapsed/Refractory Mantle Cell Lymphoma

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Abstract

A systematic literature review was conducted to evaluate the clinical effectiveness and safety of treatments for patients with relapsed/refractory mantle cell lymphoma (MCL) unsuitable for intensive treatment. Criteria for inclusion of trials were established prior to the literature review. A search of Medline, Embase and the Cochrane library databases was conducted to identify phase II or III randomised controlled trials (RCTs), published from January 1st 1994 to 29th May 2016. Relevant conference abstracts, citation lists from included articles, published guidelines and on-going clinical trial databases were also searched. Articles were included if they evaluated any single agent or combination of treatments in adult patients with relapsed/refractory MCL who had received at least one prior line of therapy. Seven RCTs were identified. Only one treatment appeared in more than one trial, and therefore results from each trial could not be quantitatively pooled by meta-analysis. Lack of common comparators, differences in baseline characteristics and inclusion and exclusion criteria and variance in the response criteria used to measure outcomes, made comparison of results difficult. Although the direction of effect for PFS and OS was in favour of the experimental drug in all trials, PFS was statistically significant in five and OS in two. None showed statistical significance for both. There are a noticeable lack of RCTs evaluating treatments for patients with relapsed/refractory MCL making meaningful comparisons of effectiveness across trials rather difficult. This trend continues as all bar one of the 85 on-going trials in this area are single arm studies. RCTs are required to enable better evaluation of the optimal treatment regimen for this group of patients.

Introduction

Mantle cell lymphoma (MCL) is a rare B-cell malignancy belonging to the non-Hodgkin lymphoma (NHL) group of diseases[1] and represents 3-10% of all newly diagnosed NHL cases[2,3] (figure 1), with an incidence of approximately 1 per 100,000 population in Europe[4] and the USA.[5] MCL more commonly affects men with a median age at presentation of 65 years[2] and is typically at an advanced stage at diagnosis, Ann Arbor stage III and IV.[6]

The hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32), resulting in overexpression of the cell cycle protein cyclin D1 and cell cycle dysregulation.[7] There are two main variants; classical MCL is the more common form of the disease[2] and has an overall survival (OS) of approximately 4.5 years. Blastoid variant is rarer but is associated with a more aggressive clinical course and poorer prognosis, with an OS of approximately 15 months.[8]

MCL frequently has an aggressive clinical course and although initial therapy can achieve high overall response rates of between 60% and 97%,[11] these tend to be short lived and the majority of patients will eventually relapse and die from their disease. Some patients, however, have a more indolent form of the disease. Although it is difficult to identify this group, there are some markers eg SOX11 negativity, that may help to distinguish it from a more aggressive phenotype. Ongoing research in the UK[12] aims to characterise the differences in a prospective trial. Some clinicians now adopt a “watch and wait” management approach with these patients if they are asymptomatic.[4]

First line treatment options will depend on the age and fitness of the patient. Intensive frontline cytarabine-based treatments are reserved for the younger, fitter patient due to their associated toxicity, and are commonly consolidated with an autologous transplant.[2,4,7] However, the majority of patients are older or more frail at presentation and this approach is not feasible. There are a number of immuno-chemotherapy options available for this group of patients[4] including bendamustine and rituximab (B-R), rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) or bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) regimens with response rates ranging from 60% to 95% and median progression free survival (median PFS) of up to 5 years. Rituximab maintenance plays a role in sustaining response following an R-CHOP induction. For the more frail patients who are

unsuitable for immuno-chemotherapy, less intensive therapies are recommended including chlorambucil, bendamustine or cladribine, usually given in combination with rituximab,[2,7,14] and the combination of rituximab, vincristine, cyclophosphamide and prednisolone[2] (R-CVP).

There is no consensus as to what the standard of care for relapsed/refractory disease should be. Experts recommend an alternative immuno-chemotherapy to that which was used initially[6] and selection of treatment will depend on a number of factors, including the presence of co-morbidities, patient fitness and patient wishes. As many patients are not suitable for an intensive treatment approach, there are several options recommended in guidelines in the relapsed/refractory setting[2,4,15] for the older patient. This systematic review therefore evaluated the available evidence for therapeutic options for patients with relapsed/refractory mantle cell lymphoma who were unsuitable for an intensive treatment approach.

Methods

The review methodology was pre-defined in a protocol available in the supplementary information and registered on Prospero. Randomised controlled trials were included if they met the following criteria: population – adult patients with relapsed/refractory MCL who had received at least 1 prior line of therapy who were not eligible for intensive treatment or transplant; intervention – any single agent or combination of agents including chemotherapy, immunotherapy, immuno-chemotherapy, targeted agents, excluding intensive treatment and transplant; comparator – any single agent or agents as above; outcomes – overall survival (OS), progression free survival (PFS), overall response rate (ORR) and safety. Electronic searches were undertaken in Medline, Embase and the Cochrane Library from January 1994 (as MCL was accepted as a separate entity in 1994) to 29th May 2016. In addition conference proceedings from the annual congresses of the American Society of Haematology (ASH), the European Haematology Association (EHA), the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), were searched for the preceding 5 years to find unpublished trials. Citation lists from included studies, review articles and published guidelines from the National Comprehensive Cancer Network (NCCN), ESMO, ASH, the British Society of Haematology (BSH) and the European Mantle Cell Lymphoma Network were also searched. Ongoing trials were identified from two research databases (www.clinicaltrials.gov and www.clinicaltrialregister.eu) up to the 24th December 2016.

Search terms for the population included 'Lymphoma, Mantle-cell Lymphoma, Non-Hodgkin Lymphoma, B-Cell Lymphoma', for the intervention and control search terms included 'Drug therapy [MeSH] OR immunotherapy (MeSH) OR molecular targeted therapy (MeSH) OR biological therapy [MeSH] OR combined modality therapy [MeSH] OR antineoplastic agents (MeSH) OR lenalidomide OR ibrutinib OR thalidomide OR bortezomib OR temsirolimus OR everolimus OR BTK inhibitor OR proteasome inhibitor'. Full details of the search strategies used are shown in appendices 1 and 2. There were no restrictions on language.

Two reviewers (MP and MK) independently screened the search results for potential inclusion/exclusion using the title and abstract, with full paper copies obtained to confirm

inclusion into the review. The final decision for inclusion of articles was based on agreement between the reviewers.

Results

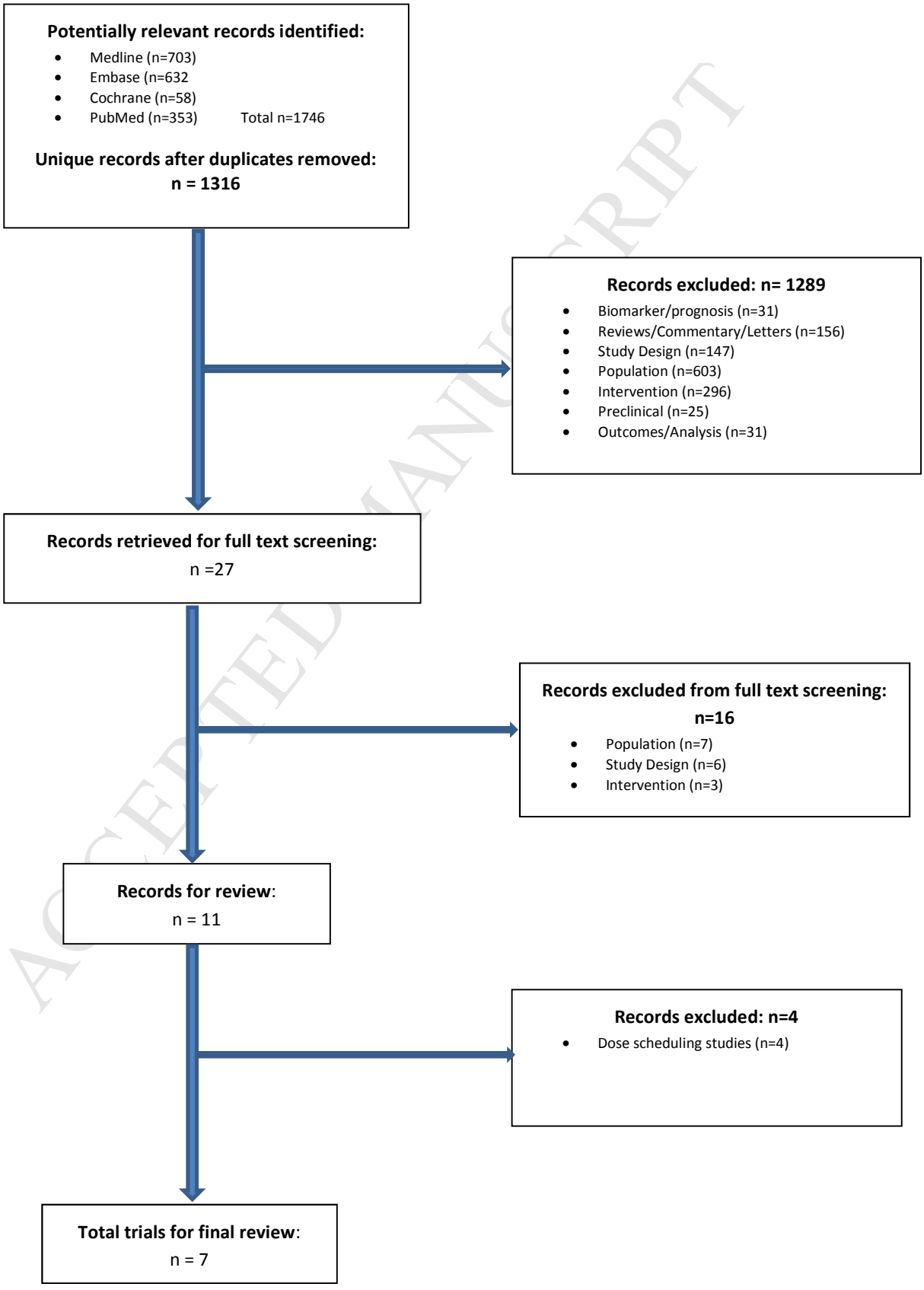
A total of 1746 articles were identified from the search as outlined in the PRISMA diagram (figure 1). After 430 duplicates were removed, 1316 articles were initially screened for inclusion from the title and abstract, with 27 published articles retrieved for full text screening. Seven randomised controlled trials met the inclusion criteria and are included in the review.[17,18,19,20,21,22,23]. There was full agreement between the reviewers with regard to included articles. The concordance between reviewers is a result of both the clearly defined criteria and the paucity of trials in this setting.

Table 1 provides a summary of the trial design for the included trials together with the treatment regimens for each trial. Follow up amongst the trials varied with the shortest median follow up of 15.9 months in the trial conducted by Trneny et al[23] and the longest median follow up of 96 months reported by Rummel and colleagues.[22] All three trials that included a variety of non-Hodgkin lymphoma sub-types in the trial[18,19,22] reported separate outcomes for the MCL sub-population and were included in this review. Only one treatment, temsirolimus, appeared in more than one trial.

Data was extracted from the articles by one reviewer (MP) which was checked by a second reviewer (MK). Study and patient characteristics were extracted as well as details of the intervention and control. Outcomes data collected were overall survival, progression free survival, tumour responses and data on safety restricted to grade 3 and 4 haematological toxicities.

Only a descriptive analysis of included trials was feasible due to heterogeneity of study populations and interventions.

Figure 1 - PRISMA Diagram



Reference	Design	Treatment		Number of MCL Patients		Inclusion Criteria
		Invest	Control	Invest	Control	
Dreyling M., 2016[17]	Phase III, multicentre, open label, randomised 1:1, ITT, IWG 2007	Ibrutinib	Tems	139	141	R/R MCL, at least 1 prior rituximab-containing therapy, ECOG PS 0-1
Forstpointner R., 2004[18]	Phase III, multicentre, open label, randomised 1:1, ITT, IWG 1999	R-FCM	FCM	24	26	R/R MCL (35%), FL (49%) and Lymphoplasmocytic (11%), Other (5%), at least 1 prior chemo inc. HSCT, PS not stated
Forstpointner R., 2006[19]	Phase III, multicentre, open label, randomised 1:1, ITT, IWG 1999	Ritux maint	No treatment	24	26	R/R MCL, FL (as above) patients achieving CR or PR on induction R-FCM, PS not stated
Furtado M., 2014[20]	Phase II, multicentre, open label, randomised 1:1, ITT, IWG 2007	V-CHOP	CHOP	23	23	R/R MCL, at least 1 prior therapy, ECOG PS $\leq$2
Hess G., 2009[21]	Phase III, multicentre, open label, randomised 1:1:1, ITT, IWG 2007	Tems HD vs LD	IC*	HD 54 LD 54	53	R/R MCL, 2-7 prior therapies, must have included an alkylating agent, an anthracycline and rituximab, ECOG PS $\leq$2
Rummel M., 2016[22]	Phase III, multicentre, open label, randomised 1:1, per proto, response criteria not stated	B-R	F-R	24	23	R/R MCL (21%), FL (51%), MZL (8%), WM (11%) Unclassified (9%), at least 1 prior therapy, WHO PS 0-2,
Trneny M., 2016[23]	Phase II, multicentre, open label, randomised 2:1, ITT, IWG 2007	Lenalid	IC**	170	84	R/R MCL, at least 1 prior comb chemo with an alkylating agent + one or more of: anthracycline, cytarabine, or fludarabine +/- ritux, ECOG PS 0-2

Invest=investigational drug; R/R=relapsed or refractory disease; MCL=mantle cell lymphoma; FL=follicular lymphoma; MZL=marginal zone lymphoma; WM=Waldenstrom's macroglobulinaemia; HSCT=haematopoitic stem cell transplant; CR=complete response; PR=partial response; PS=performance status; tems=temsirolimus; FCM=fludarabine + cyclophosphamide + mitoxantrone; R-FCM= rituximab + FCM as before; CHOP =cyclophosphamide + doxorubicin + vincristine + prednisolone; V-CHOP=bortezomib +CHOP as before; IC=investigators choice chemotherapy; B-R=bendamustine + rituximab; F-R=fludarabine + rituximab; lenalid=lenalidomide; ITT=intention-to-treat analyses; per proto=per protocol analyses; IWG 1999=international working group response criteria 1999; IWG 2007=international working group revised response criteria 2007

Table 1 – Trial Design of Included Studies

Regimens in Table 1

Ibrutinib	Oral 560mg daily until progression
Tems	IV temsirolimus 175mg on days 1,8,15 of cycle 1 followed by 75mg on days 1,8,15 subsequent 21 day cycles until progression or unacceptable toxicity
FCM	IV fludarabine 25mg/m2 on days 1-3 + IV cyclophosphamide 200mg/m2 on days 1-3 + IV mitoxantrone 8mg/m2 on day 1 for 4 cycles
R-FCM	IV rituximab 375mg/m2 day 0 + FCM as before for 4 cycles
Rituximab maintenance	2 courses of IV rituximab at 3 and 9 months after completion of induction, each course = 4 doses of IV ritux 375mg/m2 on 4 consecutive weeks
CHOP	IV cyclophosphamide 750mg/m2 + IV doxorubicin 50mg/m2 + IV vincristine 1.4m/m2 to max of 2mg on day 1 of each cycle + oral prednisolone 100mg/day for max of 8 cycles
V-CHOP	IV bortezomib 1.6mg/m2 on days 1,8 of 21 day cycle + CHOP as before for max 8 cycles
Tems HD	IV temsirolimus as before until progression or unacceptable toxicity
Tems LD	IV temsirolimus 175mg on days 1,8,15 of cycle 1 followed by 25mg on days 1,8,15 subsequent 21 day cycles until progression or unacceptable toxicity
B-R	IV bendamustine 90mg/m2 on days 1,2 + IV rituximab 375mg/m2 on day1 every 4 weeks for max 6 cycles
F-R	IV fludarabine 25mg/m2 on days 1-3 + rituximab as before for max 6 cycles
Lenalid	Oral lenalidomide 25mg on days 1-21 of 28 day cycle until progression or unacceptable toxicity
IC*	IV gemcitabine 1000mg/m2 on days 1,8,15 every 28 days for max 6 cycles OR IV fludarabine 25mg/m2 or oral fludarabine 40mg/m2 on days 1-5 every 28 days for max 6 cycles OR oral chlorambucil 0.1-0.2mg/kg daily for 3-6 weeks OR IV cladribine 5mg/m2 daily for 5 days every 28 days OR IV etoposide 50-150mg/m2 daily for 3-5 days every 21-28 days OR oral thalidomide 200mg daily OR IV vinblastine 10mg weekly OR IV alemtuzumab 30mg/day 3 times/week OR oral lenalidomide 25mg daily for 28 days
IC**	IV rituximab 375mg/m2 on days 1,8,15,22 and then once every 56 days until progression OR IV gemcitabine as before OR either fludarabine as before OR IV chlorambucil 40mg/m2 per month divided over days 3-10 until progression OR IV cytarabine 1-2g/m2 on days 1,2 every 28 days for max 6 cycles

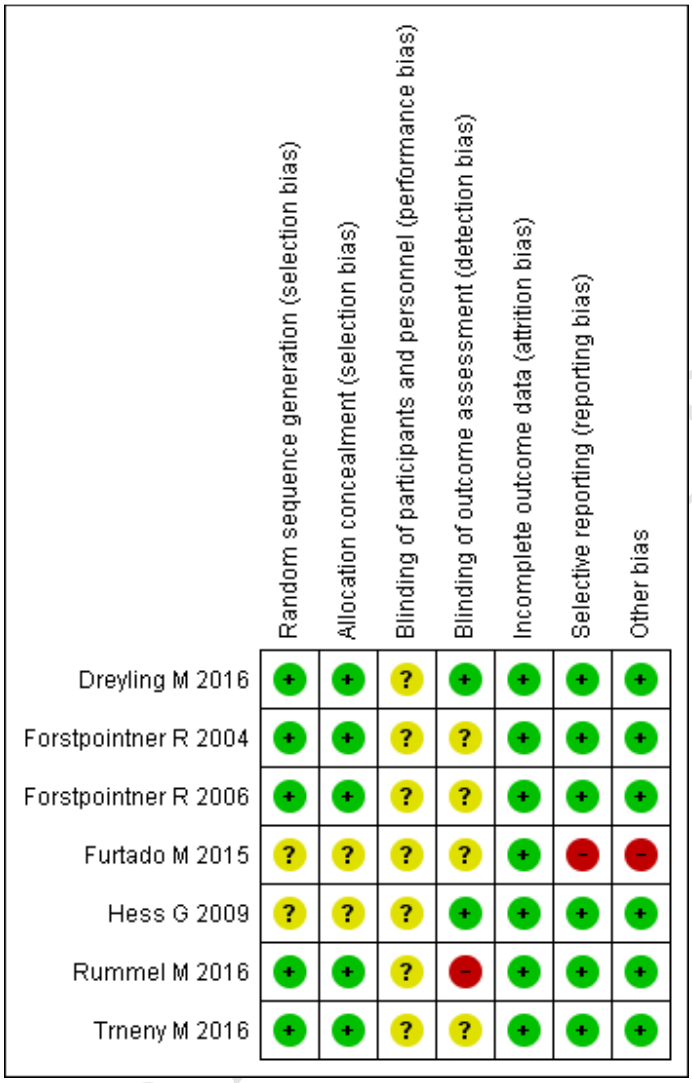
Quality Assessment of Studies

The quality of each trial was assessed using The Cochrane Collaboration's tool for assessing risk of bias. Assessment of blinding of participants and personnel was not applicable as all trials were open label and have therefore been listed as unclear due to the restrictions of choice within the tool. A full assessment of each trial is given in appendix 3. Overall two trials[17,23] were judged to be at low risk of bias across all domains, five trials[18,19,20,21,22] provided insufficient information on which to judge bias in some domains, and two trials[20,22] were judged to have some elements of high risk of bias (some trials fell into more than one category). Rummel et al[22] were judged to have detection bias by not referencing response criteria. Furtado et al[20] were judged to have selection and reporting bias in their trial based on differences in baseline characteristics between the two groups and not reporting pre-specified outcomes. A summary of the risk of bias is shown in figure 2.

Baseline Characteristics

The inclusion criteria were broadly similar between the trials with a couple of notable differences. Hess et al[21] required patients to have had two or more prior therapies, the remaining trials only required one. All trials, where stated, included patients with an ECOG performance status (PS) of up to 2. Dreyling et al[17] restricted this to PS 1. The median age of included patients was similar across trials, with median age between 67 years and 70 years of age in the majority of the trials.

The baseline characteristics are summarised in table 2 and were generally well balanced between the treatment arms in the majority of the trials. Three trials[20,21,23] did report an imbalance in some baseline characteristics. In the first the treatment groups differed with respect to blastoid variant, the median number of prior lines of treatment and prior bortezomib therapy,[21] the second differed with respect to the proportion of male patients, time since diagnosis and prior rituximab[20] and the final one differed with respect to tumour burden, bulky disease, LDH levels, number of prior therapies and numbers of patients with refractory disease.[23]



*Assessment of blinding of participants and personnel was not applicable as all trials were open label. The trials have been listed as unclear risk of bias due to the restrictions of choice within the bias tool

Low risk of bias

Unclear risk of bias

High risk of bias

Figure 2 - Risk of Bias Summary

Reference	Median Age (years)		Median Time from Original Diagnosis to Randomisation (months)		Type of Histology Blastoid vs Classical (%)		sMIPI Low vs Med vs High (%)		Relapsed vs Refractory (%)		Prior Line of Therapy 1-2 vs >2 (%)	
	Invest	Cont	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control
Dreyling M., 2016[17] Ibr v tems	67	68	38.9	46.23	12 v 88	12 v 88	32v47v22	30v49v21	74 v 26	67 v 33	68 v 32	66 v 34
Forstpointner R. 2004[18] R-FCM v FCM	65	63	24 for total population		Not stated		Not stated		Not stated		83 v 17*	84 v 17*
Forstpointner R. 2006[19] Rit main v obs	63	63	35 for total population		Not stated		Not stated		Not stated		97 v 4*	100 v 0*
Furtado M., 2014[20] V-CHOP v CHOP	69	71	24.7	19.7	Not stated		Not stated		Not stated		Not stated	
Hess G., 2009[21] Tems v IC	HD 68 LD 68.5	64.5	HD 49.6 LD 47.7	48.5	HD 0 v 85 LD 17 v 65	7 v 74	Not stated		Not stated		HD 52 v 48** LD 59 v 41**	39 v 61**
Rummel M., 2016[22] B-R v F-R	71.6	69.4	Not stated		Not stated		Not stated		96 v 4	95 v 5	79.1 v 20.8	87 v 13
Trneny M., 2016[23] Lenal v IC	68.5	68.5	54 v 45 ++	52 v 46 ++	Not stated		25v39v35 ***	25v44v30 ***	59 v 41	70 v 30	73 v 26	71 v 29

Invest=investigational drug; sMIPI=simplified mantle cell lymphoma international prognostic index; HD=high dose; LD=low dose**.** *% of 1 previous and 2 previous therapies added together for this group; **These are rates of 2-3 previous therapies vs 4-7 previous therapies; ***2% missing in both arms; ++<3 years v > 3 years; ibr=ibrutinib; tems=temsirolimus; R-FCM=rituximab, fludarabine, cyclophosphamide + mitoxantrone; rit main=rituximab maintenance; obs=observation; V-CHOP=bortezomib, cyclophosphamide, doxorubicin, vincristine + prednisolone; IC=investigator's choice; B-R=bendamustine + rituximab; F-R=fludarabine + rituximab; lenal=lenalidomide

Table 2 – Baseline Characteristics of Trial Population

Effectiveness of Treatments

Table 3 provides a summary of the progression free survival (PFS), overall survival (OS) and overall response rates (ORR) reported for MCL patients in the included trials. All the trials reported an improvement in PFS with the experimental drug which was statistically significant in all except two of the trials.[18,20] All the trials reported an improvement in OS in favour of the experimental arm, although not all the trials were powered to demonstrate a statistical difference in OS between the two groups.

Dreyling and colleagues[17] compared the oral Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib to the intravenous mTOR pathway inhibitor, temsirolimus, in patients who had been treated with at least 1 prior rituximab-containing therapy. With a median follow up of 20 months, PFS was significantly improved with ibrutinib when compared to temsirolimus (HR 0.43 [95% CI 0.32-0.58]; p<0.0001) with a median PFS with ibrutinib of 14.6 months vs 6.2 months with temsirolimus. There was a 24% relative reduction in the risk of death in patients receiving ibrutinib compared to temsirolimus (HR 0.76 [95% 0.53-1.09]; p=0.1324). Median OS was not reached in the ibrutinib arm compared with 21.3 months in the temsirolimus arm. It was noted that 23% of the patients receiving temsirolimus crossed over to the ibrutinib arm. The ORR as assessed by independent review was significantly higher for ibrutinib than for temsirolimus (72% vs 40%, (p<0.0001). Additionally, complete response (CR) rates were superior (19% with ibrutinib vs 1% with temsirolimus, odds ratio=3.98 [2.38-6.65]). At 18 months the estimated rate of response was 58% (range 46-68%) for ibrutinib compared to 20% (range 9-35%) for temsirolimus.

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		Progression Free Survival (months)			Overall Survival (months)			Overall Response Rate (%)			Complete Response (%)			Partial Response (%)	
Reference	**Outcome Analysis**	**median PFS**	**HR (95% CI)**	**p value**	**median OS**	**HR (95% CI)**	**p value**	**ORR**	**Odds Ratio (95% CI)**	**p value**	**CR**	**Odds Ratio (95% CI)**	**p value**	**PR**	**Odds Ratio (95% CI)**
Dreyling M., 2016	ITT	14.6 vs 6.2	0.43 (0.32 - 0.58)	<0.0001	NR* vs 21.3	0.76 (0.53 - 1.09)	0.1324	72 vs 40	NR**	0.0001	19 vs 1	3.98 (2.38-6.65)	NR**	NR**	NR**
Forstpointner R., 2004	ITT	8 vs 4	NR**	0.3887	NR* vs 11 (estimated)	NR**	0.0042	58 vs 46	NR**	0.282	29 vs 0	NR**	NR**	29 vs 46	NR**
Forstpointner R., 2006	Patients with initial R-FCM therapy	14 vs 12#	NR**	0.049	45% vs 9%†	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**
Furtado M., 2014	ITT	16.5 vs 8.1	0.6 (0.31 - 1.15)	0.12	35.6 vs 11.8	0.37 (0.16 - 0.83)	0.01	82.6 vs 47.8	0.14 (0.03 - 0.62)	0.01	34.8 vs 21.7	0.52 (0.14 - 1.93)	0.33	47.8 vs 26.1	0.39 (0.11 - 1.33)
Hess G., 2009©	ITT	4.8 vs 1.9	0.44 (0.25 - 0.78)	0.0009	12.8 vs 9.7	0.80 (0.50 - 1.28)	0.3519	22 vs 2	NR**	0.0019	2 vs 2	NR**	NR**	20 vs 0	NR**
Rummel M., 2016	Per protocol	17.6 vs 4.7	0.45 (0.22 - 0.76)	0.01	35.3 vs 20.9	NR**	NR**	70.8 vs 26.1	NR**	NR**	37.5 vs 13	NR**	NR**	33.3 vs 13	NR**
Trneny M., 2016	ITT	8.7 vs 5.2	0.61 (0.44 - 0.84)	0.004	27.9 vs 21.2	0.89 (0.62 - 1.28)	0.45	40 vs 11	NR**	0.001	5 vs 0	NR**	NR**	35 vs 11	NR**

NR* = not reached; NR** = not reported; # = median response duration; † = ongoing remissions beyond 2 years; © = results for higher dose; ITT = intent to treat; median PFS = median progression free survival; median OS = median overall survival; ORR = overall response rate; CR = complete response; PR = partial response;

Table 3 – Efficacy Outcomes for MCL Patients in the Included Trials

Hess et al[21] compared two IV temsirolimus regimens (175mg weekly for 3 weeks followed by either 75mg weekly or 25mg weekly) to investigator's choice (IC) chemotherapy in patients who had received between 2 and 7 prior therapies, which must have included an alkylating agent, an anthracycline and rituximab. PFS was statistically significantly improved with the higher dose temsirolimus when compared to the IC cohort (HR 0.44 [97.5% CI 0.25-0.78] p=0.0009). A non-significant improvement in PFS was noted with the lower dose (HR 0.65 [97.5% CI 0.39-1.10] p=0.062). A longer median PFS was observed in the high dose cohort compared to IC (4.8 months vs 1.9 months) and the low dose cohort (3.4 months vs 1.9 months with IC). Higher dose temsirolimus resulted in a 20% relative reduction in the risk of death when compared to IC chemotherapy (HR 0.80 [95% CI 0.50-1.28] p=0.35) but did not reach statistical significance. The lower dose achieved a 4% relative reduction in the risk of death compared to IC (HR 0.96 [95% CI 0.60-1.54] p=0.87). The final median OS analysis demonstrated an improvement in favour of the higher dose of temsirolimus, compared with IC (12.8 months vs 9.7 months, p=0.35). The median OS observed with the lower dose cohort was 10 months (p=0.87). High dose temsirolimus resulted in a superior ORR when compared to IC chemotherapy (22% vs 2%, p=0.0019). The ORR with low dose temsirolimus was 6% (p=0.61). The complete response rate with high dose temsirolimus was comparable to IC (2% vs 2%) whilst the partial response rate was improved (20% vs 0%).

The addition of rituximab (an anti-CD20 monoclonal antibody) to a combination of fludarabine, cyclophosphamide and mitoxantrone chemotherapy (R-FCM) was compared to FCM alone by Forstpointner and colleagues[18] in a mixed population of lymphoma sub-types (49% had follicular lymphoma, 35% had MCL and 11% had lymphoplasmocytic/cytoid lymphoma) who had received at least 1 prior line of treatment. The trial was stopped early with 128 patients recruited due to a significant advantage observed in favour of R-FCM. PFS was significantly improved with R-FCM compared to FCM alone in the overall population (median PFS 16 months vs 10 months; p=0.038) after a median follow up of 18 months. In an exploratory analysis for histological sub-groups, a shorter median PFS was observed for the MCL population compared with the total population (R-FCM 8 months vs 4 months FCM; p=0.389). This trial had a second randomisation[19] to maintenance rituximab or no maintenance for patients who had achieved a CR or PR. Despite the median duration of response (DoR) for MCL patients being similar in both arms (14 months maintenance vs 12 months no maintenance, p=0.049), a higher proportion

of MCL patients receiving maintenance rituximab experienced ongoing remissions beyond 2 years (45% vs 9%). A statistically significant benefit in median OS was observed in the cohort of MCL patients receiving R-FCM compared to FCM (not reached vs 11 months [estimated]; p=0.0042). These patients represented 35% of the total population. In addition, at 2 years 65% of MCL patients receiving R-FCM were still alive compared to 35% of patients treated with FCM. R-FCM resulted in a ORR when compared to FCM alone (58% vs 46%, p=0.282). More MCL patients experienced a complete response with R-FCM than with FCM (29% vs 0%), although more patients in the FCM arm achieved a partial response (29% vs 46%).

Furtado et al[20] compared a combination of bortezomib (an inhibitor of the 26S proteasome), cyclophosphamide, doxorubicin, vincristine and prednisolone (V-CHOP) for a maximum of 8 cycles to CHOP in MCL patients who had been treated with at least 1 prior line of therapy. The phase II trial recruited 46 patients and was stopped early by the independent data monitoring committee due to significant differences in overall survival between the 2 cohorts. After a median follow up of 34 months, a non-significant improvement in PFS was observed with the V-CHOP combination when compared to CHOP alone (HR 0.60 [95% CI 0.31-1.15]; p=0.12). The median PFS observed with the V-CHOP combination was 16.5 months compared to 8.1 months with CHOP, with a significant improvement in OS achieved with V-CHOP (HR 0.37 [95% CI 0.16-0.83]; p=0.01). A median OS of 35.6 months with V-CHOP was substantially longer than that observed with CHOP, 11.8 months. The addition of bortezomib to CHOP resulted in a superior ORR when compared to CHOP alone (82.6% vs 47.8%, p=0.01). A non-significant improvement in complete response rates (34.8% vs 21.7%, p=0.33) and partial response rates (47.8% vs 26.1%, p=0.13) were also noted.

Rummel et al[22] compared bendamustine and rituximab (B-R) to fludarabine and rituximab (F-R) in a mixed cohort of patients who had received at least 1 prior therapy. Fifty one percent of patients had FL, 21% had MCL, 11% had Waldenstrom's macroglobulinaemia (WM), 8% had marginal zone lymphoma (MZL), 8% had lymphoplasmacytic lymphoma and an additional 1% had low grade unclassified. A maximum of 6 cycles of either chemotherapy combination was administered to 230 patients. The protocol was amended during the course of the trial to include rituximab maintenance therapy for patients who responded to B-R or F-R, as maintenance rituximab treatment had been approved for patients with FL. In patients with MCL, PFS was

statistically significantly improved in the B-R arm (HR 0.45 [95% CI 0.22-0.76]; p=0.01), with a median PFS of 17.6 months achieved for B-R compared with 4.7 months for F-R. An improvement in median OS was also observed (B-R group 35.3 months vs 20.9 months F-R, p=not reported). The impact of maintenance rituximab was not reported for MCL patients. A superior ORR for MCL patients receiving B-R was achieved (70.8% vs 26.1%). Both the complete response rate (37.5% vs 13%) and the partial response rate (33.3% vs 13%) were substantially higher for MCL patients treated with B-R compared to patients treated with F-R.

Trneny et al[23] compared oral lenalidomide to investigator's choice (IC) single agent chemotherapy in 254 MCL patients. They had to have been treated with at least 1 combination chemotherapy regimen comprising an alkylating agent and one or more of an anthracycline, cytarabine or fludarabine with or without rituximab. After a median follow up of 15.9 months, PFS was statistically significantly improved with lenalidomide (HR 0.61 [95% CI 0.44-0.84] p=0.004) when compared to IC with a prolonged median PFS of 8.7 months compared to 5.2 months in the IC arm. A significant improvement was demonstrated in favour of lenalidomide when compared to the majority of the individual IC therapies. A non-statistically significant difference in OS was reported for patients treated with lenalidomide compared with patients treated with IC (HR 0.89 [95% CI 0.62-1.28]; p=0.45). Median OS was 27.9 months with lenalidomide compared to 21.2 months with IC. The trial was not powered to demonstrate a survival difference between the 2 arms and was further compounded by patients' crossing over to the lenalidomide arm on disease progression. A significant improvement in ORR was observed for patients receiving lenalidomide treatment when compared to IC chemotherapy (40% vs 11%, p<0.001). The CR rate was 5% with lenalidomide vs 0%, (p=0.043). The PR rate was 35% vs 11% IC). The duration of response was significantly prolonged with lenalidomide compared to IC (16.1 months vs 10.4 months, p=0.043).

Safety

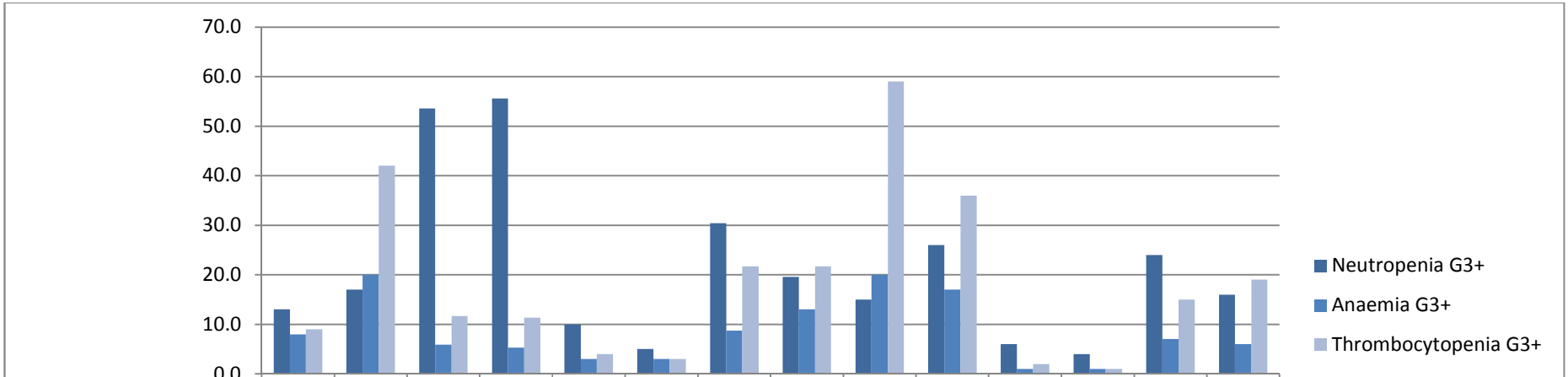
A summary of grade 3 or higher haematological toxicities observed in the trials is presented in figure 3. Patients treated with ibrutinib had a longer duration of treatment exposure compared to the control arm in the trial led by Dreying et al[17] (14.4 months vs 3 months) with a mean relative dose intensity of 99.9% for ibrutinib vs 81.8% for temsirolimus. Adverse events caused treatment discontinuation and dose reductions in 6% and 4% of patients in the ibrutinib arm compared with 26% and 43% respectively for the comparator group.

The median duration of temsirolimus 175/75mg treatment was more than double that of IC (12 weeks vs 5 weeks) in the trial led by Hess et al.[21] Significantly higher rates of thrombocytopenia, and anaemia were observed with temsirolimus. In contrast, leucopenia was more frequent with IC chemotherapy than higher dose temsirolimus (all grades 15% vs 40% IC), as was neutropenia (all grades 24% vs 40% IC). Twenty two percent of patients in the temsirolimus 175/75mg arm discontinued treatment due to an adverse event compared to 11% in the IC arm.

The frequency of grade 3/4 haematological toxicities was comparable across both treatment groups in the trial by Forstpointner et al[18] except for lymphocytopenia which was more common across grades 1-4 in the R-FCM arm when compared to the FCM arm The extended use of rituximab during the maintenance phase of the trial[19] did not result in any significant differences of adverse events between the two arms.

Furtado et al[20] reported a similar rate of grade 3 or higher thrombocytopenia between the two arms, however a significant increase in the rate of $\geq$grade 3 neutropenia was observed in the experimental arm and translated to a higher rate of febrile neutropenia with the V-CHOP regimen. Non-neutropenic infection rates were also higher, however, these were primarily low grade.

Both bendamustine-rituximab (B-R) and fludarabine-rituximab (F-R) combinations were well tolerated by patients in the trial by Rummel and colleagues.[22] The dose intensity in the B-R group was 96.3% and was 99.5% in the F-R arm, indicating good tolerability for either regimen.



	Ibrut	Tems	R-FCM	FCM	Ritux	No maint	V-CHOP	CHOP	Tems (HD)	IC	B-R	F-R	Lenalid	IC
	Dreyling M, 2016		Forstpointner R, 2004		Forstpointner R, 2006		Furtado M, 2014		Hess G, 2009		Rummel M, 2016		Trneny M, 2016	
Neutropenia G3+	13.0	17.0	53.6	55.6	10.0	5.0	30.4	19.6	15.0	26.0	6.0	4.0	24.0	16.0
Anaemia G3+	8.0	20.0	5.9	5.3	3.0	3.0	8.7	13.0	20.0	17.0	1.0	1.0	7.0	6.0
Thrombocytopenia G3+	9.0	42.0	11.7	11.3	4.0	3.0	21.7	21.7	59.0	36.0	2.0	1.0	15.0	19.0

Figure 3 – Grade 3 or Higher Haematological Toxicities

Dose reductions were more common in the lenalidomide group (41% vs 17%)[23] but discontinuations were more common in the IC group (5% vs 16%). Rates of ≥grade 3 neutropenia were higher in the lenalidomide arm, with febrile neutropenia reported in 6% of patients receiving lenalidomide compared to 2% of patients receiving IC. Rates of anaemia were comparable with thrombocytopenia being higher in the IC arm.

Unpublished and Ongoing Trials

Four trials[35,36,37,38] were presented at the 58th annual meeting of the American Society of Haematology (ASH) held in San Diego from 3-6 December, 2016, all of which assessed combinations of treatments in relapsed/refractory MCL. All of these trials were single arm studies but give an indication of emerging potential future management approaches. Jerkeman et al[35] on behalf of the Nordic Lymphoma Group combined ibrutinib with lenalidomide and rituximab. The authors reported that out of the 50 patients enrolled to date, 29 were evaluable for response achieving an impressive ORR rate of 83% and CR of 41%, with median PFS not reached. Morschhauser et al[38] presented results on behalf of the LYSA group from their study combining lenalidomide with obinutuzumab, an anti-CD20 monoclonal antibody. Seven MCL patients completed the induction phase and achieved an ORR of 38.5% with CR in 23.1% as evaluated by revised IWG 2007 criteria.[25] These improved ORR and CR rates would indicate a deeper response with the combination of therapies, which may in time translate to a longer PFS and overall survival for patients.

As of December 2016, there were 85 ongoing trials (www.clinicaltrials.gov and www.clinicaltrialsregister.eu) aiming to recruit more than 2300 patients with R/R MCL to evaluate monotherapies and combinations of agents. Of these 85 trials, 53 are phase I or phase I/II trials, 26 are in phase II, one trial is phase III and one trial is phase IV. The remaining four trials are either retrospective or stated as pilot studies with no further details. Only the phase III trial is a randomised controlled trial (appendix 4). Of the remaining 26 on-going phase II trials, 13 are evaluating combinations of treatments and 13 are assessing monotherapies. Ibrutinib is included in five combination trials, lenalidomide is included in three combination studies, one of which is with bendamustine, and bortezomib is combined with additional treatments in two trials.

Discussion

There is no consensus about the standard of care for relapsed/refractory mantle cell lymphoma and current UK[2], EU[4] and US[15] guidelines reflect this. As demonstrated by the search results there are many published studies assessing treatment regimens for this disease, but the vast majority are single arm, non-randomised trials that rely on historical controls for comparison. Indeed, bortezomib, ibrutinib and lenalidomide all received marketing authorisations based on single arm phase II trials[30,31,32] which may reflect the unmet medical need for this group of patients at the time. There is a noticeable lack of randomised controlled trials (RCT) evaluating treatments for relapsed/refractory mantle cell lymphoma, which limited the scope of this systematic review. Only seven RCTs[17,18,19,20,21,22,23] were identified for this review, six of which were distinct trials and of these, only two met all the criteria set out in the Cochrane's Collaboration tool for assessing risk of bias.

Three of the trials had mixed populations. MCL is a rare but aggressive B-cell malignancy which behaves quite differently to other sub-types of non-Hodgkin lymphoma resulting in distinctive responses to treatments as demonstrated in the trial by Rummel et al.[22] In this trial MCL patients' receiving the combination of bendamustine and rituximab achieved a median PFS of 17.6 months. In contrast, patients with follicular lymphoma achieved a median PFS of 54.5 months with the same regimen. These were exploratory sub-group analyses, nevertheless this highlights the need to evaluate treatments in a pure MCL population in order to draw clinically meaningful conclusions. It can be challenging to accrue sufficient number of patients to a trial when the disease is rare, and collaborative research groups have been established with this in mind. Forstpointner et al[18] had only included 48 patients with MCL when further recruitment was halted due to a significant advantage observed in the R-FCM arm, which had a mixed population of lymphoma sub-types. The trial by Furtado et al[20] planned to recruit 90 patients, but as the trial was stopped early due to a significant difference in survival observed at the first predetermined evaluation point, only 46 patients were included. Neither trial was statistically designed for such small numbers, therefore the statistical significance of the results may be unreliable. Indeed the median PFS observed with V-CHOP treatment was double that of CHOP alone in the trial conducted by Furtado and colleagues[20] and yet this did not achieve statistical significance.

It is difficult to make meaningful comparisons of effectiveness across the included trials in this review as the inclusion/exclusion criteria differed between the trials. The trial by Dreyling et al[17] excluded patients with an ECOG PS above 1 whilst the remaining trials allowed patients with PS 0-2.[20,21,22,23] The majority of trials included patients who had received at least 1 line of prior therapy[17,18,20,22,23] but these prior therapies differed between the trials and may have had some impact on the outcomes achieved. Prior rituximab therapy may have introduced outcome bias to those trials allowing prior exposure. Rule et al[28] has demonstrated that the addition of rituximab to fludarabine-based chemotherapy in newly diagnosed MCL patients improved OS resulting in a reduction in the hazard of death by 31%. In addition it has been suggested that prior bortezomib treatment sensitises MCL to subsequent therapies.[29] Other baseline factors that may impact outcomes include time from initial diagnosis to randomisation - the longer time may suggest that these patients have more indolent disease as they can safely wait to start therapy. The proportion of patients that have the more difficult to treat blastoid histology will impact on outcomes and the split between patients who have relapsed disease and refractory disease will influence, as refractory are generally a harder-to-treat sub-type. Additional factors that need to be considered when comparing trials are the differences in MIPI scores, the proportion of patients with high Ki67 scores indicating more aggressive disease and other biological factors such as TP53 mutation or SOX11 status that will impact outcome.The ideal would be to have these balanced between the arms of each trial and stratification prior to randomisation may achieve this. That said, in a rare disease this can be difficult to achieve in practice. Blastoid histology represents a small proportion of the total MCL population but it is important that patients with this sub-type are included in trials in order to collect data on how they respond to various treatments. It would not be feasible to run a trial on this sub-type alone, therefore imbalances in baseline characteristics of this nature between treatment arms need to be tolerated whilst acknowledging that they may impact results.

The response criteria by which outcomes were measured differed between the studies. It is important that consistent definitions of endpoints are used allowing for comparisons among clinical trials. International Working Group criteria, 1999[26] were revised in 2007[25] and eliminated the need for the response criterium, complete response unconfirmed (CRu) and incorporated the assessment of extranodal disease. In a trial recently presented at the 58th Annual Meeting of the American Society of Haematology (ASH), 2016[35] two analyses were conducted

within the same trial, one using the 1999 IWG criteria[26] demonstrating an ORR of 46.2% and a CR/CRu of 15.4%. The other used the revised IWG criteria 2007[25] and reported an ORR of 38.5% and CR of 23.2%, thus demonstrating some differences in response rates depending on the criteria used. Four of the trials[17,20,21,23] in this review used the revised 2007 IWG criteria[25] whereas both trials by Forstpointner et al[18,19] used IWG 1999 criteria.[26] The revised criteria[25] also provide clear definitions of time to event outcomes, for example, PFS and OS are measured from the time of randomisation to the date of disease progression or death from any cause. Definitions of progression free survival (PFS) were inconsistent between the trials. Three trials[17,21,23] used the IWG definition. Two trials[18,22] however, used the definition: "Progression free survival is the interval between the start of treatment/first treatment and documentation of progressive disease or death from any cause". One trial[20] did not give a definition of PFS. The authors stated that one of the secondary outcomes was "median time to progression of disease", however, reported PFS in the results.

The trial by Hess et al[21] evaluated two different dosing regimens of temsirolimus (175/75mg and 175/25mg) to a control arm of IC chemotherapy, and the results led to the regulatory approval of the 175/75mg dose in the EU. Dreyling et al[17] compared ibrutinib to temsirolimus 175/75mg. There are some similarities when comparing baseline characteristics between the two trials, thus it would be feasible to make comparisons between the outcomes of these two trials. What is striking is that across all outcome measures in the Dreyling et al[17] study, temsirolimus outperformed those achieved in the temsirolimus 175/75mg arm of the trial by Hess et al,[21] although the duration of response reported was similar between the two trials. Patients in the Hess trial[21] had received two to seven prior therapies (48% had received 4-7 prior treatments) compared to at least one in Dreyling's study[17] (68% had received a median of 1-2) which might account for the poorer performance of temsirolimus, suggesting that earlier treatment is more effective. Indeed, the abstract presented by Rule et al[33] at the 21st congress of the European Haematology Association (EHA), 2016, supports this. The authors here reported survival outcomes for ibrutinib by number of lines of prior therapy, indicating that earlier treatment is more effective. That said, ibrutinib was significantly better than temsirolimus across all outcome measures in the trial by Dreyling et al.[17]

The addition of rituximab to chemotherapy regimens for the treatment of MCL patients has been established in a number of trials. Included in this review are the trials by Forstpointner et al[18,19] which demonstrated that the addition of rituximab to the combination of fludarabine, cyclophosphamide and mitoxantrone followed by rituximab maintenance for patients in remission improved response rates and overall survival. Maintenance rituximab resulted in a higher proportion of patients experiencing ongoing remissions beyond 2 years. The impact of rituximab on the outcome for MCL patients, influenced the decision to halt the trial by Furtado et al[20] early. The authors had not incorporated rituximab into the design of their study, but during the recruitment period it had become part of standard care in the UK. Rummel et al[22] began accrual for their trial in October 2003, however the authors amended their protocol to allow patients who responded to either B-R or F-R chemotherapy regimens to receive maintenance rituximab following the publication of Forstpointner et al's trial.[19] They conducted a sub-group analysis on the total population, comparing those patients who received maintenance and those who did not. The results confirmed the impact that maintenance rituximab had on PFS and OS in the R/R setting following remission with induction chemotherapy. Maintenance rituximab reduced the risk of death or disease progression by 48% (PFS p=0.01, OS p=0.03). The group of MCL patients who received maintenance rituximab was too small to conduct this analysis upon. However, the trial reported by Rummel et al[34] at the annual meeting of the American Society of Clinical Oncology (ASCO), 2016 conducted in the first line setting, may give some indication of what might be expected in MCL patients. No statistically significant difference in PFS was observed between patients receiving maintenance rituximab following B-R chemotherapy compared with patients not receiving maintenance rituximab (HR 0.64, 95% CI 0.36–1.14, p=0.130). This trial recruited 120 patients with newly diagnosed MCL and the authors concluded that after a median observation time of 4.5 years they were not able to demonstrate statistical evidence supporting the benefit of rituximab maintenance after B-R.

Only one treatment, temsirolimus, appeared in more than one trial, which meant that the results from each trial could not be quantitatively pooled by meta-analysis. Whilst a limited network meta-analysis could theoretically have been done between Dreyling et al[17] and Hess et al[21] as they both had a temsirolimus arm, the fact that Hess et al[21] had as a comparator IC meant that it was impossible to evaluate the effectiveness of temsirolimus against particular drugs, making the comparisons meaningless.

As the majority of patients with MCL are elderly, tolerability of treatment is an important factor when comparing different therapies, and should be evaluated on the per protocol population to accurately reflect adverse events in patients actually receiving drug. Grade 3 or higher haematological adverse event rates varied considerably between the included trials. The rates of ≥grade 3 haematological toxicities were low with either the combination of bendamustine and rituximab or fludarabine and rituximab in Rummel et al's trial[22] with high dose intensities achieved in both arms of the trial. Ibrutinib was also well tolerated with low rates of myelosuppression despite treatment exposure being 3 times as long with ibrutinib compared to temsirolimus 175/75mg.[17] Dose reductions were uncommon with ibrutinib whilst 43% of patients receiving temsirolimus 175/75mg required a dose reduction due to adverse events. Nearly a quarter of patients being treated with temsirolimus 175/75mg in the trial conducted by Hess et al[21] discontinued treatment due to an adverse event. Both of these trials suggest that temsirolimus at the approved dose of 175/75mg is poorly tolerated. In Forstpointner and colleagues trial[19], it was encouraging to note that rituximab maintenance did not result in substantial additional treatment-associated haematological toxicities with ≥grade 3 adverse event rates very similar between the maintenance and no maintenance arms.

Some of the novel agents identified in this review are now being evaluated in the front-line setting which will impact on the choice of agent for when these patients subsequently relapse. A UK study[39] evaluating ibrutinib and rituximab against a rituximab and chemotherapy combination in newly diagnosed patients with MCL who are not eligible for intensive treatment is ongoing. Results are expected in 2022. In addition, the SHINE trial is assessing the combination of ibrutinib with B-R in newly diagnosed patients[40]. A similar trial evaluating the combination of the second generation BTK inhibitor, acalabrutinib with B-R[41] is ongoing, with results due in February 2021. If these prove to be successful the paradigm for relapsed or refractory disease will shift and subsequent trials for R/R MCL will need to include patients who have received prior ibrutinib or acalabrutinib treatment. A Spanish trial[42] is evaluating the combination of ibrutinib and rituximab in newly diagnosed patients with the indolent form of MCL. This trial is expected to report results in January 2023. Several trials[43,44,45] are evaluating the role of lenalidomide in the first line setting, either in combination with chemotherapy or as maintenance following chemotherapy induction. The E1411 trial[46] is evaluating the combination

of bortezomib with B-R as induction followed by rituximab+/- lenalidomide as maintenance. Results are expected in March 2019.

There are a number of new agents being assessed for R/R MCL, either as monotherapy or in combination with established treatments: venetoclax (BCL-2 inhibitor), idelalisib and buparlisib (PI3Kδ inhibitors), the second generation proteasome inihibitor carfilzomib, daratumumab (an anti-CD38 mononclonal antibody) and genetically engineered chimeric antigen receptor T-cells (CAR T-cells). All are currently in single arm trials.

As the landscape of treatment options for the management of R/R MCL becomes more complicated, comparative studies will be required to evaluate the relative advantages of one treatment over another in order to ensure the optimal use of the available therapies. The protocol only permitted the inclusion of randomised controlled trials as this study design provides the best evidence for effectiveness of treatments. Single arm trials may provide additional information to clinicians about efficacy of treatment options for this rare disease but these are biased by nature of their design. It is concerning that only one of the on-going studies is an RCT. Careful consideration should be given to future trial design to ensure that meaningful evaluation of effectiveness of treatments can be undertaken.

The challenging factor is that MCL remains a rare malignancy with a small pool of patients from which to recruit to trials. Collaboration between research groups and agreement of standards for clinical trials is essential. In addition to this, utilising adaptive trial designs for assessing the relative merits of treatments may help in addressing this challenge. Multi arm multi stage (MAMS) trials have been adopted in some therapeutic areas in order that a number of novel treatments can be compared simultaneously to a shared control group[47]. This can result in answers to research questions being provided more quickly and cost effectively with a smaller number of patients, and may be a suitable approach to adopt for evaluating future treatments or combinations of treatments for MCL patients.

The scarcity of high-quality RCTs in MCL highlights the difficulty in evaluating comparative efficacy and safety of new therapies. Historical studies lack common comparators, exhibit differences in inclusion criteria and have small sample sizes. Although prognostic indicators such as the sMIPI score or blastoid variant were reported in some of the studies, none of the

trials reported outcomes according to these important factors, due to the small numbers of patients in these groups. The original protocol intended to undertake a sub-group analysis for these prognostic indicators but due to the lack of data this analysis was not possible. Nevertheless, this review should help to guide treatment selection for elderly patients with R/R MCL who are unsuitable for intensive chemotherapy or transplant.

Authorship

MP conducted the search, extracted data, interpreted data and wrote the manuscript. SR provided clinical expertise and edited the manuscript. MK reviewed the search results and data and edited the manuscript. JW provided expert methodology support and edited the manuscript.

Disclosure of Conflict of Interest

MP is employed by Janssen-Cilag, the manufacturer of ibrutinib, as a senior Medical Scientific Liaison Manager. This review however, was written as part of the author's position as an MSc student at the Institute of Cancer Sciences, University of Birmingham and all efforts have been made to take a strictly impartial view of the evidence.

SR has provided consultancy for Janssen-Cilag, Celgene, Roche, Napp, Pharmacyclics, Gilead, Sunesis, Kite, TG Therapeutics, Astra Zeneca

MK is employed by Janssen-Cilag as a senior Medical Scientific Liaison Manager.

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Appendices

1. Medline (Ovid) Search Strategy

1. Lymphoma, Mantle-cell.mp. or *mantle cell lymphoma/

2. Lymphoma, Non-Hodgkin.mp. or *nonhodgkin lymphoma/

3. B-cell.mp. or *B lymphocyte/

4. 1 or 2 or 3

5. Drug therapy.mp. or drug therapy/

6. immunotherapy.mp. or immunotherapy/

7. molecular targeted therapy.mp. or molecularly targeted therapy/

8. biological therapy.mp. or biological therapy/

9. combined modality therapy.mp. or multimodality cancer therapy/

10. antineoplastic agents.mp. or antineoplastic agent/

11. lenalidomide.mp. or lenalidomide/

12. ibrutinib.mp. or ibrutinib/

13. thalidomide.mp. or thalidomide/

14. bortezomib.mp. or bortezomib/

15. temsirolimus.mp. or temsirolimus/

16. everolimus/ or everolimus.mp.

17. BTK inhibitor.mp. or Bruton tyrosine kinase inhibitor/

18. proteasome inhibitor.mp. or proteasome inhibitor/ or ixazomib/

19. immunomodulating agent/ or imid.mp.

20. combination chemotherapy/ or chemotherapy/ or multimodal chemotherapy/ or cancer combination chemotherapy/ or chemotherapy.mp.

21. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 4 and 21

23. limit 22 to (randomized controlled trial and yr="1994 -Current")

2. Embase (Ovid) Search Strategy

1. Lymphoma, Mantle-cell.mp. or *mantle cell lymphoma/

2. Lymphoma, Non-Hodgkin.mp. or *nonhodgkin lymphoma/

3. B-cell.mp. or *B lymphocyte/

4. 1 or 2 or 3

5. Drug therapy.mp. or drug therapy/

6. immunotherapy.mp. or immunotherapy/

7. molecular targeted therapy.mp. or molecularly targeted therapy/

8. biological therapy.mp. or biological therapy/

9. combined modality therapy.mp. or multimodality cancer therapy/

10. antineoplastic agents.mp. or antineoplastic agent/

11. lenalidomide.mp. or lenalidomide/

12. ibrutinib.mp. or ibrutinib/

13. thalidomide.mp. or thalidomide/

14. bortezomib.mp. or bortezomib/

15. temsirolimus.mp. or temsirolimus/

16. everolimus/ or everolimus.mp.

17. BTK inhibitor.mp. or Bruton tyrosine kinase inhibitor/

18. proteasome inhibitor.mp. or proteasome inhibitor/ or ixazomib/

19. immunomodulating agent/ or imid.mp.

20. combination chemotherapy/ or chemotherapy/ or multimodal chemotherapy/ or cancer combination chemotherapy/ or chemotherapy.mp.

21. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 4 and 21

23. limit 22 to (randomized controlled trial and yr="1994 -Current

3. Quality Assessment of Included Trials in MCL

Reference	Criteria from Cochrane Collaboration's Tool	Assessment	Notes
Dreying et al, 2016[17]	Was the allocation sequence adequately generated?	Yes	Central randomisation was used….based on a computer-generated randomisation schedule. Randomisation was balanced by using randomly permuted blocks.
	Was allocation adequately concealed?	Yes	Randomisation scheme was implemented within the interactive web response system
	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during the study?	Yes	Outcome assessments were conducted by an independent review committee using validated IWG criteria
	Were incomplete outcome data adequately addressed?	Yes	All data was accounted for. Analysis conducted on ITT basis.
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All pre-specified outcomes reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Although protocol was amended to allow cross over to investigational arm on progression this would have introduced bias against the investigational drug

Forstpointner et al, 2004[18]	Was the allocation sequence adequately generated?	Yes	Central randomisation procedure done by computer programme using random permutated blocks
	Was allocation adequately concealed?	Yes	Central allocation was done by telephone
	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during the study?	Unclear	An open-label study. Responses were evaluated using validated IWG criteria, although it wasn't stated whether this was centrally or locally reviewed
	Were incomplete outcome data adequately addressed?	Yes	Out of 147 randomised to the trial, 128 patients were evaluable; authors accounted for the remaining 19 patients
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All pre-specified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Although the trial was stopped early, this was pre-specified and allowed stopping when a level of significance was reached. The arms and baseline characteristics were well balanced
Forstpointner et al, 2006[19]	Was the allocation sequence adequately generated?	Yes	Central randomisation procedure done by computer programme using random permutated blocks
	Was allocation adequately concealed?	Yes	Central allocation was done by telephone
	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during	Unclear	Responses were evaluated using validated IWG criteria, although it wasn't stated whether

	the trial?		this was centrally or locally reviewed
	Were incomplete outcome data adequately addressed?	Yes	Authors accounted for all patients and gave reasons for those not included in the analysis
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All pre-specified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Analysis included 38 patients who received FCM as induction instead of R-FCM. If any bias introduced it would be against investigational arm
Furtado et al, 2014[20]	Was the allocation sequence adequately generated?	Unclear	Method of sequence generation was not described. Insufficient information to allow judgement
	Was allocation adequately concealed?	Unclear	Method of concealment was not described. Insufficient information to allow judgement
	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during the trial?	Unclear	Responses were evaluated using validated IWG criteria, although it wasn't stated whether this was centrally or locally reviewed
	Were incomplete outcome data adequately addressed?	Yes	Out of 46 patients included in the trial, 41 were assessable. The authors accounted for the 5 non-assessable patients and included them in the analysis as non-responders.
	Are reports of the study free of suggestion of selective outcome reporting?	No	The protocol pre-specified time to progression and quality of life as secondary endpoints. These were not reported.
	Was the study apparently free of other problems that could put it at a high risk of bias?	No	There were imbalances in the baselines characteristics: there were more men in the CHOP arm (91% vs 65%) time since diagnosis was shorter in the CHOP arm (19.7 vs 24.7

			months) and less patients had received prior rituximab in the CHOP arm (17% vs 43%).
Hess et al, 2009[21]	Was the allocation sequence adequately generated?	Unclear	Method of sequence generation was not described. Insufficient information to allow judgement
	Was allocation adequately concealed?	Unclear	Method of concealment was not described. Insufficient information to allow judgement
	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during the trial?	Yes	Outcome assessments were conducted by an independent review committee using validated IWG criteria on an ITT basis
	Were incomplete outcome data adequately addressed?	Yes	There were no missing outcome data.
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All pre-specified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Baseline characteristics were generally well balanced. Where imbalances occurred these were these were in favour of IC: fewer patients with bone marrow involvement (39% vs 54%),fewer patients with blastoid variant (7% vs 17%) and more patients with prior bortezomib therapy (31% vs 19%).
Rummel et al, 2016[22]	Was the allocation sequence adequately generated?	Yes	Randomisation was conducted centrally according to pre-specified randomisation lists with permuted blocks of randomly variable block size
	Was allocation adequately concealed?	Yes	Patients were randomised centrally under concealment

	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during the trial?	No	Patients were assessed locally and not by an independent review committee. Response criteria was not referenced in the study.
	Were incomplete outcome data adequately addressed?	Yes	Analysis was conducted on a per protocol basis. Authors accounted for all patients and gave reasons for those not included in the analysis
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All pre-specified outcomes were reported
	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Baseline characteristics were similar between the 2 groups
Trneny et al, 2016[23]	Was the allocation sequence adequately generated?	Yes	Permuted-block randomisation with a block size of 6 resulting in 50 blocks in each stratum was used
	Was allocation adequately concealed?	Yes	A centralized interactive voice-response system was used to allocate patients
	Was participant and personnel knowledge of the allocated intervention prevented during the study?	Unclear	Open label. Patients and investigators were unmasked to treatment assignment
	Was knowledge of the outcome assessment adequately prevented during the trial?	Yes	Outcome assessments were conducted by an independent review committee using validated IWG criteria
	Were incomplete outcome data adequately addressed?	Yes	All data was accounted for. Analysis conducted on ITT basis.
	Are reports of the study free of suggestion of selective outcome reporting?	Yes	All pre-specified outcomes reported

	Was the study apparently free of other problems that could put it at a high risk of bias?	Yes	Although protocol allowed cross over to investigational arm on progression this would have introduced bias against the investigational drug

4. On-Going Trials in Relapsed/Refractory MCL

NCT Identifier	Study Design	Line of Treatment	Target Patient Numbers	Primary Outcome	Completes
COMBINATION TRIALS					
NCT02460276	A Phase II Trial of Ibrutinib, Lenalidomide and Rituximab for Patients With Relapsed/Refractory Mantle Cell Lymphoma	At least 1 rituximab-containing prior Rx	50	ORR based on PET and CT	Mar 2017
NCT01880567	A Phase II Study of Ibrutinib Plus Rituximab in Patients With Relapsed/Refractory Mantle Cell Lymphoma or Elderly Patients With Newly Diagnosed Mantle Cell Lymphoma (MCL)	At least 1 prior treatment	100	ORR	Dec 2019
NCT01737177	Bendamustine, Lenalidomide and Rituximab (R2-B) Combination as a Second-Line Therapy for First Relapsed-Refractory Mantle Cell Lymphomas: A Phase II Study	At least 1 prior treatment	42	CR based on IWG 2007 and maintenance PFS	Jan 2017
NCT01996865	A Phase 3B Randomized Study of Lenalidomide (CC-5013) Plus Rituximab Maintenance Therapy Followed by Lenalidomide Single-Agent Maintenance Versus Rituximab in Subjects With Relapsed/Refractory Follicular, Marginal Zone, or Mantle Cell Lymphoma	At least 1 prior treatment	500	PFS based on IWG 1999	Mar 2023
NCT00980395	A Phase II, Open-Label Study of Bortezomib (Velcade), Cladribine and Rituximab (VCR) in Advanced, Newly Diagnosed and Relapsed/Refractory Mantle Cell and Indolent Lymphomas	Not stated	39	PFS at 2 years	Dec 2021

NCT02840539	A Phase 2 Trial to Evaluate the Efficacy of Bortezomib, Cytarabine, and Dexamethasone in Patients With Relapsed or Refractory Mantle Cell Lymphoma	1-3 prior lines of treatment	32	ORR	Feb 2020
NCT02736617	A Phase II Study of Obinutuzumab (GA-101) in Combination With Ibrutinib (I) for the Treatment of Relapsed Mantle Cell Lymphoma	At least 1 prior treatment	20	Best ORR of CR/PR	July 2021
NCT02471391	A Phase 2 Study of ABT-199 in Combination With Ibrutinib in the Treatment of Patients With Relapsed or Refractory Mantle Cell Lymphoma (AIM Study)	At least 1 prior treatment	24	CR at 16 weeks based on IWG 2007	June 2018
NCT01796470	A Phase 2, Open-Label Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacodynamics of GS-9973 (entospletinib)in Combination With Idelalisib in Subjects With Relapsed or Refractory Hematologic Malignancies	Not stated	66	ORR	June 2017
NCT00764517	Phase II Study of Vorinostat (SAHA), Cladribine, and Rituximab (SCR) in Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia, and Relapsed B Cell Non-Hodgkin Lymphoma	Not stated	66	ORR based on IWG 2007	Dec 2016

NCT01562977	Prospective, Open-label, Multicentric, ph. II Study of R-GemOx and Dexametasone in Patients With Agressive Lymphomas Refractory or Relapsed to Previous Treatment and Non Eligible for High-dose Chemotherapy Followed by Autologous Stem Cell Transplanted	Not stated	129	ORR based on IWG	April 2017
NCT01812005	A Phase II Study of MLN8237 (alisertib)Alone and in Combination With Rituximab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin Lymphomas	At least 1 prior treatment	50	ORR to alisertib alone	Dec 2016
EudraCT: 2015-004061-87	A Phase 2 Study to Evaluate the Efficacy and Tolerability of IMGN529 in Combination with Rituximab in Patients with Relapsed and/or Refractory Diffuse Large B-Cell Lymphoma and Other Forms of Non-Hodgkin Lymphoma	At least 1 prior treatment	75	Safety and ORR	Not stated
MONOTHERAPY TRIALS					
NCT02601313	A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-C19 in Subjects With Relapsed/Refractory Mantle Cell Lymphoma (r/r MCL) (ZUMA-2)	Up to 5 prior treatments. Must have included anthracycline,or bendamustine-containing regimen, anti-CD20 mAb and ibrutinib	70	ORR based on IWG	Sep-17
NCT02042950	A Phase II Study of Carfilzomib in the Treatment of Relapsed/Refractory Mantle Cell Lymphoma	Not stated	60	ORR based on IWG 2007	Jul-21

NCT02413489	An Open Label, Phase 2 Study to Evaluate Efficacy and Safety of Daratumumab in Relapsed or Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma	At least 2 prior lines of treatment	210	ORR	Jan-19
NCT02488512	Peptide Receptor Radionuclide Therapy With 90Y-Dotatoc in Relapsed/Refractory Diffuse Large B Cell (DLBCL) and Mantle Cell Lymphomas (MCL)	Not stated	35	ORR based on IWG	Feb-18
NCT02169180	A Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects With Relapsed or Refractory Mantle Cell Lymphoma (MCL) in Japan	At least 1 prior treatment	16	ORR based on IWG 2007	Jun-17
NCT02267915	An Open Multicenter Phase II Study of Efficacy and Toxicity of Maintenance Subcut. Rituximab After Induction With Rituximab in Patients With Relapsed or Refractory Mantle-cell Lymphoma Non-eligible for HSCT	1-2 prior lines of treatment	36	TTP	2019 November
NCT01678417	A Phase II Study of 131I-rituximab for Patients With Relapsed or Refractory Follicular or Mantle Cell Lymphoma	Not stated	29	ORR	Jun-17
NCT01693614	An Open-label Phase II Study of BKM120 in Patients With Relapsed and Refractory Diffuse Large B-cell Lymphoma, Mantle Cell Lymphoma and Follicular Lymphoma	At least 1 prior treatment	72	ORR	Dec-16
NCT02213926	An Open-label, Phase 2 Study of ACP-196 in Subjects With Mantle Cell Lymphoma	Not stated	124	ORR	Jan-18

NCT02572453	Phase 2 Study of AT13387 (Onalespib) in ALK+ ALCL, MCL, and BCL-6+ DLBCL	Prior multi-agent chemo and ibrutinib or other BTK inhibitor	50	ORR, change in protein levels of ALK, BCL6 and cyclin D1	Dec-16
NCT01799889	A Phase 2, Open-Label Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacodynamics of GS-9973 (entospletinib) in Subjects With Relapsed or Refractory Hematologic Malignancies	Not stated	385	PFS	May-19
NCT02952508	An Open-Label, Multicenter, Phase 2 Study of CLR 131 in Patients With Relapsed or Refractory (R/R) Select B-Cell Malignancies	1-2 prior treatments	80	ORR	Mar-18
NCT01261247	A Phase II Study of the Histone Deacetylase (HDAC) Inhibitor LBH589 (Panobinostat) in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma	At least 1 prior treatment	41	ORR	Nov-16