Medicinrådet

# Bilag til Medicinrådets vurdering af ibrutinib til førstelinjebehandling af mantle celle lymfom

*Vers. 1.0*

# Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ibrutinib til mantle celle lymfom
2. Forhandlingsnotat fra Amgros vedr. ibrutinib til mantle celle lymfom
3. Ansøgers endelige ansøgning vedr. ibrutinib til mantle celle lymfom

Janssen-Cilag A/S
jnj.com

19. december 2025

Til Medicinrådet

**Vedr. tilbagemelding på Medicinrådets udkast til vurdering af Ibrutinib (Imbruvica) i komb. med R-CHOP til patienter med ubehandlet mantle celle lymfom (MCL), som er egnet til autolog stamcelletransplantation (ASCT)**

Johnson & Johnson takker for det grundige udkast til vurderingen af ibrutinib i kombination med R-CHOP til patienter med ubehandlet MCL. Vi sætter stor pris på den gode dialog, som vi har haft i forløbet. Med udgangspunkt i vurderingsrapporten vil vi gerne bidrage med følgende perspektiver:

Overordnet er vi glade for at se, at Medicinrådet har været pragmatisk i afvejningen af, hvornår data eller ændringer har været nødvendige. Dette er afspejlet både i processen og i det udkast til vurderingsrapport, som vi har modtaget. Vi har haft en løbende god dialog, og det afspejles i vurderingsrapporten, at vi er enige i mange forhold.
Når det derfor nævnes, at vi ikke har delt data i vurderingsrapporten, skyldes det enten, at vi ikke er blevet spurgt (da de ikke er vurderet nødvendigt), eller at det er data, som vi ikke har.

Dog er vi ærgerlige over, at vores mikrocosting-analyse for ASCT ikke er blevet anvendt eller indarbejdet som et scenarie i vurderingsrapporten. Mikrocosting-analysen blev udarbejdet for at belyse, hvor ressourcekrævende et ASCT-forløb er — både for sundhedsvæsenet og for patienten. Vi har derfor interviewet læger, sygeplejersker og andet sundhedspersonale for at forstå, hvor meget tid der i gennemsnit anvendes på et ASCT-forløb. I mikrocosting-analysen fokuserede vi kun på den del af forløbet, som adskiller sig ved ASCT i forhold til, hvis ibrutinib bliver anbefalet som standardbehandling. Medicinrådet har i stedet anvendt DRG-taksten og omtaler ASCT som en "engangsbehandling". Det er ikke faktuelt forkert, men det kan virke misvisende at kalde en lang og risikofyldt behandlingsmodalitet  en "engangsbehandling". Vi er derfor glade for, at Medicinrådet alligevel nævner, at ASCT kan være forbundet med alvorlige senfølger for patienter — selvom dette ikke er indregnet i den sundhedsøkonomiske model.

Konsekvensen fra vores perspektiv ved at undlade analysen bliver derfor, at omkostningseffektiviteten undervurderes, budget konsekvenserne overestimeres, og sidst men ikke mindst at det reelle omfang af ressourcetræk for sundhedspersonale og patient baseret på lægerne og sygeplejerskernes eget udsagn ikke bliver synligt.

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19.12.2025

MBA/LSC

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 21.01.2026 |
| Leverandør | Johnson & Johnson |
| Lægemiddel | Imbruvica (ibrutinib) |
| Ansøgt indikation | I kombination med rituximab, cyclophosphamid, doxorubicin, vincristin og prednisolon (IMBRUVICA + R-CHOP) skiftevis med R-DHAP (eller R-DHAOx) uden Imbruvica, efterfulgt af monoterapi med Imbruvica til behandling af voksne patienter med tidligere ubehandlet mantle celle lymfom (MCL), som ville være berettigede til autolog stamcelletransplantation (ASCT). |
| Nyt lægemiddel / indikationsudvidelse | Indikationsudvidelse |

## Prisinformation

Amgros har følgende pris på Imbruvica (ibrutinib):

*Tabel 1: Forhandlingsresultat*

| Lægemiddel | Styrke (pakningsstørrelse) | AIP (DKK) | Nuværende SAIP, (DKK) | Nuværende rabat ift. AIP |
|---|---|---|---|---|
| Imbruvica | 140 mg (28 stk.) | 12.458,50 | [redacted] | [redacted] |
| Imbruvica | 280 mg (28 stk.) | 24.916,99 | [redacted] | [redacted] |
| Imbruvica | 420 mg (28 stk.) | 37.375,50 | [redacted] | [redacted] |
| Imbruvica | 560 mg (28 stk.) | 49.833,98 | [redacted] | [redacted] |

## Aftaleforhold

[redacted]

## Informationer fra forhandlingen

[redacted]

## Konkurrencesituationen

Nuværende førstelinjebehandling for patienter som er egnede til autolog stamcelletransplantation (ASCT), vil for størstedelen være kemoterapi efterfulgt af højdosis kemoterapi (HDT) med BEAM og ASCT, jf. Medicinrådets vurdering af ibrutinib til behandling af mantle celle lymfom.

[redacted]

Tabel 2 viser lægemiddeludgifter på Imbruvica for første års behandling. Der er ikke medregnet lægemiddeludgifter til kemoterapi, da disse udgør en mindre del af den samlede lægemiddeludgift.

*Tabel 2: Lægemiddeludgift pr. patient pr. år*

| Lægemiddel | Styrke (pakningsstørrelse) | Dosering | Pris pr. pakning (SAIP, DKK) | Lægemiddeludgift pr. år (SAIP, DKK) |
|---|---|---|---|---|
| Imbruvica | 560 mg (28 stk.) | Induktion, 6 serier af 21 dage: 560 mg dagligt på dag 1-19 i serie 1, 3, 5, p.o.<br>Vedligeholdelse: 560 mg dagligt, p.o. | [redacted] | [redacted] |

## Status fra andre lande

*Tabel 3: Status fra andre lande*

| Land | Status | Link |
|---|---|---|
| **Norge** | Under vurdering | Link til status |
| **England** | Under vurdering | Link til status |
| **Sverige** | Anbefalet | Link til vurdering |

## Opsummering

[redacted]

# Application for the assessment of ibrutinib (IMBRUVICA®) for previously untreated advanced mantle cell lymphoma in patients eligible for autologous stem cell transplantation

| Color scheme for text highlighting | |
|---|---|
| Color of highlighted text | Definition of highlighted text |
| | Confidential information |
| [Other] | [Definition of color-code] |

# Contact information

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[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to ansogning@medicinraadet.dk.]

# Table of contents

# Tables and Figures

# Abbreviations

| Abbreviation | Full name |
|---|---|
| AEs | adverse events |
| AlloSCT | allogeneic stem cell transplantation |

| | |
|---|---|
| ASCT | autologous stem cell transplantation |
| ATM | ataxia-telangiectasia mutated |
| ATMP | advanced therapy medicinal products |
| BCR | B-cell receptor |
| BEAM | carmustine, etoposide, cytosar, and melphalan |
| BMI | body mass index |
| BR | bendamustine and rituximab |
| BTK | Bruton's tyrosine kinase |
| CI | confidence interval |
| CLL | chronic lymphocytic leukaemia |
| CR | complete response |
| CT | computerised tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLG | Danish Lymphoma Group |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EoI | End of induction |
| ESMO | European Society for Medical Oncology |
| FAS | Full analysis set |
| FFS | failure-free survival |
| GoF | goodness of fit |
| HDT | high-dose chemotherapy |
| HRQoL | health-related quality of life |
| ICER | incremental cost-effectiveness ratio |
| KM | Kaplan-Meier |
| MCL | mantle cell lymphoma |
| MIPI | Mantle Cell Lymphoma International Prognostic Index |
| N/A | not available/not applicable |
| NCT | National Clinical Trial number |
| NHL | non-Hodgkins lymphoma |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PPS | post-progression survival |
| PR | partial response |
| PSM | partitioned survival model |
| QALYs | quality-adjusted life years |
| R/R | relapsed/refractory |
| R-AraC | rituximab plus cytarabine |
| R-CHOP | rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone |
| R-DHAP | rituximab, dexamethasone, cytarabine, and cisplatin |

| | |
|---|---|
| R-maxiCHOP | rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone |
| SAE | seriouse adverse event |
| SD | stable disease |
| SoC | standard of care |
| SOX11 | SRY (sex determining Y region)-box transcription factor 11 |
| TEAE | treatment-related adverse events |
| TP53 | tumour protein 53 |

# 1. Regulatory information on the medicine

| Overview of the medicine | |
|---|---|
| **Proprietary name** | IMBRUVICA |
| **Generic name** | Ibrutinib |
| **Therapeutic indication as defined by EMA** | IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (ibrutinib + R-CHOP) alternating with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or rituximab, dexamethasone, cytarabine and oxaliplatin (R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).[1] |
| **Marketing authorization holder in Denmark** | Janssen-Cilag A/S, a Johnson & Johnson Company |
| **ATC code** | L01EL01 |
| **Combination therapy and/or co-medication** | Ibrutinib is given as part of a regimen in combination with R-CHOP and R-DHAP (or R-DHAOx). This is followed by two years of ibrutinib maintenance if patients are failure-free after induction combined with rituximab maintenance for three years. |
| **(Expected) Date of EC approval** | July 2025 |
| **Has the medicine received a conditional marketing authorization?** | No |
| **Accelerated assessment in the European Medicines Agency (EMA)** | No |
| **Orphan drug designation (include date)** | Ibrutinib was originally designated as an orphan drug; however, this is no longer the case. |

| Overview of the medicine | |
|---|---|
| **Other therapeutic indications approved by EMA** | In addition to the indication relevant for this submission, ibrutinib is approved for the following indications:<br>• as a single agent is indicated for the treatment of adult patients with relapsed or refractory MCL.<br>• as a single agent or in combination with rituximab, obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)<br>• as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.<br>• as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.<br>• in combination with rituximab is indicated for the treatment of adult patients with WM.[2] |
| **Other indications that have been evaluated by the DMC (yes/no)** | Yes, ibrutinib has been assessed as a first line treatment for CLL (alone and in combination with venetoclax). Ibrutinib was directly placed in the DMC treatment guideline for CLL.[3] |
| **Joint Nordic assessment (JNHB)** | Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? **Yes**<br>Is the product suitable for a joint Nordic assessment? **No**<br>If no, why not? **Imbruvica doesn't have the same reimbursement status across indications in the Nordics.** |
| **Dispensing group** | BEGR |
| **Packaging – types, sizes/number of units and concentrations** | • Coated tablets, 140mg, package of 28<br>• Coated tablets, 280mg, package of 28<br>• Coated tablets, 420mg, package of 28<br>• Coated tablets, 560mg, package of 28[4] |

Abbreviations: ASCT, autologous stem cell transplantation; BR, bendamustine and rituximab; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; WM, Waldenström's macroglobulinaemia.

# 2. Summary table

| Summary | |
|---|---|
| **Indication relevant for the assessment** | Ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or rituximab, dexamethasone, cytarabine and oxaliplatin (R-DHAOx) is indicated for the treatment of adult patients with previously untreated MCL who are eligible for ASCT. |
| **Dosage regiment and administration** | Ibrutinib is administered in combination with induction immunochemotherapy consisting of six alternating 21-day cycles of R-CHOP and R-DHAP/R-DHAOx, followed by |

| Summary | |
|---|---|
| | maintenance treatment with ibrutinib for 2 years. The dosing schedule for ibrutinib is:<br>**Induction**: Ibrutinib 560 mg daily on days 1-19 in the three R-CHOP cycles.<br>**Maintenance:** Ibrutinib 560 mg orally once daily for to 2 years in patients who remain failure-free after induction in combination with rituximab administered once every 2nd month for 3 years[1]. |
| **Choice of comparator** | Standard immunochemotherapy (alternating R-maxiCHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone) and R-AraC (rituximab plus cytarabine) (3 cycles each) followed by HDT (carmustine, etoposide, cytosar, and melphalan [BEAM]) and ASCT and maintenance treatment with rituximab. |
| **Prognosis with current treatment (comparator)** | The majority of MCL patients require treatment at the time of diagnosis. MCL is currently considered incurable[5].<br>In the clinical guideline published by the Danish Lymphoma Group, results of studies in ASCT eligible MCL patients are shown. In a phase II study from Eskelund et al., patients received R-CHOP/R-HD AraC + ASCT – the median PFS was 7.4 years and the median OS was not reached (10 year overall survival was 64%)[6]. Long-term follow-up from the same study showed a median PFS and OS for all patients of 8.5 and 12.7 years, respectively[7]. |
| **Type of evidence for the clinical evaluation** | Head-to-head study (TRIANGLE; NCT02858258) |
| **Most important efficacy endpoints (Difference/gain compared to comparator)** | **Primary endpoint**<br>Failure-free survival (FFS): After a median follow-up of 54.9 months, patients demonstrated a statistically significant improvement of FFS for participants in ibrutinib without ASCT arm compared with participants in ASCT arm (HR: 0.639 [98.33% CI: 0.428-0.953], two-sided p: 0.0068)[8]<br>**Secondary endpoint**<br>Overall survival (OS): A significant improvement in OS was observed for ibrutinib without ASCT vs. ASCT (HR: 0.522 [95% CI: 0.341–0.799]; two-sided p=0.0023)[8]. |
| **Most important serious adverse events for the intervention and comparator** | For both the intervention (ibrutinib without ASCT) and comparator (ASCT), the most common serious TEAEs (≥5%) included febrile neutropenia (10.6% and 7.1%, respectively) and acute kidney injury (6.8% and 5.2%, respectively).<br>Overall, the profile of serious TEAEs was consistent with the known safety profiles of the respective treatments |
| **Impact on health-related quality of life** | **Clinical documentation:** HRQoL was not collected in the TRIANGLE trial.<br>**Health economic model:** HRQoL values are taken from the SHINE trial, RAY-3001 trial, and relevant external literature. |
| **Type of economic analysis that is submitted** | Partition survival model |
| **Data sources used to model the clinical effects** | The TRIANGLE trial (NCT02858258) |

| Summary | |
|---|---|
| **Data sources used to model the health-related quality of life** | The RAY trial (NCT01646021)<br>The SHINE trial (NCT01776840) |
| **Life years gained** | 2.79 years |
| **QALYs gained** | 2.36 QALY |
| **Incremental costs** | [redacted] DKK |
| **ICER (DKK/QALY)** | [redacted] DKK/QALY |
| **Uncertainty associated with the ICER estimate** | The biggest uncertainties are the parameterisations of the OS and FFS, followed by the cost of ibrutinib. |
| **Number of eligible patients in Denmark** | Incidence: 87<br>Prevalence: 701 |
| **Budget impact (in year 5)** | [redacted] DKK |

Abbreviations: ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytosar, and melphalan; CI, confidence interval; FFS, failure-free survival; HDT: high-dose chemotherapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PFS; progression-free survival; QALYs, quality-adjusted life years; R-AraC, rituximab plus cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; R-maxiCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; TEAEs, treatment-related adverse events.

# 3. The patient population, intervention, choice of comparator(s) and relevant outcomes

## 3.1 The medical condition

Mantle cell lymphoma (MCL) is a rare, incurable B-cell non-Hodgkins lymphoma (NHL), associated with the accumulation of abnormal B lymphocytes in the lymphoid tissues (e.g., lymph nodes, bone marrow, spleen) and body organs (e.g., gastrointestinal [GI] tract, liver)[9-11].

### Pathogenesis

MCL is a heterogenous malignancy with a broad spectrum of clinical, pathological and biological features rather than a single condition[12,13]. Two main categories are generally recognised: conventional (also referred to as 'classical') nodal MCL, comprising 80–90% of cases, and leukaemic non-nodal MCL[11,14,15].

B-cell receptor (BCR) activity plays a fundamental role in the pathogenesis of MCL[16-18]. BCR activates several protein tyrosine kinases, forming a signalosome[19], which

coordinates several processes including B-cell fate decisions, as well as the survival and proliferation of MCL cells[20].

### Diagnosis

MCL is typically diagnosed through a combination of clinical evaluation, blood tests, one or more histologic biopsies (including histopathological and molecular biological analyses) and a PET-CT scan. Several cytologic variants of MCL have been described, including the classic, blastoid, small cell, and pleomorphic variants, which have different clinical behaviour and prognosis[21,22].

### Prevalence and presentation

In Denmark, approximately 60 to 100 people are diagnosed annually[23]. The prevalence of MCL is increasing, with 1 to 2 new cases per 100,000 individuals per year. MCL is three times more likely to affect men than women, and most people are diagnosed around the age of 65[24]. Patients eligible for ASCT are, however, typically younger. In particular, the 15-year updated results of the Nordic MCL2 study[7], the mean age of patients deemed eligible for ASCT was 56 years.

Most MCL patients present with an advanced stage disease, with >70% of newly diagnosed patients having an Ann Arbor/Lugano Stage III or IV disease. Despite presenting with advanced disease, only one-third of patients have B symptoms, including fever, weight loss, and night sweats, at diagnosis[25].

### Mortality and prognosis

In 2022, NHL was the 11$^{th}$ most common cause of cancer-related mortality worldwide, with an estimated age-standardised mortality rate of 2.9% among males and 1.9% among females[26]. Specific mortality rates for MCL are not well-described in Denmark; however inferior overall and net survival outcomes for MCL compared to other forms of NHL have been reported[27-29].

Survival outcomes for MCL are influenced by a variety of factors, including: (i) disease characteristics; (ii) disease stage; (iii) prognostic factors including age; (iv) fitness (e.g., performance status [PS] and suitability for autologous stem cell transplant (ASCT), comorbidities); (v) presence of gene aberrations (e.g., TP53 aberrations).

Disease characteristics associated with poor prognosis include bulky disease, high Ki-67 proliferation index and blastoid histology.

Age is a significant prognostic factor in MCL, with younger patients generally having better prognosis than older patients. Older patients often have comorbidities and reduced tolerance to intensive therapies and ASCT, leading to poorer outcomes[30]. An analysis of SEER data from 2010-2016 showed the five-year relative survival rate is 71.2% (95% CI: 68.5 to 73.8) for patients diagnosed between the ages of 20 and 64, compared with 54.9% (95% CI: 51.9 to 57.8) for those diagnosed at ≥65 years[31].

Given the frequent presentation at an advanced stage and the need for long-term or continuous treatment, MCL has been shown to negatively affect patients' health-related

quality of life (HRQoL). Both the disease itself and treatment-related toxicities contribute to impairments in physical, emotional, social functioning and overall wellbeing, especially in patients undergoing prolonged therapeutic regimens[32].

## 3.2 Patient population

The incidence and prevalence of MCL are presented in Table 1 and the estimated number of patients eligible for treatment, which are adult patients with previously untreated MCL who are eligible for ASCT, are presented in Table 2. The numbers were validated by Danish clinical experts[33].

**Table 1 Incidence and prevalence in the past 5 years**

| Year | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **Incidence in Denmark** | 85 | 87 | 89 | 92 | 87 |
| **Prevalence in Denmark** | 569 | 612 | 648 | 692 | 701 |

**Table 2 Estimated number of patients eligible for treatment**

| Year | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of patients in Denmark who are eligible for treatment in the coming years** | 45 | 45 | 45 | 45 | 45 |

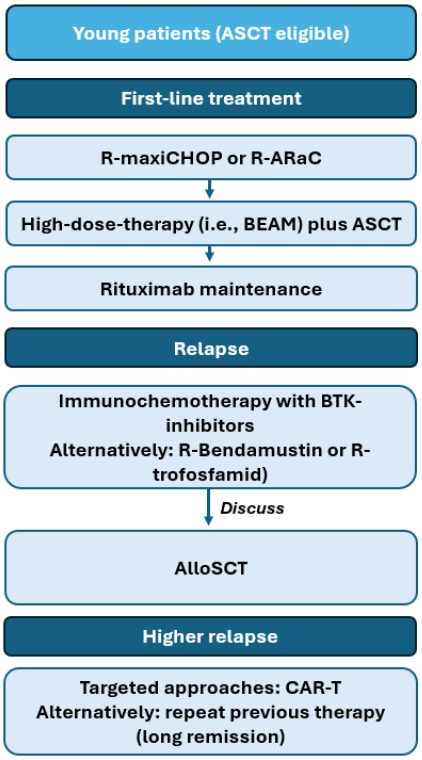
## 3.3 Current treatment options

The treatment recommendations for lymphoma from Danish Lymphoma Group (DLG) were last updated in July 2022[5] and are generally aligned with international guidelines published by European Society for Medical Oncology (ESMO)[34]. The main difference between the Danish and the ESMO guidelines lies in the induction treatment, as ESMO recommends immunotherapy alternating R-CHOP. For the majority of previously untreated transplant-eligible patients with MCL in Denmark, standard immunochemotherapy alternating R-maxiCHOP and R-AraC, followed by high-dose chemotherapy (HDT) [BEAM] with ASCT is currently recommended as first-line treatment. This is followed by maintenance treatment with rituximab every 2nd month for 3 years. A more detailed description of DLG treatment recommendations is presented in Figure 1. A new version is pending.

For previously untreated transplant-eligible patients with MCL who progress on standard immunochemotherapy followed by high-dose therapy (HDT) and ASCT (HDT/ASCT) and rituximab maintenance therapy, DLG[35] recommends treatment with Bruton's tyrosine

kinase (BTK)-inhibitors. CAR-T cell can be indicated in case of further progression or relapse during treatment with a BTK-inhibitor, although CAR-T therapy remains limited in accessibility and is not yet standardised for MCL in Denmark. Other options include agents such as BCL-2 inhibitors, immunomodulatory agents and bispecific antibodies.

**Figure 1 Current treatment algorithm**




Abbreviations: AlloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytosar, and melphalan; BTK, Bruton's tyrosine kinase; R-AraC, rituximab plus cytarabine; R-maxiCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.
Adapted from: DMCG[5]; Eskelund et al.[7]

### Unmet need

Despite improvements in MCL treatment, resistance, intolerance and healthcare resource burden continue to be significant challenges. As such, there is a persistent unmet need for first-line therapy options in MCL that provide more efficacious and tolerable treatments, that maintain HRQoL, while minimising healthcare resource utilisation and potentially postponing the need for subsequent treatment.

Current treatment options are associated with relatively poor prognosis, including short median overall survival (OS) between 5–7 years, and low survivability, with only 32% of patients surviving for >10 years[15,36]. These outcomes deteriorate with progression, underscoring the rationale for early therapeutic intervention. Median progression-free survival (PFS) is 47.4 months in first-line (with 46% of patients receiving ASCT), falling to 14.0 months, 6.5 months, and 5.0 months in second-line, third-line, and fourth-line, respectively[37]. Younger, transplant eligible patients (median age: 56 years) have a median OS of 12.7 years, but this is still 14.3 years shorter than that of the general population in Europe[7,38-40].

Tolerable treatment options are needed for newly diagnosed, younger, ASCT-eligible MCL patients, as ASCT is associated with severe short-term toxicities and long-term complications[39,40]. HDT and ASCT contribute to early death during the first six months of treatment, leading to an ASCT-related death rate ranging from 2.0% to 6.8% at 100 days post-ASCT, with the most common cause of death being infections[41-44]. Eight years post-HDT and ASCT, 98% and 56% of survivors had at least one moderate, or severe or life-threatening late effect, respectively[39].

Additionally, more convenient treatment options that reduce the burden on patients and the healthcare system are needed for patients with MCL eligible for ASCT. The high burden of adverse events (AEs) due to HDT and ASCT leads to patients typically requiring hospitalisation for at least three weeks during this treatment period to recover from ASCT, and 1 in 20 patients are admitted to intensive care unit, primarily due to sepsis, spending a median duration of 30 days (range: 18-51 days) in hospital[40,45]. More than a quarter of patients eligible for ASCT are either unable or unwilling to receive ASCT, with studies reporting ASCT utilisation rates among eligible patients of only 45–75%[46,47].

The TRIANGLE regimen provides an outpatient, effective approach that eliminates the need for highly toxic HDT/ASCT consolidation.

## 3.4 The intervention

Ibrutinib, a small-molecule inhibitor of BTK, in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), is indicated for the treatment of adult patients with previously untreated MCL who are eligible for ASCT.

A CHMP positive opinion was given on 19 June 2025. The expected EMA approval is based on the results from the phase III trial, TRAINGLE[1,48].

Ibrutinib has previously been approved by the European Medicines Agency (EMA) in July 2014 for the treatment of relapsed/refractory (R/R) MCL and CLL (both after at least one prior therapy).[49] Initial Phase I and II clinical trials demonstrated the efficacy of ibrutinib in patients with CLL and MCL. In a Phase II study of 111 patients with MCL who had disease relapse or no improvement after at least one line of therapy (of which, 86% had intermediate or high-risk disease), single-agent ibrutinib treatment resulted in durable efficacy after over a year of follow-up (median follow-up: 15.3 months).[50] Since approval, ibrutinib has continued to demonstrate long-term efficacy and safety in the MCL patient population, resulting in continuous approval in Europe. [49]

In this application, ibrutinib without ASCT will denote the intervention, encompassing the full treatment regimen. An overview of the intervention is presented in Table 3.

**Table 3 Key descriptive information of ibrutinib in combination with R-CHOP/R-DHAP**

| Overview of intervention | |
|---|---|
| **Indication relevant for the assessment** | Ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or rituximab, dexamethasone, cytarabine and |

| Overview of intervention | |
|---|---|
| | oxaliplatin (R-DHAOx) is indicated for the treatment of adult patients with previously untreated MCL who are eligible for ASCT. |
| **ATMP** | N/A |
| **Method of administration** | Tablet, oral (ibrutinib); Intravenous and oral administration for chemotherapy components (R-CHOP and R-DHAP/R-DHAOx). |
| **Dosing** | Patients receive induction ibrutinib in combination with six alternating 21-day cycles of R-CHOP (cycles 1, 3, and 5) and R-DHAP/R-DHAOx (cycles 2, 4, and 6), followed by maintenance therapy with rituximab and ibrutinib:<br><br>Ibrutinib induction: 560 mg orally once daily on days 1 to 19 during the three R-CHOP cycles.<br>Maintenance: ibrutinib 560 mg orally once daily for to 2 years in patients who remain failure-free after induction in combination with rituximab administered once every 2nd month for 3 years[1]. |
| **Dosing in the health economic model (including relative dose intensity)** | As described above. Dose intensity is described in section 11.1. |
| **Should the medicine be administered with other medicines?** | Ibrutinib is administered with R-CHOP during cycles 1, 3, and 5 during induction and with rituximab every 2nd month during maintenance. Ibrutinib does not require supportive co-medications. |
| **Treatment duration / criteria for end of treatment** | Described above, or until unacceptable toxicity or disease progression. Maintenance phase up to 2 years post-induction. |
| **Necessary monitoring, both during administration and during the treatment period** | Monitoring of blood counts, renal and liver function, cardiac function (including ECG and echocardiography), neurological status, bleeding risk, and infections. Imaging (CT), bone marrow biopsies, and adverse event assessments are performed regularly during treatment and follow-up[2]. |
| **Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?** | No. |
| **Package size(s)** | • Coated tablets, 140mg, package of 28<br>• Coated tablets, 280mg, package of 28<br>• Coated tablets, 420mg, package of 28<br>• Coated tablets, 560mg, package of 28[4] |

Abbreviations: ASCT, autologous stem cell transplantation; ATMP, advanced therapy medicinal products; CT, computerized tomography; ECG, electrocardiogram; MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin.

The recent TRIANGLE trial has demonstrated a clear improvement in OS without HDT associated toxicity with the addition of ibrutinib to R-CHOP and R-DHAP in younger patients (i.e., <65 years) undergoing induction therapy, compared to the current standard of care (SoC) including HDT/ASCT[1]. Furthermore, the introduction of the TRIANGLE regimen (Arm I) as the new standard treatment is expected to significantly reduce resource use due to the exclusion of ASCT and decrease severe toxicity and potential treatment related impairment. The omission of HDT significantly decreases the

workload on the inpatient clinics and shifts the management of younger MCL patients to an outpatient home-based approach.

In a cost analysis [51] of health expenditures related to the HDT/ASCT procedure, by interviewing 5 HDT experienced clinicians from Aarhus, Odense and Roskilde, an estimated cost of appr. 420.000 kr. pr. patient was found. This analysis was made to clarify the resource usage of today's standard of care from a healthcare and patient perspective. Even though the DRG tariff for ASCT exists, it doesn't show how many hours that healthcare personnel and patients spend on the procedure. Replacing ASCT with an ibrutinib tablet treatment will substantially reduce time spent in hospital for both patients and healthcare personnel. For full transparency the full analysis with all calculations is shared separately.

### 3.4.1 Description of ATMP

N/A

### 3.4.2 The intervention in relation to Danish clinical practice

Based on the study results of the TRIANGLE trial[1] and the treatment recommendations published by the DLG[5], it is expected that ibrutinib alternating R-maxiCHOP and R-AraC followed by ibrutinib maintenance therapy will partially or fully replace the current SoC. The shift is likely to alter subsequent treatment strategies, although the change is not fully elucidated.

## 3.5 Choice of comparator(s)

The relevant comparator for this submission is the current SoC, defined as induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT/ASCT, with HDT typically consisting of BEAM (carmustine, etoposide, cytarabine, and melphalan)[39], and rituximab maintenance therapy for up to 3 years. This aligns with the current clinical practice as per the DLG[5].

It is assumed that the treatment regimen in the control arm of the TRIANGLE trial (i.e., alternating 3 cycles R-CHOP plus placebo (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by HDT [BEAM/THAM] and ASCT with rituximab maintenance) and the current SoC are clinically equivalent, as supported by key efficacy endpoint data from pivotal clinical trials. In a phase II study conducted by Eskelund et al.[7], patients (n=160) receiving an alternating regimen of R-maxiCHOP and R-AcaC demonstrated an overall response rate (ORR) of 54% and a median PFS of 8.5 years. Of the 145 patients who proceeded to ASCT, the median PFS was 11 years. These results are consistent with those reported in a phase III trial by Hermine et al.[52], where patients treated with alternating cycles of R-CHOP and R-DHAP achieved a comparable ORR of 61% and a median PFS of 7.3 years. Together, these findings support the clinical equivalence of the treatment regimens.

Furthermore, data from Tseng, Stevenson[53] indicate that TBI-based conditioning, as used in the THAM regimen, is safe and confers similar efficacy to BEAM-based conditioning in

patients with MCL undergoing ASCT, with no significant differences in PFS, OS, or toxicity observed between the two regimens[53]. Therefore, the use of both regimens in the TRIANGLE trial does not compromise its relevance for the Danish SoC, where only BEAM is specified. The distribution of who received BEAM or THAM in arm A of TRIANGLE is summarised in Appendix N.

In this application, ASCT is used as a collective term for the full comparator regimen.

**Table 4 Key descriptive information of R-maxiCHOP/R-AraC with ASCT**

| **Overview of comparator** | |
|---|---|
| **Generic name** | Standard immunochemotherapy, defined as alternating R-maxi-CHOP and rituximab with high-dose cytarabine (R-AraC), followed by HDT/ASCT[39], and rituximab maintenance therapy, is indicated for the treatment of adult patients with previously untreated MCL who are eligible for ASCT. |
| **ATC code** | • Rituximab (L01FA01)<br>• Cyclophosphamide (L01AA01)<br>• Doxorubicin (L01DB01)<br>• Vincristine (L01CA02)<br>• Prednisolone (H02AB06)<br>• Cytarabine (L01BC01)<br>An overview of the HDT BEAM/THAM regimen can be found in Appendix K. |
| **Mechanism of action** | Rituximab is a monoclonal antibody that targets the CD20 protein on the surface of lymphoma cells. By targeting CD20, rituximab promotes cell lysis while sparing hematopoietic and plasma cells without this surface antigen[54].<br>Cyclophosphamide's active metabolites are alkylating agents that transfer alkyl groups to DNA during cell division, thereby preventing normal DNA synthesis and thus cell death[55].<br>Vincristine sulfate is an antineoplastic drug with broad-spectrum anti-tumour activity in humans. The drug act by mitotic inhibition, causing an arrest of cell division in metaphase[56].<br>Doxorubicin is an antitumour agent. Tumour cells are probably killed through drug-induced alterations of nucleic acid synthesis although the exact mechanism of action has not yet been clearly elucidated[57].<br>Prednisolone is a synthetic glucocorticoid with immunosuppressive and pro-apoptotic properties. It reduces immune responses, and prevent allergic reactions to rituximab[58].<br>Cytarabine (AraC) is metabolised *in vivo* to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA[59]. |
| **Method of administration** | Described below. |

| Overview of comparator | |
|---|---|
| **Dosing** | Patients receive six alternating 21-day cycles of:<br>R-maxiCHOP (cycles 1, 3, 5): rituximab 375 mg/m² IV (from cycle 2), cyclophosphamide 1,200 mg/m² IV, doxorubicin 75 mg/m² IV, vincristine 2 mg IV, and prednisone 100 mg orally on days 1 to 5.<br>R-AraC (cycles 2, 4, 6): rituximab 375 mg/m² IV, cytarabine 3,000 mg/m² IV q12h on days 1 to 2.<br>Following induction, patients undergo HDT/ASCT and subsequently receive rituximab maintenance (375 mg/m² IV) every 2 months for up to 3 years. |
| **Dosing in the health economic model (including relative dose intensity)** | Patients receive induction therapy with six alternating cycles of R-maxiCHOP (cycles 1, 3, 5) and R-DHAP (cycles 2, 4, 6) every 21 days. Following induction, patients receive HDT followed by ASCT. Rituximab maintenance therapy is administered every 2 months for 3 years following ASCT. Dose intensity is described in section 11.1. |
| **Should the medicine be administered with other medicines?** | No* |
| **Treatment duration/ criteria for end of treatment** | Described above, or until unacceptable toxicity or disease progression. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Monitoring includes physical examination and blood counts,. Furthermore, imaging (typically PET-CT and later on CT),a bone marrow biopsy, and adverse event assessments are performedduring treatment, end of treatment and at follow-up as per national guidelines[34].<br>Electrocardiogram, cardiac ultrasound (before ASCT), and pulmonary function (before ASCT)[34]. |

| Overview of comparator | |
|---|---|
| Package size(s) | Cytarabine:<br>• Concentrate for solution for infusion, 100 mg/ml, 10 ml vial<br>• Concentrate for solution for infusion, 100 mg/ml, 20 ml vial<br>Cyclophosphamide:<br>• Coated tablets, 50 mg, package of 100<br>• Powder for solution for injection, 1 g, package of 1<br>• Powder for solution for injection, 200 mg, package of 1<br>• Powder for solution for injection, 500 mg, package of 1<br>Doxorubicin:<br>• Powder for solution for injection, 50 mg, package of 1 vial<br>• Concentrate for solution for infusion, 2 mg/ml, 5 ml vial<br>• Concentrate for solution for infusion, 2 mg/ml, 25 ml vial<br>• Concentrate for solution for infusion, 2 mg/ml, 100 ml vial<br>Vincristine:<br>• Solution for injection, 1 mg/ml, 1 ml vial<br>• Solution for injection, 1 mg/ml, 2 ml vial<br>Prednisolone:<br>• Tablets, 2.5 mg, package of 100<br>• Tablets, 5 mg, package of 25<br>• Tablets, 5 mg, package of 100<br>• Tablets, 5 mg, package of 300<br>• Tablets, 25 mg, package of 10<br>• Tablets, 25 mg, package of 100<br>Rituximab:<br>• Solution for subcutaneous injection, 1400 mg, package of 1<br>• Concentrate for solution for infusion, 100 mg, package of 1 |

Abbreviations: ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytosar, and melphalan; HDT, high-dose chemotherapy; MCL, mantle cell lymphoma; R-AraC, rituximab plus cytarabine; R-maxiCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; THAM, TBI (total body irradiation), cytarabine and melphalan.
Source: Cancer research UK[58], Janssen Research & Development [Data on file][8], Promedicin.dk[60-64]
*G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is < 1,000/mm3 in subsequent cycles[57]

## 3.6 Cost-effectiveness of the comparator(s)

The treatment regimen alternating induction therapy with R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance has not previously been assessed by the DMC for the treatment of adult patients with previously untreated MCL who are eligible for ASCT. As stated in Section 3.3, DLG recommends that previously untreated patients with MCL who are eligible for ASCT should be treated with R-maxiCHOP and R-AraC followed by HDT and ASCT and rituximab maintenance therapy. According to the DMC methods guideline[65], if a comparator has not previously been assessed by the DMC, a comparison against placebo should be made, including cost-effectiveness.

However, standard immunotherapies in combination with HDT and ASCT, and rituximab maintenance therapy are widely recognised as the established SoC for treating patients with untreated MCL who are eligible for ASCT in Denmark, as well as and internationally. In this context, an additional analysis appears redundant.

## 3.7 Relevant efficacy outcomes

### 3.7.1 Definition of efficacy outcomes included in the application

The primary study outcome was investigator-assessed FFS. Key secondary outcomes included OS, PFS, and ORR. Key efficacy outcomes are defined in Table 5.

**Table 5 Efficacy outcome measures relevant for the application**

| Outcome measure | Time point[a] | Definition | How was the measure investigated/method of data collection |
|---|---|---|---|
| **FFS** [TRIANGLE] | 9 May 2024 (54 months) | Investigator assessed FFS, defined as the time from randomisation to SD at the end of induction immunochemotherapy, progressive disease, or death from any cause, whichever comes first | Response assessments were performed by the investigator, based on physical examinations, CT scans, laboratory results and bone marrow examinations through use of the Revised Response Criteria for Malignant Lymphoma[66]. KM estimates were used for analysis. |
| **OS** [TRIANGLE] | 9 May 2024 (54 months) | OS is defined as the start of treatment until death from any cause | KM estimates were used for analysis. |
| **PFS** [TRIANGLE] | 9 May 2024 (54 months) | PFS is defined as the time to progression or the date of first documented progression | Investigator assessment as described above[66]. KM estimates were used for analysis. |
| **ORR** [TRIANGLE] | 9 May 2024 (54 months) | ORR is defined as the proportion of subjects with a best response of CR or PR | Investigator assessment as described above[66]. |

Abbreviations: CR, complete response; CT, computerised tomography; FFS, failure-free survival; KM, Kaplan-Meier; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

a. Time point for data collection used in analysis (follow up time for time-to-event measures)
Source: ClinicalTrial.gov[67], Janssen Research & Development [Data on file][8]

#### 3.7.1.1.1.1 Validity of outcomes

The primary efficacy outcome, FFS, was assessed by a central medical European MCL Network case evaluation of investigator assessment per protocol. FFS was selected as the primary endpoint because it reflects the treatment paradigm for patients with MCL who are eligible for ASCT[8]. According to current clinical guidelines[34], only patients who achieve at least a partial response (PR) to induction immunochemotherapy are eligible to proceed to high-dose chemotherapy followed by ASCT. Patients who do not achieve at least PR, but only stable disease (SD), are considered treatment failures. FFS captures this by counting SD as an event, whereas PFS does not. This is the only distinction between the two endpoints. The clinical validity of FFS is supported by evidence from the

Phase 3 MCL Younger study, which showed that the difference between FFS and PFS was limited[52]. Secondary efficacy outcomes included OS, PFS, and ORR, all of which are standard, validated outcome measures that have previously been accepted by the DMC in assessments for treatments in NHL[68].

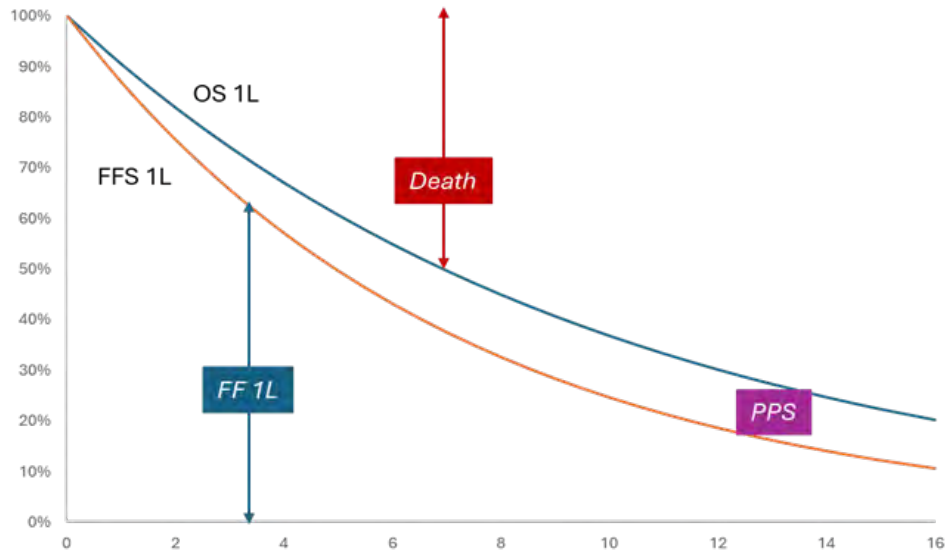
# 4. Health economic analysis

## 4.1 Model structure

The model utilises a simple Partitioned Survival Model (PSM) structure with three mutually exclusive states: FFS, post-progression survival (PPS) and death. FFS and PPS together constitute the OS. The simplicity of the model structure ensures easy interpretation of the results and no further statistical complications.

The OS and FFS curves are directly projected from the clinical efficacy data from TRIANGLE trial, described in section 6. As illustrated in Figure 2, the OS curve and the FFS curve are directly projected using parameterisations that are deemed appropriate (for details, see section 8 and Appendix D), and the vertical distance between the two curves is PPS. The key features of the economic model are summarised in section 4.2.

**Figure 2 Features of the economic model**




Abbreviations: 1L, first line; FF, failure-free; FFS, failure-free survival; OS, overall survival; PPS, post-progression survival

## 4.2 Model features

The key features of the economic model are summarised in Table 6.

**Table 6 Features of the economic model**

| Model features | Description | Justification |
|---|---|---|
| **Patient population** | Adult patients with previously untreated stage II to IV MCL, aged ≤65 years, who are eligible for ASCT. | EMA indication [69] |
| **Perspective** | Limited societal perspective | According to DMC guidelines[70] |
| **Time horizon** | Lifetime (43 years) | To capture all health benefits and costs in line with DMC guidelines[70].<br>Based on mean age at diagnosis in TRIANGLE. |
| **Cycle length** | 3 weeks | Consistent with the treatment cycle of induction regimens in the TRIANGLE trial (day 1 every 21 days)[1] |
| **Half-cycle correction** | Yes | To account for costs and benefits which can occur any time during the cycle. |
| **Discount rate** | 3.5 % | The DMC applies a discount rate of 3.5 % for all years [70] |
| **Intervention** | Ibrutinib | Intervention of interest |
| **Comparator(s)** | Alternating R-CHOP/R-DHAP induction chemotherapy followed by ASCT with BEAM or THAM conditioning | According to national treatment guideline [3]. Validated by Danish clinical expert |
| **Outcomes** | FFS, OS, PFS, ORR | **Key trial data outcomes are used to populate the partitioned-survival model** |

Abbreviations: EMA, European Medicines Council; ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytosar, and melphalan; DMC, Danish Medicine Council; FFS, failure-free survival; MCL, mantle cell lymphoma; N/A, not avalible/not aplicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin.

# 5. Overview of literature

## 5.1 Literature used for the clinical assessment

A head-to-head study, TRIANGLE, comparing R-CHOP+Ibrutinib/R-DHAP without ASCT to R-CHOP/R-DHAP with ASCT was identified, and thus a literature search was omitted in accordance with to the DMC guidelines[65]. An overview of the study is presented in Table 7.

**Table 7 Relevant literature included in the assessment of efficacy and safety**

| Reference (Full citation incl. reference number)* | Trial name* | NCT identifier | Dates of study (Start and expected completion date, data cut-off and expected data cut-offs) | Used in comparison of* |
|---|---|---|---|---|
| Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. 2024;403(10441):2293-2306. doi:10.1016/S0140-6736(24)00184-3[1] | TRIANGLE | NCT02858258 | Start: 25/07/2016<br>Completion: 01/05/2026<br>Data cut-off: 22/05/2022<br>Future data cut-offs: 09/05/2024 | R-CHOP+Ibrutinib/R-DHAP without ASCT vs. R-maxiCHOP/R-AraC followed by HDT and ASCT for adult patients with previously untreated MCL who are eligible for ASCT |
| Janssen Research & Development. Autologous Transplantation after a Rituximab/Ibrutinib/Ara-c Containing Induction in Generalized Mantle Cell Lymphoma –a Randomized European MCL Network Trial: TRIANGLE - Clinical Study Report [Data on file]. 2024[8] | TRIANGLE | NCT02858258 | Start: 25/07/2016<br>Completion: 01/05/2026<br>Data cut-off: 09/05/2024 | R-CHOP+Ibrutinib/R-DHAP without ASCT vs. R-maxiCHOP/R-AraC followed by HDT and ASCT for adult patients with previously untreated MCL who are eligible for ASCT |

Abbreviations: ASCT, autologous stem cell transplantation; HDT, high-dose chemotherapy; MCL, mantle cell lymphoma; NCT, National Clinical Trial number; R-AraC, rituximab plus cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; R-maxiCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

* The relevant comparator for this submission is the current SoC, induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance therapy. This aligns with the current clinical practice as per the Danish Lymphoma Group[5]. It is assumed that the treatment regimen in the control arm of the TRIANGLE trial (i.e., alternating 3 cycles R-CHOP (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by HDT [BEAM/THAM] and ASCT), and the current standard of care are clinically equivalent, as supported by key efficacy endpoint data from pivotal clinical trials.[7,52]

## 5.2 Literature used for the assessment of health-related quality of life

HRQoL associated with health states was informed by data from the SHINE and RAY-3001 trials. In addition, a targeted systematic literature review conducted in July 2025 identified other relevant utility estimates (see Appendix I). The literature sources used to inform HRQoL values are summarised in Table 8.

**Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)**

| Reference (Full citation incl. reference number) | Health state/Disutility | Reference to where in the application the data is described/applied |
|---|---|---|
| Janssen Research & Development. A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma: SHINE - Clinical Study Report [Data on file]. 2022.[71] | Failure-free survival | Section 10.3 |
| Janssen Research & Development. A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, versus Temsirolimus in Subjects with Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy: RAY - Clinical Study Report [Data on file]. 2017.[72] | Progressed disease | Section 10.3 |
| NICE Technology appraisal guidance: Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia - TA343. p. 161 [73] | Disutility decrement for: IV treatment, oral treatment and SC treatment<br>Decrement of IV treatment calculated by taking the difference of PFS utility under oral treatment and PFS utility under IV treatment. | Section 10.3 |
| NICE Technology appraisal guidance: Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia - TA891. p. 166[74] | Disutility decrement for: Sepsis, neutropenia, anaemia, thrombocytopenia, febrile neutropenia, leukopenia, platelet count decreased, neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, gamma-glutamyl transferase increased, hypokalaemia, diarrhoea | Section 10.3 |

| Reference (Full citation incl. reference number) | Health state/Disutility | Reference to where in the application the data is described/applied |
|---|---|---|
| Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ.* 2013;14(5):749-759. doi:10.1007/s10198-012-0419-2[75] | Disutility decrement for: Pneumonia | Section 10.3 |

## 5.3 Literature used for inputs for the health economic model

**Table 9 Relevant literature used for input to the health economic model**

| Reference (Full citation incl. reference number) | Input/estimate | Method of identification | Reference to where in the application the data is described/applied |
|---|---|---|---|
| Petersohn S, Salles G, Wang M, Wu J, Wade SW, Simons CL, Bennison C, Siddiqi R, Peng W, Kloos I, Castaigne G, Hess G. Cost-effectiveness analysis of KTE-X19 CAR T therapy versus real-world standard of care in patients with relapsed/refractory mantle cell lymphoma post BTKi in England. J Med Econ. 2022 Jan-Dec[76] | KTE-X19 acquisition | Targeted literature review | Section 11.6 |
| Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. | Time horizon, cycle length, efficacy data, adverse event frequencies | Trial of interest | Section 4.2 |

| Reference (Full citation incl. reference number) | Input/estimate | Method of identification | Reference to where in the application the data is described/applied |
|---|---|---|---|
| 2024;403(10441):2293-2306. doi:10.1016/S0140-6736(24)00184-3[1] | | | |
| Sundhedsdatastyrelsen. DRG-takster 2025 2025[77], Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025 | Adverse event cost | As per DMC guidelines | Section 11.5 |
| Sundhedsdatastyrelsen. InteraktivDRG[78], Available from: https://casemix360.solutions.iqvia.com/InteractiveProd. | | | |
| DMC. Catalogue for unit cost v.1.8. 2024. [79] | Healthcare resource use costs | As per DMC guidelines | Section 11.4<br>Section 11.7 |
| Medicinpriser.dk [80] Available from: https://medicinpriser.dk | Medicine costs | As per guidelines | Section 11.1<br>Section 11.6 |
| Micro-costing study for the cost of autologous stem cell transplant, Johnson & Johnson [51] | Medicine costs | To better capture the cost of autologous stem cell transplants | Section 11.6 |

# 6. Efficacy

## 6.1 Efficacy of ibrutinib without ASCT compared to ASCT for previously untreated MCL in patients eligible for ASCT

### 6.1.1 Relevant studies

This application builds on the TRIANGLE head-to-head trial (NCT02858258) investigating the efficacy and safety of ibrutinib without ASCT versus ASCT. The design for the TRIANGLE study (randomised, controlled, and multicentre) generally aligns with national treatment guidelines for MCL in Denmark as it is assumed that the current SoC and the TRIANGLE treatment basket (arm A) are clinical equivalent (refer to Section 3.5). Therefore, the TRIANGLE trial was used in this submission as the main source of evidence for the direct comparison of ibrutinib with ASCT, and no indirect comparison or data synthesis was necessary.

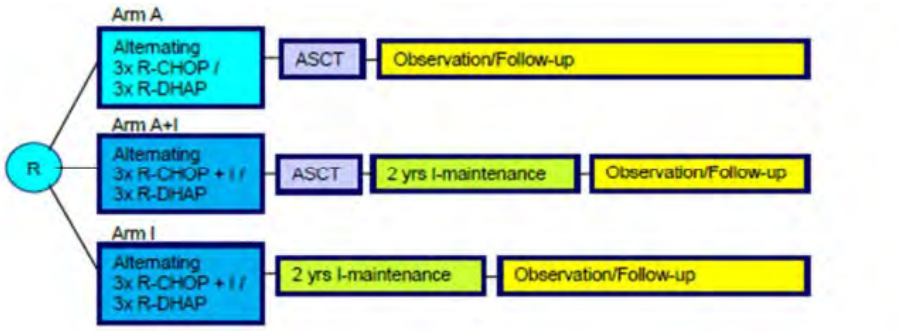
An interim analysis of the TRIANGLE trial, based on data collected up to May 22, 2022, was published in *The Lancet* by Dreyling et al.[1] However, the comparison of interest in this application (Arm A vs. Arm I) was evaluated in a later analysis based on a predefined data cutoff date of May 9, 2024, with a median follow-up time was 54.9 months. This is the latest available data cut, together with the publication will be the main reference for this application. An overview of the TRIANGLE sTtudy is presented in Table 10. Further details are provided in Appendix A.

The planned total sample size was up to 870 participants allocated to 1 of 3 treatment arms at a 1:1:1 ratio with randomisation stratified by study group and Mantle Cell Lymphoma International Prognostic Index (MIPI) risk group at study entry:

- **Arm A (control):** alternating 3 cycles R-CHOP (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by high-dose therapy (THAM or BEAM) and ASCT.
- **Arm A+I (experimental):** alternating 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by high-dose therapy (THAM or BEAM) and ASCT, and 2 years ibrutinib maintenance.
- **Arm I (experimental):** alternating 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by 2 years ibrutinib maintenance

As mentioned previously only Arm A (i.e., ASCT) and Arm I (i.e., ibrutinib without ASCT) are of interest in this application. A diagrammatic representation of the study design is presented in Figure 3.

**Figure 3 TRIANGLE: Schematic Overview of the Study Design**




Abbreviations: ASCT, autologous stem cell transplantation; Arm A; ASCT; Arm A+I; ibrutinib with ASCT; Arm I, ibrutinib without ASCT; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin

Participants with a treatment response of stable disease at the end of induction (EoI) immunochemotherapy or progressive disease (PD) were to discontinue study treatment. Therefore, THAM or BEAM conditioning prior to ASCT (Arm A+I and Arm A) and ibrutinib maintenance (Arm I) was only to be applied to participants who achieved a complete or partial remission after induction immunochemotherapy. Similarly, ibrutinib maintenance was only to be applied to participants randomized to Arm A+I who achieved a complete or partial remission after ASCT. In participants who did not achieve a remission at EoI (which was considered treatment failure), further treatment was considered upon the discretion of the treating physician. Participants who discontinued treatment for reasons other than PD were to continue to have regular response evaluations per protocol.

As evidence supporting rituximab maintenance treatment (Le Gouill 2017[81]) was not yet established at the start of the study, rituximab maintenance was not considered a study treatment in TRIANGLE trial However, upon its implementation in the national guidelines for a participating country (please see clinicaltrials.gov [NCT02858258] for full list of study locations), rituximab maintenance was to be administered to participants, per the recommendation of the site´s study group since the decision on rituximab maintenance had to be consistent for all 3 study arms to avoid treatment-related bias. Application and management of rituximab maintenance therapy followed the standards of the participating study groups. Refer to Appendix M for median duration of rituximab maintenance therapy in Arm I+A and Arm A.

**Table 10 Overview of study design for studies included in the comparison**

| Trial name, NCT-number (reference) | Study design | Study duration | Patient population | Intervention | Comparator | Outcomes and follow-up time |
|---|---|---|---|---|---|---|
| TRIANGLE, NCT02858258 (Dreyling et al.[1]; Data on file[8]) | A three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network | This study was initiated in July 2016, and the primary completion was in May 2024. The median survival follow-up time for this data-cut of 54.9 months. The study is still ongoing with estimated full completion in May 2026. | Adult patients with previously untreated MCL who are eligible for ASCT. | 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by 2 years ibrutinib maintenance*<br><br>Induction: 560 mg oral ibrutinib on days 1-19 of R-CHOP cycles<br><br>Maintenance: 2 years of daily 560 mg oral ibrutinib for patients that were failure-free after induction. | 3 cycles R-CHOP (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by HDT (THAM or BEAM) and ASCT, and rituximab maintenance* | **Primary endpoint:**<br>• FFS (09 May 2024) [Median follow-up: 54 months]<br>**Secondary endpoints:**<br>• OS (09 May 2024) [Median follow-up: 54 months]<br>• PFS (09 May 2024) [Median follow-up: 54 months]<br>• CR rate and Overall response rate (09 May 2024)<br>• PR to CR conversion rate (09 May 2024)<br>• Rates of AEs, and SAEs during the overall treatment-emergent period (09 May 2024)<br>• Cumulative incidence rates of second primary malignancies (09 May 2024) |

Abbreviations: AEs, adverse events; ASCT, autologous stem cell transplantation; CR, complete response; FFS, failure-free survival; HDT, high-dose chemotherapy; MCL, mantle cell lymphoma; NCT, National Clinical Trial number; OS, overall survival; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; SAEs, seriouse adverse events.

*Six alternating cycles of intravenous rituximab 375 mg/m$^2$ on day 0 (if given one day before the start of chemotherapy) or day 1 (the first day of chemotherapy), intravenous cyclophosphamide 750 mg/m$^2$ on day 1, intravenous doxorubicin 50 mg/m$^2$ on day 1, intravenous vincristine 1–4 mg/m$^2$ on day 1, and oral prednisone 100 mg on days 1–5 (R-CHOP) and either intravenous rituximab 375 mg/m$^2$ on day 0 or 1, intravenous or oral dexamethasone 40 mg on days 1–4, intravenous cytarabine 2×2 g/m$^2$ for 3 h every 12 h on day 2, and intravenous cisplatin 100 mg/m$^2$ over 24 h on day 1 (R-DHAP) or alternatively intravenous rituximab 375 mg/m$^2$ on day 0 or 1, intravenous or oral dexamethasone 40 mg on days 1–4, intravenous cytarabine 2×2 g/m$^2$ for 3 h every 12 h on day 2, and intravenous oxaliplatin 130 mg/m$^2$ on day 1 (R-DHAOx), with subsequent G-CSF (filgrastim) support (subcutaneous 5 µg/kg daily from day 6) every 21 days

Note: The relevant comparator for this submission is the current SoC, induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance therapy. This aligns with the current clinical practice as per the Danish Lymphoma Group[5]. It is assumed that the treatment regimen in the control arm of the TRIANGLE trial (i.e., alternating 3 cycles R-CHOP (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by HDT [THAM or BEAM] and ASCT), and the current standard of care are clinically equivalent, as supported by key efficacy endpoint data from pivotal clinical trials.[7,52]

### 6.1.2 Comparability of studies

Not relevant. Comparison based on head-to-head study TRIANGLE.

#### 6.1.2.1 Comparability of patients across studies

Subjects enrolled in the TRIANGLE trial[1] were generally believed to be representative of previously untreated MCL patients eligible for ASCT. Patient characteristics and demographics were generally similar across both treatment arms (Table 11)[8].

**Table 11 Baseline characteristics of patients in Triangle study included for the comparative analysis of efficacy and safety; Full Analysis Set**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) |
|---|---|---|
| **Mean age (SD)** | 55.5 (7.49) | 56.0 (6.85) |
| **Median age, years (range)** | 57.0 | 57.0 |
| **Age group, n (%)** | | |
| 18-25 | 0 | 0 |
| 26-50 | 58 (21.6) | 48 (17.8) |
| 51-64 | 202 (75.4) | 204 (75.8) |
| >=65 | 8 (3.0) | 17 (6.3) |
| **Male sex, n (%)** | 214 (79.9) | 205 (76.2) |
| **BMI, n (%)** | | |
| Underweight<18.5 | 5 (1.9) | 0 |
| Normal 18.5-<25 | 109 (41.3) | 114 (43.0) |
| Overweight 25-<30 | 101 (38.3) | 98 (37.0) |
| Obese>=30 | 49 (18.6) | 53 (20.0) |
| **MIPI Risk Group, n (%)** | | |
| Low risk | 152 (56.7) | 153 (56.9) |
| Intermediate risk | 76 (28.4) | 75 (27.9) |
| High risk | 40 (14.9) | 41 (15.2) |
| **ECOG performance status, n (%)** | | |
| 0 | 187 (70.0) | 191 (71.8) |
| 1 | 75 (28.1) | 71 (26.7) |
| 2 | 5 (1.9) | 4 (1.5) |

| | | |
|---|---|---|
| Not done | 1 | 3 |
| **Cytology (MCL), n (%)** | | |
| Blastoid/Pleomorphic | 29 (11.8) | 27 (11.3) |
| Classic/Small cell | 217 (88.2) | 211 (88.7) |
| Not done | 22 | 31 |
| **Ann Arbor stage, n (%)** | | |
| I | 0 | 1 (0.4) |
| II | 16 (6.0) | 8 (3.0) |
| III | 26 (9.7) | 22 (8.2) |
| IV | 226 (84.3) | 236 (88.4) |
| Not done | 0 | 2 |
| **p53 expression, n (%)** | | |
| N | | |
| <=50% | 149 (84.2) | 149 (87.6) |
| >50% | 28 (15.8) | 21 (12.4) |
| Not done | 91 | 99 |
| **Ki-67, n (%)** | | |
| N | | |
| <30% | 161 (67.4) | 157 (66.8) |
| >=30% | 78 (32.6) | 78 (33.2) |
| Not done | 29 | 34 |

Abbreviations: ASCT, autologous stem cell transplantation; BMI, body mass index; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index.
Note: Baseline results include values collected outside of the 28-day screening window
Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.
a. Patients were stratified by mantle cell lymphoma international prognostic index (MIPI) score (low risk [<5.7] vs. intermediate risk [>=5.7 and <6.2] vs. high risk [>=6.2).

### 6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The characteristics used in the health economic model is taken from the TRIANGLE trial. The difference between the values used in the health economic model and the Danish population is not very significant except the median age.

**Table 12 Characteristics in the relevant Danish population and in the health economic model**

| | Value in Danish population (DLG[5]; Nordic MCL2 study[7]). | Value used in health economic model (TRIANGLE [8]) |
|---|---|---|
| **Median age, years** | 56 | 57 |
| **Gender, proportion of males %** | 75% | 78% |
| **Patient weight** | 81.8 kg | 80 kg |
| **Body surface** | N/A | 2 $m^2$ |

Abbreviations: DLG, Danish Lymphoma Group; MCL, mantel cell lymphoma
Source: DLG mantle cell lymphoma – diagnostic and treatment [5]; Nordic MCL2 study [7]; Janssen Research & Development [Data on file] [8].

### 6.1.4 Efficacy – results per TRIANGLE

In the following sections, a summary of key efficacy findings obtained from the TRIANGLE study included in the comparative analysis is provided. The TRIANGLE data presented in this assessment is based on the primary analysis (data cutoff date 9 May 2024). Detailed information about the results of all outcomes included in the comparative analysis alongside the method for each analysis are provided in Appendix B.

**Patient disposition**

A total of 809 participants (ibrutinib without ASCT: 268; ASCT: 269; ibrutinib with ASCT: 272) were randomised. However, only the ibrutinib without ASCT arm and the ASCT arm are considered in this application. Thus, for the application the target population of interest consisted of a total of 537 patients from the TRIANGLE trial[8].

Of the 809 randomised participants, 268 participants in the ibrutinib without ASCT arm and 269 participants in the ASCT arm received study treatment.

A summary of the treatment disposition, including the proportion of patients who discontinued the study in each study arm is presented in the Table 13.

Reasons for discontinuation are reported in Appendix L

**Table 13 Summary of Treatment Disposition; Full Analysis Set (TRIANGLE)**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) | Total (N=537) |
|---|---|---|---|
| Subjects randomized but not treated, n (%) | 0 | 1 (0.4) | 1 (0.2) |
| Subjects who received study treatment, n (%) | 268 (100.0) | 268 (99.6) | 536 (99.8) |

| | | | |
|---|---|---|---|
| Subjects who completed treatment, n (%) | 180 (67.2) | 234 (87.0) | 414 (70.1) |
| Subjects who are still on treatment, n (%) | 0 | 0 | 0 |
| Subjects who discontinued study treatment, n (%) | 88 (32.8) | 34 (12.6) | 122 (22.7) |
| Safety Analysis Set, n* | 265 | 268 | 533 |

Abbreviations: ASCT, autologous stem cell transplant.
*One participant from Arm A did not receive study treatment, thus is not included in the safety analysis set. In addition, 3 participants who were randomly assigned to Arm I received ASCT, and therefore are considered as part of Arm A+I for safety analysis and reporting.

Fewer participants in the ASCT arm (34 [12.6 %]) discontinued treatment compared with the ibrutinib without ASCT arm (88 [32.8 %]). In the ibrutinib without ASCT arm, the most common reason for discontinuation of study treatment was AEs (21.3%). For the ASCT arm the most common reason for discontinuation of study treatment was progressed disease (4.5%).

#### 6.1.4.1 Failure-free survival (FFS)

The primary endpoint is FFS defined as time from randomisation to stable disease at end of immuno-chemotherapy, progressive disease, or death from any cause, whichever comes first. Calculation of FFS uses the following data from medical review: end of induction response, date of first progression, date of death, date of end of induction staging, last date without progression. For patients without evaluable end of induction staging result, FFS is censored 1 day after randomisation. Patients who progressed or died during induction or after response to induction will have an FFS event recorded at date of progression or date of death. Patients with stable disease at end of induction will have an FFS event at the end of induction staging. If two or more FFS events occur, the earlier event counts for FFS evaluation. In patients with complete or partial remission to induction and without progression or death, FFS will be censored at the last contact date without progression. FFS is calculated in months from date of randomisation to either the date of the first FFS event or the censoring date.

FFS is described by KM plots and KM estimates uncorrected for the sequential design with selected survival probabilities with two-sided 95% confidence intervals reported in 1-year steps and compared by one-sided log rank tests with significance level of 0.016665. The analysis was done using Cox regression with two-sided 98.33% CIs for HR.

**Kaplan Meier estimates of FFS – Full analysis set**
At the time of the data cut-off for the primary analysis (9th May, 2024), a total of 148 FFS events (61 in the ibrutinib without ASCT [including 1 stable disease at end of induction], and 87 in the ASCT arm [including 5 stable disease at end of induction]) were observed by the EU MCL Network case evaluation of investigator assessment per protocol criteria[8]. The median time on study for all TRIANGLE participants was 54.9 months (range: 0–91)[8].

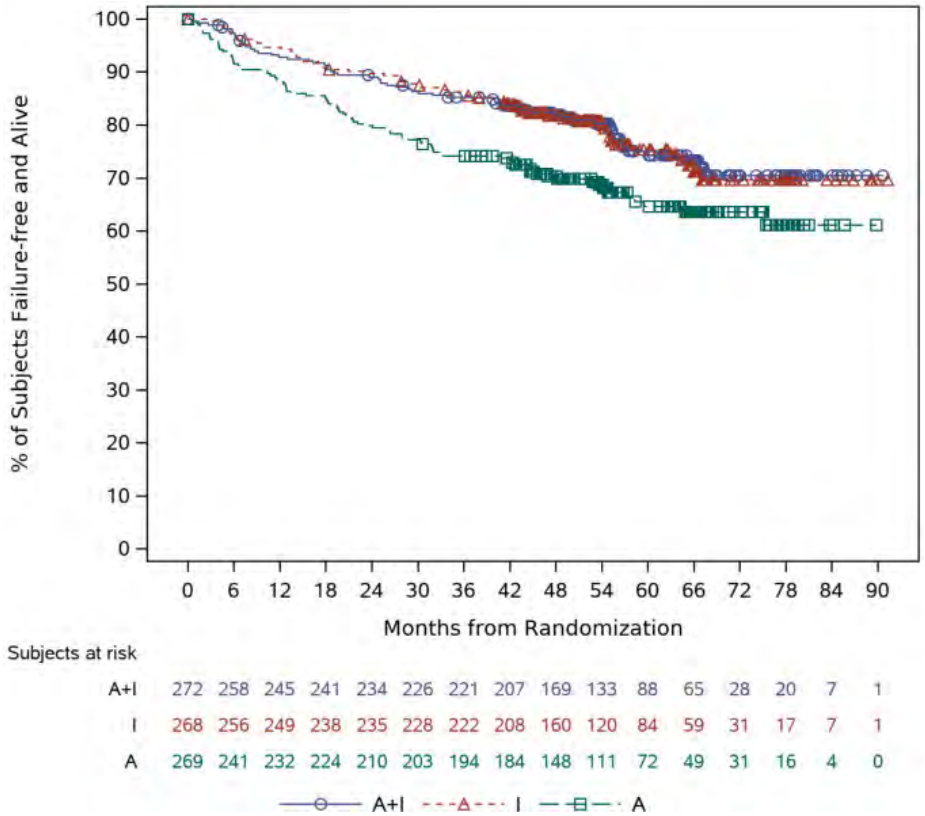
Statistically significant improvement of FFS was demonstrated for participants in ibrutinib without ASCT arm compared with participants in ASCT arm (HR: 0.639 [two-sided 98.33% CI: 0.428-0.953], two-sided p-value: 0.0068) (Refer to Table 14). This represents a 35.4% reduction in the hazard of SD at EoI, disease progression, or death for participants in ibrutinib without ASCT arm versus ASCT[8]. While the median FFS was not reached for either treatment arm, the Kaplan-Meier (KM) estimate FFS rates at 54 months were 80.7% for participants in the ibrutinib without ASCT arm and 68.7% for participants in the ASCT arm (Table 14)[8]. The KM curves for FFS are provided in Figure 4.

**Table 14 FFS – TRIANGLE full analysis set**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) |
|---|---|---|
| **FFS events, n (%)** | 61 (22.8) | 87 (32.3) |
| Stable disease at end of induction therapy, n (%) | 1 (0.4) | 5 (1.9) |
| Disease progression, n (%) | 49 (18.3) | 60 (22.3) |
| Death, n (%) | 11 (4.1) | 22 (8.2) |
| **Censored, n (%)** | 207 (77.2) | 182 (67.7) |
| **Median FFS, months (95% CI)** | N/A | N/A |
| Range (months) | (0.0+, 91.3+) | (0.0+, 89.8+) |
| **12-month FFS rate, % (95% CI)** | 94.7 (0.912, 0.968) | 88.2 (0.837, 0.916) |
| **24-month FFS rate, % (95% CI)** | 89.7 (0.854, 0.928) | 79.8 (0.745, 0.842) |
| **36-month FFS rate, % (95% CI)** | 85.9 (0.811, 0.896) | 74.1 (0.684, 0.790) |
| **54-month FFS rate, % (95% CI)** | 80.7 (0.753, 0.851) | 68.7 (0.626, 0.741) |
| **Unstratified analysis** | | |
| Hazard ratio (two-sided 98.33% CI)[a] | 0.639 (0.428, 0.953) | |
| Two-sided p-value[b] | 0.0068 | |

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; FFS, failure-free survival; N/A, not available/not applicable.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.
a. Hazard ratio is from an unstratified Cox regression model.
b. Two-sided p-value is from an unstratified log-rank test.
Data cutoff date: 09 May 2024.
Source: Janssen Research & Development [Data on file][8]

**Figure 4 Kaplan-Meier curves of FFS (Ibrutinib without ASCT vs. ASCT; FAS)**



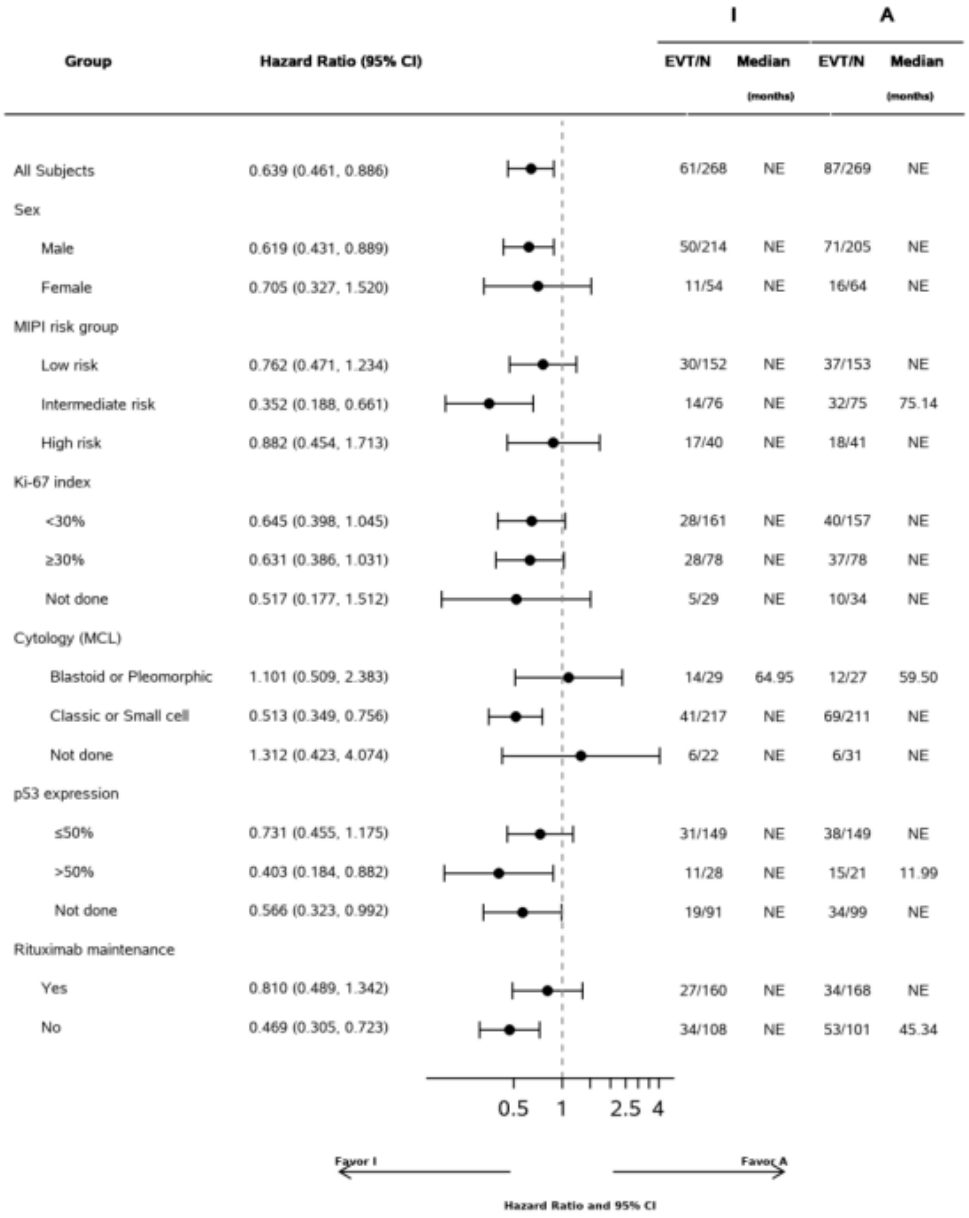

Abbreviations: ASCT, autologous stem cell transplant; A+I, ibrutinib with ASCT arm; FFS, failure-free survival; I, ibrutinib without ASCT arm, A, ASCT arm.
Source: Janssen Research & Development [Data on file][8]

**Kaplan Meier estimates of FFS – Subgroup analyses**

Forest plots of FFS by central EU MCL Network case evaluation for subgroups defined by baseline clinical disease characteristics (sex [male, female], MIPI risk group [low, intermediate, high], Ki-67 index [<30%, ≥30%, not done], cytology of MCL [blastoid or pleomorphic, classic or small cell, not done], p53 expression [≤50%, >50%, not done], and rituximab maintenance [yes, no]) are presented for ibrutinib without ASCT vs. ASCT in Figure 5[8].

The treatment effect was generally consistent across these subgroups, demonstrating greater improvements for participants in the ibrutinib without ASCT arm compared with participants in the ASCT arm[8]. The exception to this was participants with a blastoid or pleomorphic MCL diagnosis. Among these patients, similar FFS outcomes were reported in the ibrutinib without ASCT and the ASCT arms[8]. However, given the low number of participants with blastoid or pleomorphic MCL (29 vs. 27 in the ibrutinib without ASCT and ASCT arms, respectively), no conclusions can be drawn[8].

**Figure 5 Forest plot of subgroup analyses on FFS (Ibrutinib without ASCT vs. ASCT; FAS)**




Abbreviations: A, ASCT arm; FAS, full analyses set; I, ibrutinib without ASCT arm; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index.
Note: For the comparison of the treatment effect between the subgroups of patients who received and did not receive rituximab maintenance, it should be considered that fixed-duration ibrutrinib/rituximab maintenance was only initiated in those patients who achieved a response to treatment after induction or ASCT in the ibrutinib without ASCT and ASCT arms, respectively.
Source: Janssen Research & Development [Data on file][8]

### 6.1.4.2 Overall survival (OS)

OS is defined as time from randomisation to death. In patients without documented death during observation time, OS is censored at the last contact date alive. If the last contact date is before randomisation, OS is censored one day after randomisation.

OS is described by KM plots in one plot with all groups. KM estimates uncorrected for the sequential design are calculated and selected survival probabilities with two-sided 95% confidence intervals reported in 1-year steps. The exploratory analysis was done using Cox regression with two-sided 95% CIs for HR.

**Kaplan Meier estimates of OS – full analysis set**

At the time of the data cut-off for the primary analysis (9th May, 2024), a total of 33 (12.3%) and 60 (22.3%) deaths were reported in the ibrutinib without ASCT and ASCT arms, respectively[8]. A significant and clinically meaningful improvement in OS was observed for ibrutinib without ASCT vs. ASCT (HR: 0.522 [95% CI: 0.341–0.799]; two-sided nominal p=0.0023]), representing a statistically significant 47.8% reduction in the hazard of death for participants receiving ibrutinib without ASCT relative to those receiving ASCT (Table 15 and Figure 6)[8]. While the median OS was not reached for either arm, the KM OS rate estimates at 54 months were 87.3% and 77.9% in the ibrutinib without ASCT and ASCT arms, respectively (Table 15)[8]. The initial drop observed in the KM plot of OS for the ASCT arm at approximately six months correlates with the initiation of HDT and ASCT and, thus, is considered to be reflective of HDT-toxicity (Table 15 and Figure 6)[8].

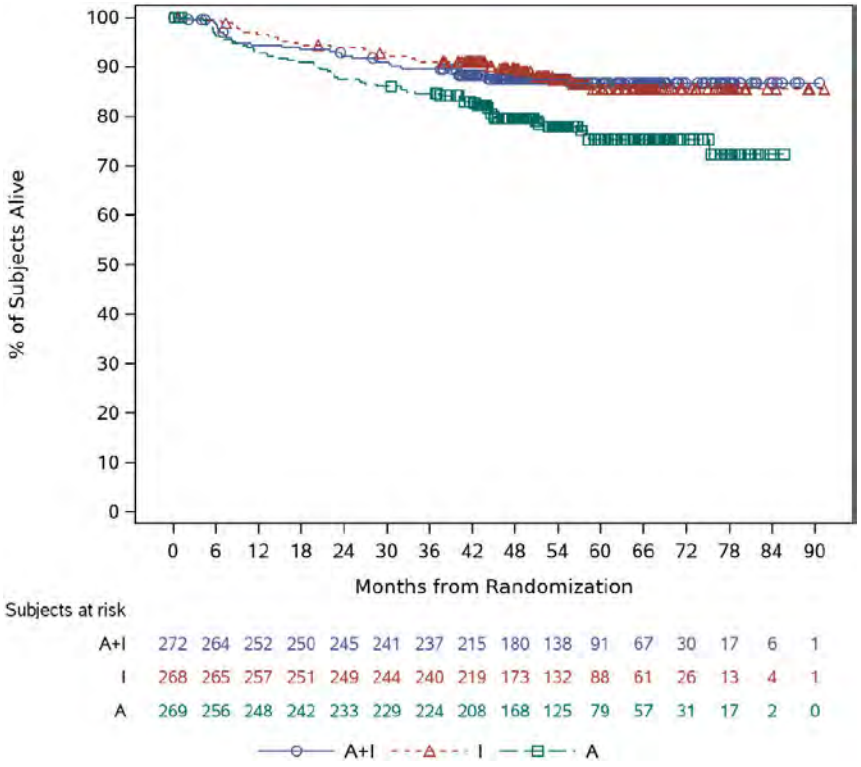
**Table 15 Overall survival (OS) – TRIANGLE full analysis set**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) |
|---|---|---|
| **Death, n (%)** | 33 (12.3) | 60 (22.3) |
| **Censored, n (%)** | 235 (87.7) | 209 (77.7) |
| **Median OS, months (95% CI)** | N/A | N/A |
| Range | (0.7+, 91.3+) | (0.2+, 85.7+) |
| **12-month OS rate, % (95% CI)** | 96.6 (0.936, 0.982) | 93.2 (0.895, 0.957) |
| **24-month OS rate, % (95% CI)** | 94.0 (0.904, 0.963) | 87.6 (0.830, 0.910) |
| **36-month OS rate, % (95% CI)** | 91.0 (0.868, 0.938) | 84.6 (0.796, 0.884) |
| **54-month OS rate, % (95% CI)** | 87.3 (0.824, 0.910) | 77.9 (0.722, 0.826) |
| **Unstratified analysis** | | |
| HR[a] (two-sided 95% CI) | 0.522 (0.341, 0.799) | |
| Two-sided p-value[b] | 0.0023 | |

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; N/A, not available/not applicable; OS, overall survival.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators. + = censored observation.
a. Hazard ratio is from an unstratified Cox regression model.

b. Two-sided p-value is from an unstratified log-rank test.
Data cutoff date: 09 May 2024.
Source: Janssen Research & Development [Data on file][8]

**Figure 6 Kaplan-Meier curves of overall survival (Ibrutinib without ASCT vs. ASCT; FAS)**

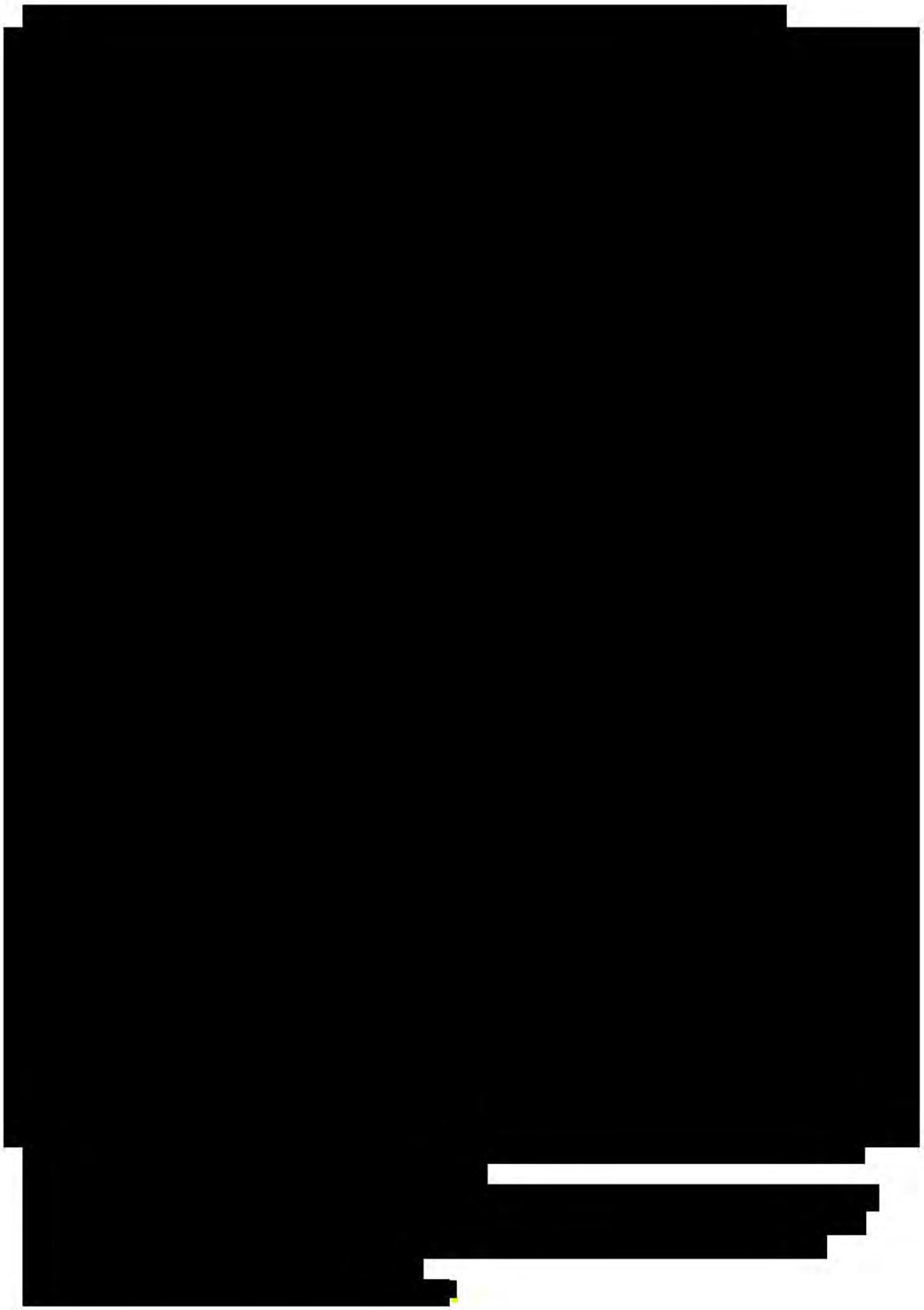



Abbreviations: ASCT, autologous stem cell transplant; A, ASCT arm; A+I, ibrutinib with ASCT arm; I, ibrutinib without ASCT arm; PFS, progression-free survival.
Source: Janssen Research & Development [Data on file][8]

**Kaplan Meier estimates of OS – Subgroup analyses**

Forest plots of OS by central EU MCL Network case evaluation for subgroups defined by baseline clinical disease characteristics (sex [male, female], MIPI risk group [low, intermediate, high], Ki-67 index [<30%, ≥30%, not done], cytology of MCL [blastoid or pleomorphic, classic or small cell, not done], p53 expression [≤50%, >50%, not done], and rituximab maintenance [yes, no]) are presented for ibrutinib without ASCT vs. ASCT in Figure 7[8].

[redacted]



#### 6.1.4.3 Progression-free survival (PFS)

PFS is defined as time from randomisation to progressive disease or death from any cause. For patients without evaluable staging result, PFS from randomisation is censored 1 day after randomisation. In patients without documented progression or death during observation, PFS will be censored at the last contact date without progression.

**Kaplan Meier estimates of PFS – Full Analysis Set**

At the time of the data cut-off for the primary analysis (9th May, 2024), a total of 147 PFS events (60 in the ibrutinib without ASCT arm, and 87 in the ASCT arm) were observed by the central EU MCL Network case evaluation of the investigator assessment per protocol criteria (Table 16)[8].

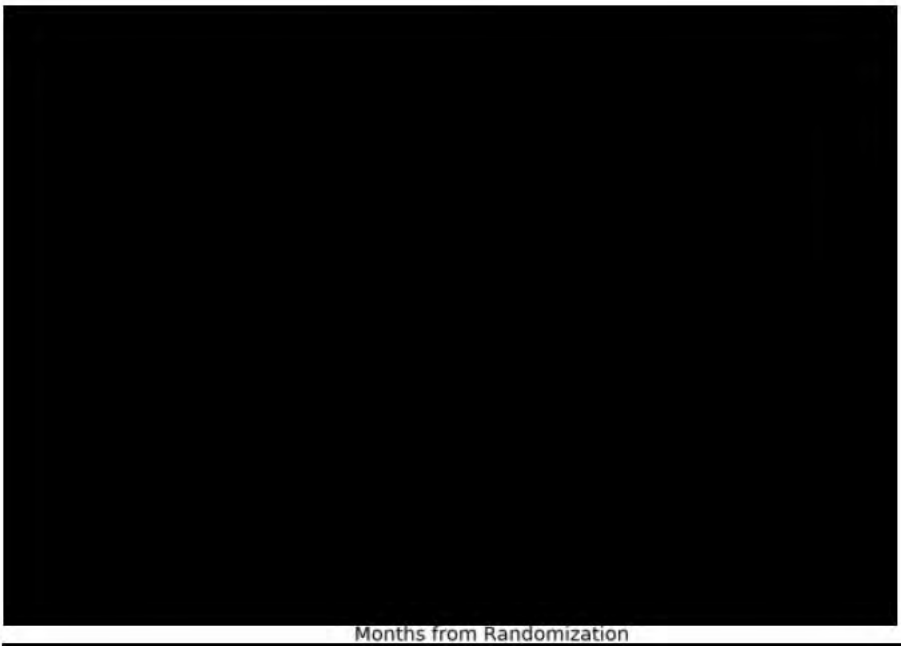
PFS results were reported from randomisation, based on the primary analysis of a two-sided test at an overall significance level (1.67% after Bonferroni correction). A significant improvement of PFS was demonstrated for participants in the ibrutinib without ASCT arm compared with participants in the ASCT arm (HR: 0.633 [98.33% CI: 0.424-0.946; two-sided p=0.0060]; Table 16). This represents a 36% reduction in the hazard of PD or death for participants treated in ibrutinib without ASCT arm compared with participants in the ASCT arm[8]. While the median PFS was not reached for either treatment arm, KM PFS rates were estimated at 54 months to be 81.3% and 69.4% for participants in the ibrutinib without ASCT and ASCT arms, respectively (Table 16 and Figure 8)[8].

**Table 16 PFS – TRIANGLE full analysis set**

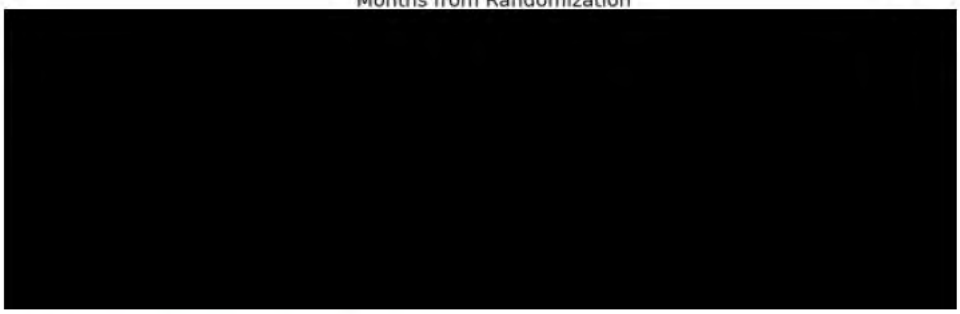
| | Ibrutinib without ASCT (N=268) | ASCT (N=269) |
|---|---|---|
| **PFS events, n (%)** | 60 (22.4) | 87 (32.3) |
| Disease progression, n (%) | 49 (18.3) | 63 (23.4) |
| Death, n (%) | 11 (4.1) | 24 (8.9) |
| **Censored, n (%)** | 208 (77.6) | 182 (67.7) |
| **Median PFS, months (95% CI)** | N/A | N/A |
| Range (months) | (0.6+, 91.3+) | (0.0+, 89.8+) |
| **12-month PFS rate, % (95% CI)** | [redacted] | [redacted] |
| **24-month PFS rate, % (95% CI)** | [redacted] | [redacted] |
| **36-month PFS rate, % (95% CI)** | [redacted] | [redacted] |
| **54-month PFS rate, % (95% CI)** | 81.3 (0.759-0.856)) | 69.4 (0.633-0.747) |
| **Unstratified analysis** | | |
| Hazard ratio (two-sided 98.33% CI)[a] | 0.633 (0.424-0.946) | |
| Two-sided p-value[b] | 0.0060 | |

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; PFS, progression-free survival; N/A, not available/not applicable.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.

a. Hazard ratio is from an unstratified Cox regression model.
b. Two-sided p-value is from an unstratified log-rank test.
Data cutoff date: 09 May 2024.
Source: Janssen Research & Development [Data on file][8]



Months from Randomization



#### 6.1.4.4 Overall response rates (ORR)

ORR at midterm, at end of induction, and at 3 months after end of induction were analysed according to the response data from medical review. Response categories are CR, PR, SD, PD, and NE in case of non-evaluable response. Response assessments are determined by the investigator based on the Revised Response Criteria for Malignant Lymphoma[66].

The ORR is the percentage of patients with CR or PR among those with evaluable response. The ORR, and PR to CR conversion rates were compared using relative risk with their associated 2-sided 95% CIs using Fisher's exact test. Tests of these endpoints were considered independent from the primary outcome and each other.

ORR rate, as assessed by the central EU MCL Network case evaluation was comparable between the ibrutinib without ASCT arm (96.3%) and the ASCT arm (92.2%); RR: 1.044 [two-sided 95% CI: 1.001–1.089], p=0.0627; Table 17)[8].

**Table 17 Overall response rate (ORR) - TRIANGLE full analysis set**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) |
|---|---|---|
| **ORR (CR, PR), n (%)** | 258 (96.3) | 248 (92.2) |
| Relative risk (two-sided 95% CI)[a] | 1.044 (1.001–1.089) | |
| Two-sided p-value[b] | 0.627 | |
| **Best overall response, n (%)** | | |
| CR | 180 (67.2) | 174 (64.7) |
| PR | 78 (29.1) | 74 (27.5) |
| SD | 1 (0.4) | 3 (1.1) |
| PD | 3 (1.1) | 11 (4.1) |
| NE | 6 (2.2) | 7 (2.6) |

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.
a. RR > 1 favours IMBRUVICA without ASCT vs. ASCT.
b. *p*-value was calculated using the Fisher's exact test.
Data cutoff date: 09 May 2024.
Source: Janssen Research & Development [Data on file][8]

### 6.1.5 Efficacy – results per [study name 2]

N/A

# 7. Comparative analyses of efficacy

### 7.1.1 Differences in definitions of outcomes between studies

Head-to-head study used. Not applicable.

### 7.1.2 Method of synthesis

Head-to-head study used. Not applicable.

### 7.1.3 Results from the comparative analysis

Table 18 presents the results from the comparative analyses of ibrutinib vs. ASCT derived from the head-to-head trial: TRIANGLE (NCT02858258).

**Table 18 Results from the comparative analysis of Ibrutinib vs. ASCT for adult patients with previously untreated MCL who are eligible for ASCT**

| Outcome measure | Ibrutinib without ASCT (N=268) | ASCT (N=269) | Result |
|---|---|---|---|
| **Failure-free survival (FFS)**<br>(Kaplan-Meier FFS rate estimate at 54 months) | 80.7%<br>(95% CI: 0.753, 0.851) | 68.7%<br>(95% CI: 0.626, 0.741) | HR: 0.639[a]<br>(98.33% CI: 0.428-0.953)<br>p=0.0068[b] |
| **Overall survival (OS)**<br>(Kaplan-Meier OS rate estimates at 54 months) | 87.3%<br>(95% CI: 0.824, 0.910) | 77.9%<br>(95% CI: 0.722, 0.826) | HR: 0.522[a]<br>(95% CI: 0.341-0.799)<br>p=0.0023[b] |
| **Progression-free survival (PFS)**<br>(Kaplan-Meier PFS rate estimate at 54 months) | 81.3%<br>(95% CI: 0.759, 0.856) | 69.4%<br>(95% CI: 0.633, 0.747) | HR: 0.633[a]<br>(98.33% CI: 0.424-0.946)<br>p=0.0060[b] |
| **Overall response rates (ORR)*** | 258 (96.3%) | 248 (92.2%) | RR: 1.044[c]<br>(95% CI: 1.001–1.089)<br>p=0.0627[d] |

Abbreviations: ASCT, autologous stem cell transplant; HR, hazard ratio; RR, relative risk.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.
*Appendix B presents the breakdown of ORR components.
[a] Hazard ratio is from an unstratified Cox regression model
[b] Two-sided p-value is from an unstratified log-rank test.
[c] Relative Risk >1 favors I vs. A, A+I vs. A, or A+I vs. I.
[d] p-value is from the Fisher's exact test.
Source: Janssen Research & Development [Data on file][8]

### 7.1.4 Efficacy – results per [outcome measure]

All results per efficacy outcome of interest are summarised in Section 6.

# 8. Modelling of efficacy in the health economic analysis

## 8.1 Presentation of efficacy data from the clinical documentation used in the model

This section presents the efficacy data used in the model. The clinical data is from the TRIANGLE trial, on which the modelling effect is based. The data used in the health economic model is from the same data cut as described in sections 6 and 7. The extrapolation of the efficacy data is presented below.

### 8.1.1 Extrapolation of efficacy data

In this analysis, extrapolations of OS and FFS are generated using joint parametric curves and separate curves, respectively, using standard parametric models. Standard parametric modelling estimates patient movement over a specified time-period using a variety of different distributions, including exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalized gamma. Parametric modelling can be selected for use for both treatment arms, in OS and FFS.

The assumption of proportional hazards is examined using Schoenfeld residuals and log-cumulative hazard plots; the proportional hazards assumption holds for OS, but not FFS. Separate fits are used both for OS and FFS to allow greater flexibility for OS, and by requirement for FFS. The selection of base case parametric functions for OS and FFS for ibrutinib as well as ASCT was informed by Goodness-of-fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]), visual inspection to assess the concordance between predicted and observed FFS and OS curves, and clinical plausibility of long-term extrapolations. Survival estimates were corrected for all-cause mortality in the Danish general population.

For more details on the choices of extrapolation, see Appendix D.

### 8.1.2 Extrapolation of OS

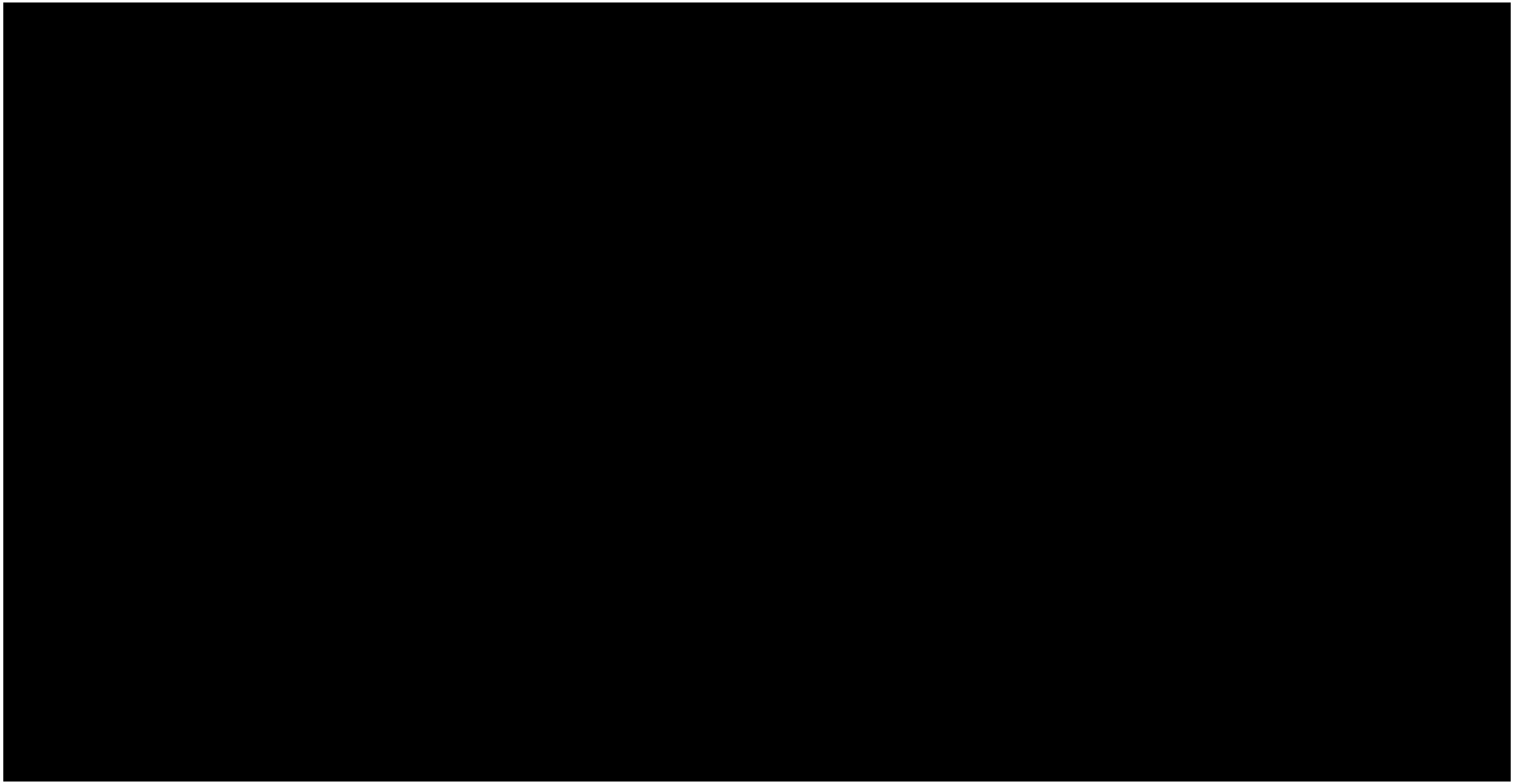
**Table 19 Summary of assumptions associated with extrapolation of OS**

| Method/approach | Description/assumption |
|---|---|
| **Data input** | TRIANGLE |
| **Model** | Full parametrisation was applied in extrapolating the efficacy data. Seven functional forms were used to fit OS curves: exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalised gamma |
| **Assumption of proportional hazards between intervention and comparator** | Yes, but separate fit is used as it is deemed more suitable. See Appendix D.1 |
| **Function with best AIC fit** | Ibrutinib: generalised gamma<br>ASCT: generalised gamma |
| **Function with best BIC fit** | Ibrutinib: exponential<br>ASCT: exponential |
| **Function with best visual fit** | N/A |
| **Function with best fit according to evaluation of smoothed hazard assumptions** | Ibrutinib: log-normal<br>ASCT: Weibull |

| Method/approach | Description/assumption |
|---|---|
| **Validation of selected extrapolated curves (external evidence)** | N/A |
| **Function with the best fit according to external evidence** | N/A |
| **Selected parametric function in base case analysis** | Ibrutinib: exponential<br>ASCT: Weibull |
| **Adjustment of background mortality with data from Statistics Denmark** | Yes |
| **Adjustment for treatment switching/cross-over** | No |
| **Assumptions of waning effect** | No |
| **Assumptions of cure point** | No |

Abbreviations: AIC, Akaike Information Criterion; ASCT, autologous stem cell transplant; BIC, Bayesian Information Criterion; OS, overall survival.

See Figure 9 and Figure 10 for different extrapolations together with the Kaplan-Meier curves for ibrutinib and ASCT arms, respectively. Figure 11 shows both arms combined, with extrapolation, with general population overall survival.



### 8.1.3 Extrapolation of FFS

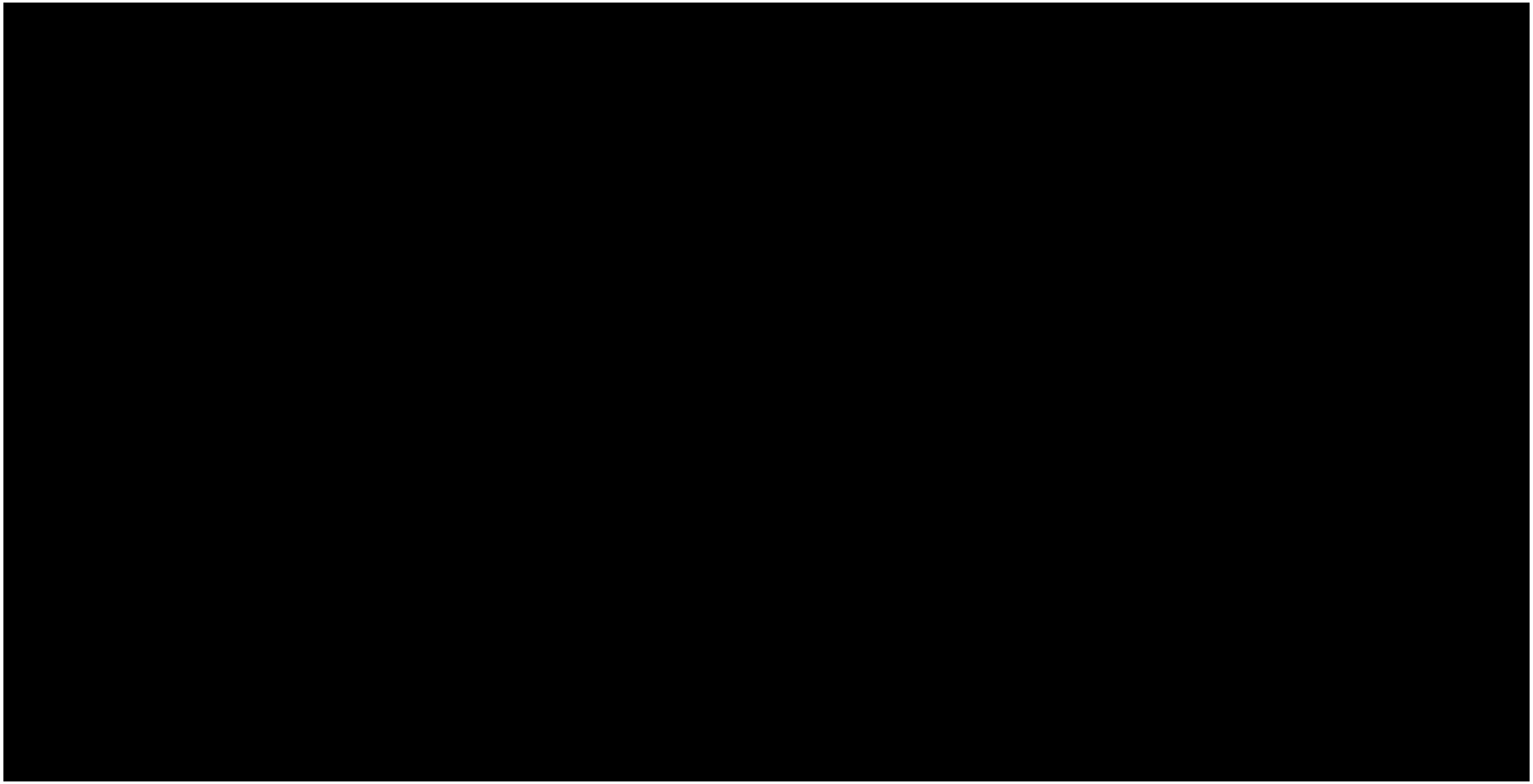
**Table 20 Summary of assumptions associated with extrapolation of FFS**

| Method/approach | Description/assumption |
|---|---|
| **Data input** | TRIANGLE |
| **Model** | Full parametrisation was applied in extrapolating the efficacy. Seven functional forms were used to fit FFS curves: exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalized gamma |
| **Assumption of proportional hazards between intervention and comparator** | No |
| **Function with best AIC fit** | Ibrutinib: exponential<br>ASCT: log-normal |
| **Function with best BIC fit** | Ibrutinib: exponential<br>ASCT: log-normal |
| **Function with best visual fit** | N/A |
| **Function with best fit according to evaluation of smoothed hazard assumptions** | Ibrutinib: log-normal<br>ASCT: Weibull |
| **Validation of selected extrapolated curves (external evidence)** | N/A |
| **Function with the best fit according to external evidence** | N/A |
| **Selected parametric function in base case analysis** | Ibrutinib: exponential<br>ASCT: Weibull |
| **Adjustment of background mortality with data from Statistics Denmark** | Yes |
| **Adjustment for treatment switching/cross-over** | No |
| **Assumptions of waning effect** | No |
| **Assumptions of cure point** | No |

Abbreviations: AIC, Akaike Information Criterion; ASCT, autologous stem cell transplant; BIC, Bayesian Information Criterion; FFS, failure free survival.

See Figure 12 and

Figure 13 for different extrapolations together with the Kaplan-Meier curves for ibrutinib and ASCT arms, respectively. Figure 14 shows both arms combined, with extrapolation



### 8.1.4 Calculation of transition probabilities

Not applicable.

**Table 21 Transitions in the health economic model**

| Health state (from) | Health state (to) | Description of method | Reference |
|---|---|---|---|
| Disease-free survival | Recurrence | N/A | N/A |
| | Death | N/A | N/A |
| Recurrence | Death | N/A | N/A |
| Health state/Transition | N/A | N/A | N/A |

## 8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

## 8.3 Modelling effects of subsequent treatments

The subsequent lines of therapy are the same for both ibrutinib and ASCT arms, albeit different compositions. The subsequent treatment effects are modelled using the same extrapolations from the trial data.

## 8.4 Other assumptions regarding efficacy in the model

Not applicable.

## 8.5 Overview of modelled average treatment length and time in model health state

**Table 22 Estimates in the model**

| | Modelled average FFS [months] | Modelled median FFS [months] | Modelled average OS [months] | Modelled median OS [months] | Observed median from relevant study, OS and FFS |
|---|---|---|---|---|---|
| **Ibrutinib** | 92.30 | 153.21 | 176.26 | 296.67 | Not reached |

| | Modelled average FFS [months] | Modelled median FFS [months] | Modelled average OS [months] | Modelled median OS [months] | Observed median from relevant study, OS and FFS |
|---|---|---|---|---|---|
| **ASCT** | 82.76 | 113.30 | 102.03 | 161.45 | Not reached |

Abbreviation: ASCT, autologous stem cell transplant.

Table 23 summarises the treatment length and time in model health states. The treatment lengths were calculated from the overall survival rate (the Kaplan-Meier curves).

**Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)**

| Treatment | Treatment length [months] | FFS [months] | PD [months] |
|---|---|---|---|
| **Ibrutinib** | 33.41 | 92.30 | 83.96 |
| **ASCT** | 31.08 | 82.76 | 19.27 |

Abbreviation: ASCT, autologous stem cell transplant.

# 9. Safety

## 9.1 Safety data from the clinical documentation

Safety data were derived by the treatment arm using the safety analysis set from the TRIANGLE head-to-head trial (data cut-off May 9 2024 [NCT02858258])[8].

The Safety Analysis Set included all randomised participants from the full analysis set who received at least 1 dose of study treatment (808 participants). One participant from ASCT did not receive study treatment, thus is not included in the safety analysis set. In addition, 3 participants who were randomly assigned to ibrutinib without ASCT received ASCT and therefore are not considered as part of ibrutinib without ASCT arm for safety analysis and reporting. For this application only the arms of interest (i.e., ibrutinib without ASCT and ASCT) are included. Thus, for the application the safety population of interest consisted of a total of 537 patients from the TRIANGLE trial. In this application, safety data (AEs) are presented as treatment-emergent adverse events (TEAEs) (Table 24).

As noted previously, rituximab maintenance was not considered study treatment. However, upon its implementation in the national guidelines for a participating country, rituximab maintenance was to be administered to participants, as per the recommendation of the site´s study group. As such, rituximab maintenance treatment

was initiated for participants in the ASCT arm at the time when the treatment-emergent period ended (30 days after the last study treatment or ASCT was administered, as applicable), whereas it was administered concomitantly with the ibrutinib maintenance treatment for participants in the ibrutinib without ASCT arm, thus captured within the treatment-emergent period for the ibrutinib-containing arm.

In evaluating the safety findings in this section, it is important to note that the median time on treatment for participants in the ibrutinib without ASCT arm was 28.45 months, as compared with 5.16 months for the ASCT arm. This is equivalent to a treatment exposure that is more than 5-fold longer for participants in the ibrutinib without ASCT arm compared with participants in the ASCT arm. All participants were off study treatment and were past the treatment-emergent period at primary analysis.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 26.0. Laboratory values were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 4.03 criteria.

Meta-analyses or indirect treatment comparisons of safety have not been conducted, as a single RCT provides head-to-head evidence of ibrutinib without ASCT versus ASCT.

**Summary of AEs**

The overall incidence of TEAEs (any grade) was similar between participants in the ibrutinib without ASCT arm (99.2%), and the ASCT arm (99.6%). The proportion of participants with Grade 3 or higher AEs was similar (<1% difference) for the ibrutinib without ASCT arm and the ASCT arm (93.2%, and 93.3%, respectively).

**Table 24 Overview of safety events; Safety analysis set (Data cut off: 9 May 2024)**

| | Intervention (N=265) TRIANGLE | Comparator (N=268) TRIANGLE | Difference, % (95 % CI) |
|---|---|---|---|
| **Number of adverse events, n** | N/A | N/A | (N/A) |
| **Number and proportion of patients with ≥1 adverse events, n (%)** | 263 (99.2) | 267 (99.6) | -0.4 (N/A) |
| **Number of serious adverse events[a], n** | N/A | N/A | N/A |
| **Number and proportion of patients with ≥ 1 serious adverse events[a], n (%)** | 171 (64.5) | 123 (45.9) | 18.6 (N/A) |
| **Number of CTCAE grade ≥ 3 events, n** | N/A | N/A | (N/A) |

| | Intervention (N=265) TRIANGLE | Comparator (N=268) TRIANGLE | Difference, % (95 % CI) |
|---|---|---|---|
| **Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[b], n (%)** | 247 (93.2) | 250 (93.3) | -0.1 (N/A) |
| **Number of adverse reactions, n** | N/A | N/A | (N/A) |
| **Number and proportion of patients with ≥ 1 adverse reactions, n (%)** | 212 (80.0) | N/A[c] | (N/A) |
| **Number and proportion of patients who had a dose reduction, n (%)** | 43 (16.2) | N/A[c] | (N/A) |
| **Number and proportion of patients who discontinue treatment regardless of reason, n (%)[d]** | [redacted] | [redacted] | (N/A) |
| **Number and proportion of patients who discontinue treatment due to adverse events, n (%)[d]** | [redacted] | [redacted] | (N/A) |

Abbreviations: CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; N/A, not available/not applicable.
a. A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
b. CTCAE v. 5.0 must be used if available.
c. To note, the causal relation of an AE to any study treatment was only collected for ibrutinib in the eCRF, whereas information on relationship of an AE with any other study treatment was not collected.
d. Number and proportion from the full analysis set

The proportions of participants with SAEs were 64.5% for the ibrutinib without ASCT arm, and 45.9% for the ASCT arm with the latter having a 5-fold shorter treatment-emergent period than participants in the ibrutinib without ASCT arm. Considering the difference in the median treatment duration, while the number of fatal AEs was low in both treatment arms, it was numerically higher in the ASCT arm (11 participants [4.1%]) compared with the ibrutinib without ASCT arm (6 participants [2.3%]). An increase in

early fatal events shortly after the induction phase for the ASCT-containing regimen was correlated with early decreases in the OS curve for the ASCT-containing regimen around 6 months that corresponded to the HDT and ASCT period. Thus, these findings may be reflective of the known HDT and ASCT-related mortality.

The most frequently reported (≥5%) SAEs in any treatment arm by PT were:

- Febrile neutropenia: ibrutinib without ASCT: 10.6%, ASCT: 7.1%
- Acute kidney injury: ibrutinib without ASCT: 6.8%, ASCT 5.2%

**Table 25 Serious adverse events; Safety analysis set (Data cut off: 9 May 2024)[8]**

| Adverse events | Intervention (N=265) | | Comparator (N=268) | |
|---|---|---|---|---|
| | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events |
| **Adverse event, n (%)** | | | | |
| **Overall** | 171 (64.5) | N/A | 123 (45.9) | N/A |
| Febrile neutropenia | 28 (10.6) | N/A | 19 (7.1) | N/A |
| Acute kidney injury | 18 (6.8) | N/A | 14 (5.2) | N/A |

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The frequencies of the adverse events used in the health economics model are the same as the ones described in the TRIANGLE trials. No modifications or exclusions were performed.

**Table 26 Adverse events used in the health economic model**

| Adverse events | Intervention | Comparator | | |
|---|---|---|---|---|
| | Frequency used in economic model for intervention | Frequency used in economic model for comparator | Source | Justification |
| **Adverse event, n (%)** | | | | |
| Neutropenia | [redacted] | [redacted] | CSR[8] | Directly from TRIANGLE |
| Anaemia | [redacted] | [redacted] | CSR | Directly from TRIANGLE |

| Adverse events | Intervention | Comparator | | |
|---|---|---|---|---|
| Thrombocytopenia | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Febrile neutropenia | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Leukopenia | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Platelet count decreased | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Neutrophil count decreased | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| White blood cell count decreased | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Lymphocyte count decreased | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Gamma-glutamyltransferase increased | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Pneumonia | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Sepsis | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Stomatitis | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Nausea | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Diarrhoea | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Mucosal inflammation | [redacted] | [redacted] | CSR | Directly from TRIANGLE |
| Hypokalaemia | [redacted] | [redacted] | CSR | Directly from TRIANGLE |

Abbreviation: CSR, clinical study report.
Source: Janssen Research & Development [Data on file] [6]

## 9.2 Safety data from external literature applied in the health economic model

No safety data from external literature is applied in the health economic model.

**Table 27 Adverse events that appear in more than X % of patients**

| Adverse events | Intervention (N=x) | | | Comparator (N=x) | | | Difference, % (95 % CI) | |
|---|---|---|---|---|---|---|---|---|
| | Number of patients with adverse events | Number of adverse events | Frequency used in economic model for intervention | Number of patients with adverse events | Number of adverse events | Frequency used in economic model for comparator | Number of patients with adverse events | Number of adverse events |
| Adverse event, n | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

# 10. Documentation of health-related quality of life (HRQoL)

**Table 28 Overview of included HRQoL instruments**

| Measuring instrument | Source | Utilization |
|---|---|---|
| EQ-5D-5L | SHINE trial (NCT01776840) | HRQoL data was collected to estimate HSUVs for FFS |
| EQ-5D-5L | RAY trial (NCT05305963) | HRQoL data was collected to estimate HSUVs for PD |

Abbreviations: EQ-5D, EuroQol 5 Dimensions; HSUV, health state utility values; FFS, failure free survival; PD, progressed disease.

## 10.1 Presentation of the health-related quality of life

All HRQoL instruments included in this submission is informed by other trials (Table 28) and literature described in section 10.3.

### 10.1.1 Study design and measuring instrument

N/A

**Table 29 Pattern of missing data and completion**

| Time point | HRQoL population N | Missing N (%) | Expected to complete N | Completion N (%) |
|---|---|---|---|---|
| **N/A** | N/A | N/A | N/A | N/A |

### 10.1.2 Data collection

N/A

### 10.1.3 HRQoL results

N/A

**Table 30 HRQoL [instrument 1] summary statistics**

| | Intervention | Comparator | Intervention vs. comparator |
|---|---|---|---|
| N/A | N/A | N/A | N/A |

## 10.2 Health state utility values (HSUVs) used in the health economic model

### 10.2.1 HSUV calculation

Not applicable. HSUV were based on external literature.

#### 10.2.1.1 Mapping

Not applied.

### 10.2.2 Disutility calculation

Not applicable. The disutility calculations were based on external literature.

### 10.2.3 HSUV results

Not applicable. The HSUV results were based on external literature.

**Table 31 Overview of health state utility values [and disutilities]**

| | Results [95% CI] | Instrument | Tariff (value set) used | Comments |
|---|---|---|---|---|
| N/A | N/A | N/A | N/A | N/A |

## 10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

### 10.3.1 Study design

As the TRIANGLE trial did not collect HRQoL data, utility values for relevant health states were sourced from external data. Specifically, FFS state was informed by the SHINE trial, which investigated ibrutinib in a 1L MCL population ineligible for transplant. SHINE is a randomised, double-blind, placebo-controlled, international Phase 3 study that evaluated the efficacy and safety profile of therapy with ibrutinib in combination with BR (bendamustine and rituximab) in elderly subjects (65 years of age or older) with newly diagnosed MCL. The primary objective was to evaluate whether the addition of ibrutinib to bendamustine and rituximab would result in prolongation of PFS in the aforementioned patient population. The trial ran from 28 April 2013 (the date when the first subject signed informed consent) to 30 June 2021 (the date of the last observation recorded as part of the database for primary analysis). The patients discontinued all study treatment once they reach the PD stage. After the first line of treatment, some patients initiated subsequent anti-cancer treatment. Subsequent anti-MCL treatment includes systemic therapy, radiotherapy and surgery. The most common type of anti-cancer treatment received was systemic antineoplastic therapy, with the most common classes of agents being monoclonal antibodies, nitrogen mustard analogues and protein

kinase inhibitors (12.3%, 11.9% and 3.8% in the ibrutinib+BR treatment group and 19.8%, 16.8% and 18.3% in the placebo+BR treatment group, respectively). Subsequent BTK inhibitors (including ibrutinib) were received by 11 (4.2%) subjects in the ibrutinib+BR treatment group and by 52 (19.8%) subjects in the placebo+BR treatment group.

The main differences between the populations of TRIANGLE and SHINE from which the utilities are derived are: 1) The TRIANGLE population is younger than the SHINE population (median age 57 vs. 71 years in SHINE), 2) the population for TRIANGLE is transplant-eligible while the population for SHINE is ineligible for ASCT, and 3) the primary end point is PFS in SHINE and FFS in TRIANGLE. For more details, see Appendix A.

To address the differences in the two trials, SHINE data were used with an applied utility decrement in the cycle where transplant occurs to account for the impact of the transplant. As for the age difference, FFS utilities were adjusted using a utility multiplier derived from the Danish general population utility. However, the FFS utility from the SHINE trial might exceed the corresponding age adjusted general population utility in the Danish population, and the effect will persist even after adjusted to the younger TRIANGLE trial population. Finally, FFS is a more stringent measure of patients' disease progression (see section 6), which will likely result in a higher health-state utility than the PFS. Therefore, using PFS state utility to proxy the FFS state utility is likely to be a conservative approach. A scenario analysis, in Section 12.2.1, using the PFS state categorisation for patients instead of FFS in the health economics model is explored.

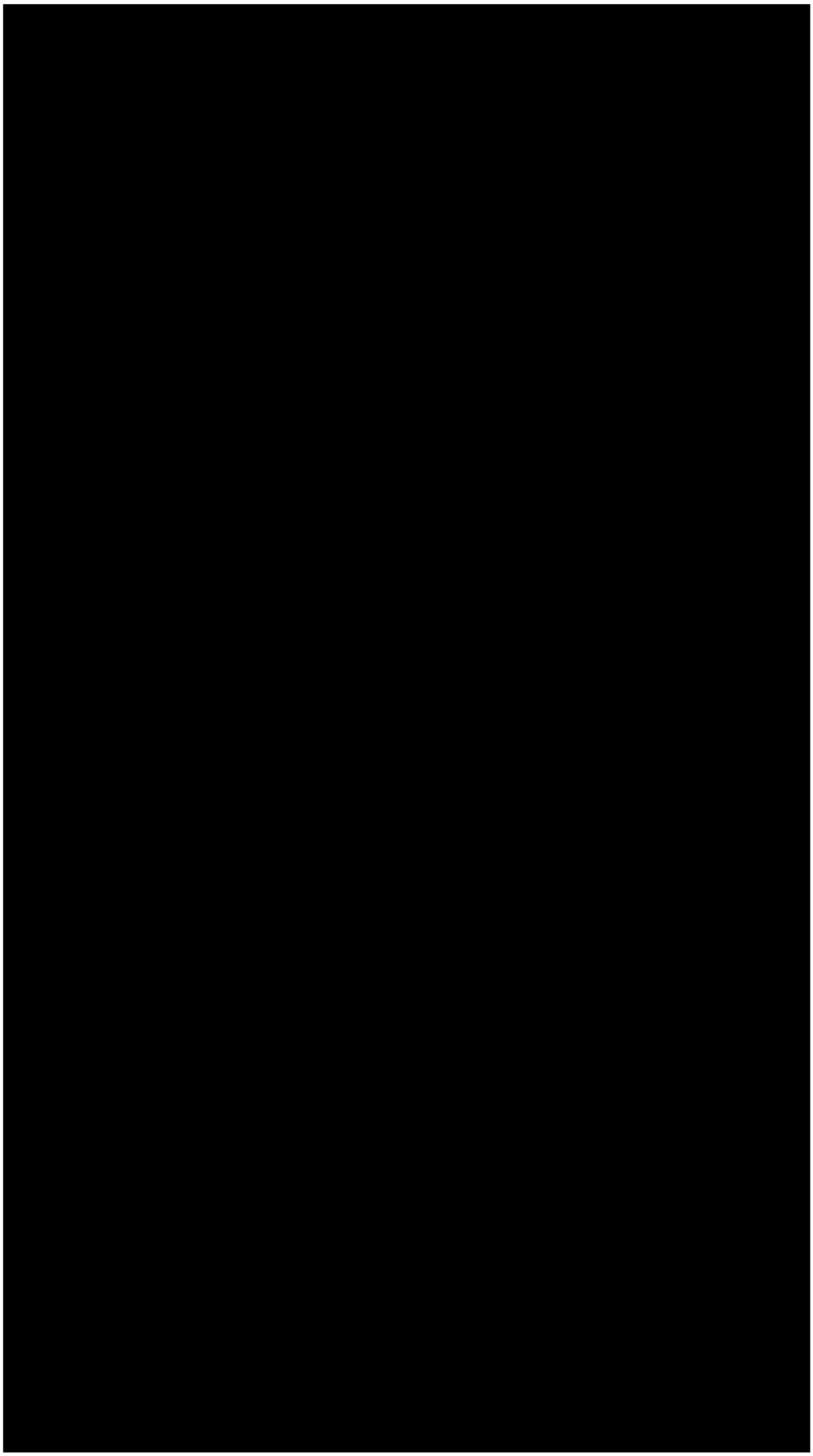
Utility values in the PD are derived from the RAY-3001 trial, which analysed patients with R/R MCL. RAY-3001 is a randomised, controlled, open-label, multicenter, Phase 3 study of approximately 280 eligible subjects to evaluate the efficacy and safety of ibrutinib when compared with temsirolimus in subjects with relapsed or refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen. The primary objective of the study is to evaluate whether treatment with ibrutinib compared with temsirolimus would result in prolongation of progression-free survival in subjects that are described above. The study ran from 3 December 2012 to 15 December 2016 (clinical data cutoff date for final analysis). At the final analysis, subsequent antineoplastic systemic therapy was received by 63 subjects (45.3%) in the ibrutinib arm and 100 subjects (70.9%) in the temsirolimus arm. As observed at primary analysis, subsequent therapy use was generally lower for the ibrutinib arm compared with the temsirolimus arm. Ibrutinib was the most common subsequent therapy in the temsirolimus arm, received by 55 subjects (39.0%) at the final analysis compared with 32 subjects (22.7%) at the primary analysis; at final analysis 1 subject (0.7%) in the ibrutinib group received retreatment with ibrutinib after stopping treatment with ibrutinib for reasons not related to PD. In the ibrutinib arm, 7 subjects received subsequent treatment with temsirolimus. The most common other subsequent systemic antineoplastic therapies for both treatment arms were the same as those reported at primary analysis and included: rituximab (24.5% of subjects in the ibrutinib arm and 28.4% of subjects in the temsirolimus arm), bendamustine (17.3% and 18.4%, respectively), cytarabine (12.2% and 14.2%, respectively), and cyclophosphamide (11.5% and 16.3%, respectively). Stem cell transplants were received as subsequent therapy by 2 subjects (1.4%) in the ibrutinib arm and 4 (2.8%) subjects in the temsirolimus arm.

The main difference between the populations in RAY-3001 and TRIANGLE is the age (67 in RAY-3001 and 57 in TRIANGLE). This is addressed by using the utility multiplier derived from the Danish general population utility.

Two trials were used to inform utility values due to differences in data availability. SHINE did not collect HRQoL data after progression, as patients discontinued treatment at the PD stage, and could therefore only inform the pre-progression health state. In contrast, RAY-3001 included HRQoL data after relapse, making it suitable for informing the PD state. However, as a second-line trial, RAY-3001 does not provide data for the pre-progression health state relevant to first-line treatment.

### 10.3.2 Data collection

In the SHINE trial, EQ-5D-5L assessments were administered at baseline prior to the first dose of study treatment, on Day 1 of the first six cycles, then every 12 weeks during the first year, and subsequently every 16 weeks. To avoid bias, questionnaires were completed prior to any procedures or physician interactions. In the posttreatment follow-up phase, EQ-5D-5L data were collected every 16 weeks, for up to three assessments following disease progression, until death or study end. Subjects unable to complete the questionnaire were documented with the reason. In the RAY trial, EQ-5D assessments began at Cycle 2 and demonstrated a durable improvement in scores, which was maintained throughout the treatment phase. The summary statistics are presented in Table 32 and Table 33.



Abbreviations: HRQoL, health related quality of life.

**Table 33 Pattern of missing data and completion (RAY) Intent-to-Treat Analysis Set**

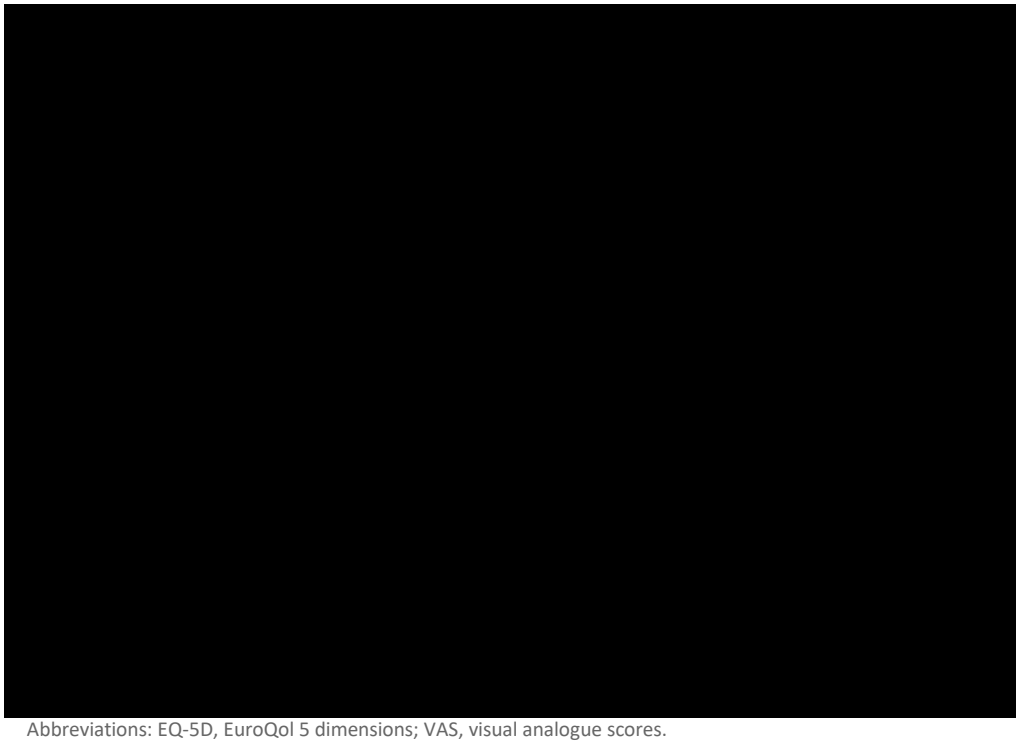
| Time point | HRQoL population N | Missing N (%) | Expected to complete N | Completion N (%) |
|---|---|---|---|---|
| | Number of patients at randomisation | Number of patients for whom data is missing (% of patients at randomisation) | Number of patients "at risk" at time point X | Number of patients who completed (% of patients expected to complete) |
| **Baseline** | 139 | 12 (8.6) | 139 | 127 (91.4) |
| **Cycle 2** | 139 | 16 (12.3) | 130 | 114 (87.7) |
| **Cycle 3** | 139 | 8 (6.3) | 126 | 118 (93.7) |
| **Cycle 4** | 139 | 11 (9.3) | 118 | 107 (90.7) |
| **Cycle 5** | 139 | 9 (7.8) | 115 | 106 (92.2) |
| **Cycle 6** | 139 | 7 (6.3) | 111 | 104 (93.7) |
| **Cycle 7** | 139 | 7 (6.4) | 110 | 103 (93.6) |
| **Cycle 8** | 139 | 8 (7.7) | 104 | 96 (92.3) |
| **Cycle 11** | 139 | 6 (6.2) | 97 | 91 (93.8) |
| **Cycle 14** | 139 | 13 (14.8) | 88 | 75 (85.2) |
| **Cycle 17** | 139 | 8 (9.9) | 81 | 73 (90.1) |
| **Cycle 20** | 139 | 4 (5.6) | 72 | 68 (94.4) |
| **Cycle 28** | 139 | 25 (52.1) | 48 | 23 (47.9) |
| **Cycle 36** | 139 | 3 (30.0) | 10 | 7 (70.0) |

Abbreviations: HRQoL, health related quality of life.

### 10.3.3 HRQoL Results

The results of the EQ-5D-5L assessment from the RAY trial are presented in Figure 15 Patients treated with ibrutinib reported improvements over time in the visual analog scale (VAS) of the EQ-5D-5L, while patients treated with temsirolimus reported a worsening of QoL on the VAS at all but 2 time points (cycle 20, cycle 28)82.

The results of the EQ-5D-5L assessment from the SHINE trial is presented in **Figure** 16. Change from baseline in EQ-ED-5L scores were similar for patients treated with ibrutinib + bendamustine and rituximab (BR) compared to patients only treated with BR.



Abbreviations: EQ-5D, EuroQol 5 dimensions; VAS, visual analogue scores.

### 10.3.4 HSUV and disutility results

As described in section 9.1, the model includes all grade ≥ 3 treatment-emergent AEs experienced by at least 5% of patients in the safety population in either the ibrutinib arm

or the ASCT arm. It was assumed that minor AEs that affected less than 5% of patients would have a negligible impact on QALYs and costs, and that all relevant adverse events are captured. The model also includes sepsis and increased gamma-glutamyl transferase in the AEs, given the severe nature of the adverse events.

AE-related utility decrements and durations were informed by literature (Table 34). The QALY losses associated with AEs were calculated by dividing the utility loss by the numbers of days in a year, then multiplied by the duration of the adverse event to get the QALYs lost per event. They were then multiplied by the proportion of patients experiencing the adverse events to get the aggregated disutility due to adverse events.

**Table 34 Overview of literature-based health state utility values**

| Adverse event | Duration in days | Source duration | Utility | Source utility |
|---|---|---|---|---|
| Neutropaenia | 15.09 | NICE TA 891[74] | -0.16 | NICE TA 891[74] |
| Anaemia | 23.21 | NICE TA 891[74] | -0.09 | NICE TA 891[74] |
| Thrombocytopaenia | 23.21 | NICE TA 891[74] | -0.11 | NICE TA 891[74] |
| Febrile neutropaenia | 15.09 | Assumed to be the same as Neutropaenia | -0.16 | Assumed to be the same as Neutropaenia |
| Leukopaenia | 15.09 | Assumed to be the same as Neutropaenia | -0.16 | Assumed to be the same as Neutropaenia |
| Platelet count decreased | 23.21 | Assumed to be the same as Thrombocytopaenia | -0.11 | Assumed to be the same as Thrombocytopaenia |
| Neutrophil count decreased | 15.09 | Assumed to be the same as Neutropaenia | -0.16 | Assumed to be the same as Neutropaenia |
| White blood cell count decreased | 15.09 | Assumed to be the same as Neutropaenia | -0.16 | Assumed to be the same as Neutropaenia |
| Lymphocyte count decreased | 15.09 | Assumed to be the same as Neutropaenia | -0.16 | Assumed to be the same as Neutropaenia |

| Adverse event | Duration in days | Source duration | Utility | Source utility |
|---|---|---|---|---|
| Gamma-glutamyltransferase increased | 15.09 | Assumed to be the same as Neutropaenia | -0.16 | Assumed to be the same as Neutropaenia |
| Pneumonia | 18.21 | NICE TA 891[74] | -0.20 | Tolley K et al[75] |
| Sepsis | 14.00 | Duration is derived via an assumption | -0.22 | NICE TA891; Disutility used for infection |
| Stomatitis | 14.00 | No data, assumed the same as the AE with the highest decrement (infection) | -0.22 | No data, assumed the same as the AE with the highest decrement (infection) |
| Nausea | 14.00 | No data, assumed the same as the AE with the highest decrement (infection) | -0.22 | No data, assumed the same as the AE with the highest decrement (infection) |
| Diarrhoea | 3.00 | NICE TA891[74] | -0.20 | NICE TA891[74] |
| Mucosal inflammation | 14.00 | No data, assumed the same as the AE with the highest decrement (infection) | -0.22 | No data, assumed the same as the AE with the highest decrement (infection) |
| Hypokalaemia | 15.09 | Assumed to be the same as Neutropenia | -0.16 | Assumed to be the same as Neutropenia |

Abbreviations: NICE, National Institute for Health and Care Excellence.

HSUVs applied in the cost-effectiveness model for the health states FFS and PD are based on EQ-5D-5L data from the SHINE and RAY3001 trials. The base-case analysis uses HSUVs valued with Danish tariffs, following the methodology described by Jensen et al[82]. The values for FFS and PD are estimated using data from the overall population in the TRIANGLE trial, with adjustments for age applied in line with DMC's guidance and source: "*Appendiks: Aldersjustering for sundhedsrelateret livskvalitet*"[83].

Utility values for patients entering the model in FFS are based on mean estimates from a mixed model for repeated measures fitted to the ibrutinib arm of SHINE, as utilities were

not collected in TRIANGLE. The subjects were asked to fill out the EQ-5D-5L questionnaire multiple times under the trial (see compliance rates in Table 32). The data was then collected and fit into the regression. The values were then adjusted according to the starting age of the TRIANGLE cohort. Utility values in the PD health states are derived from the RAY-3001 TRIAL, which analysed patients with R/R MCL. The patient utility is adjusted using a multiplier derived from the Danish utility related to age in the general population.

Table 35 presents the HSUVs used in the model along with disutility decrements related to treatment administrations and AEs, derived from published sources.

**Table 35 Overview of literature-based health state utility values [and disutilities]**

| | Results [SE] | Instrument | Tariff (value set) used | Comments |
|---|---|---|---|---|
| **HSUVs** | | | | |
| FFS | 0.887 [0.033] | EQ-5D-5L | DK | Estimated based on mean utility estimated from ibrutinib arm data in the SHINE trial, derived from a mixed model (MMRM)[71] |
| PD | 0.838 [0.010] | EQ-5D-5L | DK | Estimated based on mean utility estimated from ibrutinib arm data in the RAY3001 trial derived from a mixed model (MMRM)[72] |
| **Disutilities** | | | | |
| Utility decrement due to IV treatment | -0.040 [0.008] | EQ-5D-5L | UK | NICE TA343[73] |
| Utility decrement due to DRG: inpatient R-DHAP treatment | -0.280 [0.056] | EQ-5D-5L | UK | Assumed to be the same disutility as IV administration (there are 7 IV administrations in a R-DHAP cycle) |
| Utility decrement due to DRG: Inpatient High-dose chemotherapy treatment | -0.160 [0.032] | EQ-5D-5L | UK | Assumed to be the same disutility as IV administration (there are 4 IV administrations in a high-dose chemotherapy cycle) |
| Utility decrement due to ASCT | 0.00 [0.00] | EQ-5D-5L | UK | Assumption |

Abbreviations: MMRM, mixed model for repeated measures; NICE, National Institute for Health and Care Excellence; EQ-5D, EuroQol 5 Dimensions; TA, technical appraisal; HSUV, health state utility value; FFS, failure free survival; PD, progressed disease; ASCT, autologous stem cell transplant; R-DHAP, Rituximab + Dexamethasone, High-dose Ara-C (cytarabine), and Platinum (cisplatin); IV, introveneous.

# 11. Resource use and associated costs

## 11.1 Medicines - intervention and comparator

The dosing regimens for each first-line (1L) treatment strategy are based on the TRIANGLE trial protocol. The treatment strategy for Arm A (comparator) consists of four sequential phases: 1) induction phase in which R-CHOP and R-DHAP are alternatively administered every 21 days; 2) conditioning phase which involves stem-cell apheresis and high-dose chemotherapy to prepare the patients for transplant; 3) transplant phase where patients undergo the ASCT procedure, and 4) maintenance phase where patients receive ibrutinib maintenance or rituximab maintenance for a fixed duration (maximum 24 months). For Arm I (intervention), the conditioning phase and transplant phase are not applicable.

Medicines used in the model are presented in Table 36. The packages used in the model are those with the lowest price per unit. The dosing of some IV treatments is dependent on a patient's body surface area (BSA). The BSA was derived from the TRIANGLE trial and set at 1.98 $m^2$. Vial sharing was not considered in the base case. In the base case, the drug cost of IV drugs will be counted on a per vial basis. Oral wastage is also included. The cost is incurred for the whole dose (for example, 560 mg for ibrutinib), rounding up to match the nearest package.

**Table 36 Medicines used in the model**

| Medicine | Dose | Relative dose intensity | Frequency | Vial sharing |
|---|---|---|---|---|
| **Ibrutinib arm:** **ibrutinib** | Ibrutinib: 560 mg | 95.3% | Every day on days 1-19 | No |
| **Ibrutinib arm:** **R-CHOP** | IV rituximab: 375 mg/$m^2$ | 100% | On day 0 or 1 | No |
| | Cyclophosphamide: 750 mg/$m^2$ | 100% | On day 1 | No |
| | IV vincristine 1.4 mg/$m^2$ | 100% | On day 1 | No |
| | Oral prednisone 100mg | 100% | On days 1-5 | No |
| **Ibrutinib arm:** **R-DHAP** | IV rituximab: 375 mg/$m^2$ | 100% | On day 0 or 1 | No |
| | IV or oral dexamethasone: 40 mg | 100% | On days 1-4 | No |

| Medicine | Dose | Relative dose intensity | Frequency | Vial sharing |
|---|---|---|---|---|
| | IV cytarabine: 2×2g/m² | 100% | Twice on day 2 | No |
| | IV cisplatin: 100 mg/m² | 100% | 100mg/m² over 24 h on day 1 | No |
| **Ibrutinib arm: maintenance** | Rituximab: 375 mg/m² | 106% | Once every other month for three years | No |
| | Ibrutinib: 560 mg | 95.3% | Daily for two years | No |
| **ASCT arm: R-CHOP** | Same as the ibrutinib arm | Same as the ibrutinib arm | Same as the ibrutinib arm | No |
| **ASCT arm: R-DHAP** | Same as the ibrutinib arm | Same as the ibrutinib arm | Same as the ibrutinib arm | No |
| **ASCT arm: Conditioning** | BCNU: 300 mg/m² | 100% | On day -7 | No |
| | Etoposide: 2×100 mg/m² | 100% | Every day from day -6 to day -3 | No |
| | Cytarabine: 2×200 mg/m² | 100% | Every day from day -6 to day -3 | No |
| | Melphalan: 140mg/m² | 100% | On day -2 | No |
| **ASCT arm: maintenance** | Rituximab: 375mg/m² | 100% | Once every other month for three years | No |

Abbreviations: ASCT, autologous stem cell transplant; R-CHOP, Rituximab + Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone; R-DHAP, Rituximab + Dexamethasone, High-dose Ara-C (cytarabine), and Platinum (cisplatin); BCNU, Carmustine.

Besides medicine costs, the costs of two procedures are also taken into account: stem-cell apheresis and the transplant itself. The stem-cell apheresis costs are taken from the DRG catalogue. However, the DRG cost for the transplant procedure itself is thought to be underestimated as it leaves out several important components, particularly, the time and medical resource use. Therefore, the cost used is from a micro-costing study conducted by J&J [51]. In a scenario analysis, the cost from the DRG catalogue is used. The costs are summarised in Table 37.

**Table 37 Procedure costs in the ASCT arm**

| Procedure | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|
| **Stem-cell apheresis** | 25,006 | 26MP24 | DRG 2025 [77] |
| **Transplant** | [redacted] | N/A | Micro-costing study[51] |

## 11.2 Medicines– co-administration

Not applicable.

## 11.3 Administration costs

Administration costs were estimated using the Danish Health Data Authority's website Interactive DRG. No administration cost was applied for orally administered medicines.

**Table 38 Administration costs used in the model**

| Administration type | Frequency | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **IV administration cost** | According to the schedule described in Section 11.1 | 2,136 | 17MA98 | DRG 2025 [77] |
| **Inpatient R-DHAP per episode administration cost** | According to the schedule described in Section 11.1 | 2,136 | 17MA98 | DRG 2025 |
| **Inpatient Conditioning per episode administration cost** | According to the schedule described in Section 11.1 | 2,136 | 17MA98 | DRG 2025 |
| **Inpatient Initial Rituximab Maintenance per episode administration cost** | According to the schedule described in Section 11.1 | 2,136 | 17MA98 | DRG 2025 |

Abbreviations: IV, intraveneous; SC, subcutaneous; R-DHAP, Rituximab + Dexamethasone, High-dose Ara-C (cytarabine), and Platinum (cisplatin).

## 11.4 Disease management costs

The disease management costs are summarised in Table 39. The frequencies were broken down by the disease stages and validated by Danish clinical experts[33]. The DRG codes were attained using the interactive DRG. When no exact match is found in interactive DRG, the closest approximation is obtained from the DRG codes.

**Table 39 Disease management costs used in the model**

| Activity | Frequency | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **Full blood count** | Induction: 10<br>Consolidation: 2<br>Maintenance: 20 (Arm A), 18 (Arm I)<br>PD: 1 | 330 | N/A | Rigshospitalets Labportal 2024[84] NPU02319, NPU01961, NPU02593, NPU19748, NPU19674, NPU03688, NPU02725, NPU03568, NPU08694, NPU04998 |
| **Biopsy** | Induction: 2<br>PD: 1 | 6,027 | 05PR02: Nålebiopsi på kar el. lymfesystem | DRG 2025[77] |
| **Haematologist visit** | Induction: 8<br>Consolidation: 3<br>Maintenance: 18<br>PD: 1 | 1,066 | N/A | Værdisætning af enhedsomkostninger - Ledende overlæger/professorer[79] |
| **CT Scan** | Maintenance: 3 | 2,701 | 30PR06: CT-scanning, kompliceret | DRG 2025[77] |
| **PET Scan** | Induction: 2<br>Consolidation: 1<br>PD: 1 | 3,737 | 36PR07: Klinisk fysiologi/nuklearmedicin grp. G | DRG 2025[77] |
| **Infection Prophylaxis** | Induction: 1<br>Consolidation: 1<br>Maintenance: 1<br>PD: 1 | 2,136 | 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år | DRG 2025[77] |

Abbreviations: CT, computed tomography; PET, positron emission tomography; PD, progressed disease.

In addition, there is a one-time disease progression cost when patients fail/progress 1L treatment. The frequency and percentages of patients requiring each activity are summarised in Table 40. The frequencies were validated by Danish clinical experts[33].

**Table 40 Disease failure/Progression cost**

| Activity | Frequency | Unit cost [DKK] | DRG code | Reference | Percentage of patients needing it |
|---|---|---|---|---|---|
| **Full blood count** | 1 | 330 | N/A | Rigshospitalets Labportal 2024 NPU02319, NPU01961, NPU02593, NPU19748, NPU19674, NPU03688, NPU02725, NPU03568, NPU08694, NPU04998 | 100% |
| **Imaging** | 1 | 2,603 | 30PR02: MR-scanning, kompliceret | DRG 2025 | 100% |
| **Biopsy** | 1 | 6,207 | 05PR02: Nålebiopsi på kar el. lymfesystem | DRG 2025 | 50% |

## 11.5 Costs associated with management of adverse events

The adverse events included in the model are presented in Table 41. The frequencies of the adverse events included as input in the model are presented in Section 9. All unit costs were applied as one-off costs at the beginning of the time horizon. The unit costs are sourced from the Danish Health Data Authority's website Interactive DRG [78].

**Table 41 Cost associated with management of adverse events**

| | DRG code | Unit cost/DRG tariff [DKK] |
|---|---|---|
| **Neutropenia** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Anaemia** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Thrombocytopenia** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |

| | DRG code | Unit cost/DRG tariff [DKK] |
|---|---|---|
| **Febrile neutropenia** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Leukopenia** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Platelet count decreased** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Neutrophil count decreased** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **White blood cell count decreased** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Gamma-glutamyltransferase increased** | 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DD649<br>Secondary diagnosis: DC679M | 2,208 |
| **Pneumonia** | 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DJ129 | 1,330 |
| **Sepsis** | 18MA98: MDC18 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DA419<br>Secondary diagnosis: DA419C | 2,781 |
| **Stomatitis** | 03MA98: MDC03 1-dagsgruppe, pat. mindst 7 år<br>Action diagnosis: DK121<br>Secondary diagnosis: DK121B | 2,060 |
| **Nausea** | 70OP99: Ikke gruppérbar pga. manglende oplysninger<br>Action diagnosis: BUBT1 | 1,175 |
| **Diarrhoea** | 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.<br>Action diagnosis: DK529B<br>Secondary diagnosis: DK529B1 | 4,977 |
| **Mucosal inflammation** | 03MA98: MDC03 1-dagsgruppe, pat.mindst 7 år<br>Action diagnosis: DB088<br>Secondary diagnosis: DB088M | 2,060 |

| | DRG code | Unit cost/DRG tariff [DKK] |
|---|---|---|
| **Hypokalaemia** | 10MA98: 10MA98 MDC10 1-dagsgruppe, pat.mindst 7 år<br>Action diagnosis: DE835<br>Secondary diagnosis: DE835D | 1,992 |

In addition to adverse events, the model accounts for a fraction of patients experiencing ICU events. ICU incidence is treatment specific and is incurred as a one-off cost. The ICU costs are summarised in Table 42. The percentage and frequency of the ICU use are validated by the Danish clinical experts [33] .

**Table 42 ICU costs**

| Treatment arms | Frequency | Unit cost [DKK] | DRG code | Reference | Percentage of patients needing it | Duration (days) |
|---|---|---|---|---|---|---|
| **Ibrutinib** | One-off | 3,682 | 30SP04: Sammedagspakke: UL, flere procedurer, meget kompl. + kompl. | DRG 2025 [77] | 2% | 5 [33] |
| **ASCT** | One-off | 3,682 | 30SP04: Sammedagspakke: UL, flere procedurer, meget kompl. + kompl. | DRG 2025 | 5% | 5 |

Abbreviations: ASCT, autologous stem cell transplant.

## 11.6 Subsequent treatment costs

The dosing regimens for subsequent treatments are presented in Table 43. For treat-to-progression therapies, patients were assumed to remain in the progressed disease stage for as long as they were alive. For fixed-duration regimens such as BR and R-BAC, patients were assumed to be on treatment as long as they were in the progress disease stage, treatment costs were capped by the maximum treatment duration of six 28-day cycles.

**Table 43 Medicines of subsequent treatments**

| Medicine | Dose | Relative dose intensity | Frequency | Vial sharing |
|---|---|---|---|---|
| **Ibrutinib** | 560 mg | 100% | Daily until death | No |
| **Brexu-cel** | N/A | N/A | N/A | No |

The percentages of subsequent treatment (detailed in Table 44) are based on input from Nordic key opinion leaders and assumptions.

**Table 44 Percentages of the subsequent treatment in two arms**

| | Ibrutinib arm | ASCT arm |
|---|---|---|
| **Subsequent treatments** | | |
| **Ibrutinib** | 66.7% | 66.7% |
| **Brexu-cel** | 33.3% | 33.3% |

Abbreviations: BR, bendamustine + rituximab; R-BAC, rituximab + bendamustine + cytarabine

Brexu-cel is currently not available in Denmark. However, a positive decision is expected from Medicinrådet. The clinical experts also agree that it will be widely used once it is approved [33]. The cost of Brexu-cel is calculated using a micro-costing approach in a UK setting (for details see model, "CAR-T Cost calculation" sheet), and the values were converted to Danish kroner using the exchange rate from Danmarks nationalbank [85]. The cost comes to 3,149,221 kr., which is in line with the estimates from Israeli Hospitals for Brexu-cel in Europe [86].

## 11.7 Patient costs

Transportation (DKK 140.48 per visit) and patient costs (DKK 188.64 per hour) are included in the economic analysis as indicated in the DMC guidelines. Unit cost sourced from the DMC's catalogue of unit costs[79]. The time associated with each visit and transportation are present in Table 45.

**Table 45 Patient costs used in the model**

| Activity | Time spent [hours] |
|---|---|
| **Hours spent per healthcare visit** | 3 |
| **Hours spent per inpatient visit** | 24 |
| **Hours spent in transportation per visit** | 1 |

## 11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

# 12. Results

## 12.1 Base case overview

**Table 46 Base case overview**

| Feature | Description |
|---|---|
| Comparator | ASCT |
| Type of model | Partitioned Survival Model |
| Time horizon | 43 years (lifetime horizon) |
| Treatment line | 1st line. Subsequent treatment lines included. |
| Measurement and valuation of health effects | Health-related quality of life measured with EQ-5D-5L in RAY and SHINE trials [71] [72]. Danish population weights were used to estimate health-state utility values |
| Costs included | Medicine costs<br>Hospital costs<br>Costs of adverse events<br>Subsequent treatment events<br>Patient costs |
| Dosage of medicine | Fixed dose |
| Average time on treatment | Ibrutinib: 33.41 months<br>ASCT: 31.08 months |
| Parametric function for FFS | Ibrutinib: exponential<br>ASCT: Weibull |
| Parametric function for OS | Ibrutinib: exponential<br>Comparator: Weibull |
| Inclusion of waste | Yes |
| Average time in model health state | |
| FFS | Ibrutinib: 92.30 months |
| | ASCT: 82.76 months |
| PD | Ibrutinib: 83.96 months |

| Feature | Description |
|---|---|
| | ASCT: 19.27 months |

Abbreviations: ASCT, autologous stem cell transplant; EQ-5D, EuroQol 5 Dimensions; PD, progressed disease; FFS, failure free survival.

### 12.1.1 Base case results

**Table 47 Base case results, discounted estimates**

| | Ibrutinib | ASCT | Difference |
|---|---|---|---|
| Medicine costs (DKK) | [redacted] | [redacted] | [redacted] |
| Medicine costs – co-administration (DKK) | [redacted] | [redacted] | [redacted] |
| Administration (DKK) | [redacted] | [redacted] | [redacted] |
| Disease management costs (DKK) | [redacted] | [redacted] | [redacted] |
| Adverse event costs (DKK) | [redacted] | [redacted] | [redacted] |
| Subsequent treatment costs (DKK) | [redacted] | [redacted] | [redacted] |
| Patient costs (DKK) | [redacted] | [redacted] | [redacted] |
| **Total costs (DKK)** | [redacted] | [redacted] | [redacted] |
| Life years gained (FFS) | 10.87 | 9.49 | 1.38 |
| Life years gained (PD) | 3.08 | 1.67 | 1.41 |
| **Total life years** | **13.95** | **11.16** | **2.79** |
| QALYs (FFS) | 11.94 | 9.58 | 2.36 |
| QALYs (PD) | 2.51 | 1.38 | 1.13 |
| QALYs (adverse reactions) | -0.10 | -0.12 | 0.02 |
| **Total QALYs** | | | |
| **Incremental costs per life year gained** | | **DKK** [redacted] | |
| **Incremental cost per QALY gained (ICER)** | | **DKK** [redacted] | |

Abbreviations: QALY, quality-adjusted life years; PD, progressed disease; FFS, failure free survival.

## 12.2 Sensitivity analyses

### 12.2.1 Deterministic sensitivity analyses

Table 48 presents the 10 most influential factors in the one-way deterministic sensitivity analysis. As shown in the chart, the most influential factors are the parametrisations of the clinical data. The price of ibrutinib also plays a significant role. The tornado chart is presented in Figure 17.

**Table 48 One-way sensitivity analyses results**

| | Change | Reason / Rational / Source | Incremental cost (DKK) | Incremental benefit (QALYs) | ICER (DKK/QALY) |
|---|---|---|---|---|---|
| **Base case** | | | [redacted] | [redacted] | [redacted] |
| **FFS – Group A – Weibull scale** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **FFS – Group A – Weibull shape** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **FFS – Group I – Weibull scale** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **Unit Cost - Ibrutinib** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **OS -Group A – Weibull shape** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **Utility – FFS** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **Transplant cost** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |

| | Change | Reason / Rational / Source | Incremental cost (DKK) | Incremental benefit (QALYs) | ICER (DKK/QALY) |
|---|---|---|---|---|---|
| **OS – Group I – Weibull scale** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **OS – Group A – Weibull scale** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |
| **Cost for conditioning** | +15% | Convention | [redacted] | [redacted] | [redacted] |
| | -15% | Convention | [redacted] | [redacted] | [redacted] |

Abbreviations: OS, overall survival; FFS, failure free survival.

**Figure 17 Tornado chart**

Abbreviations: ASCT, autologous stem cell transplant; R-CHOP, Rituximab + Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone; R-DHAP, Rituximab + Dexamethasone, High-dose Ara-C (cytarabine), and Platinum (cisplatin); FFS, BSA, body surface area; PF, progression free; BCNU, carmustine

### Scenario analysis

The results for the scenario analyses are presented in Table 49.

**Table 49 Scenario analyses**

| Scenario Name | Incremental Costs (DKK) | Incremental LYs | Incremental QALYs | ICER (DKK) | Difference to base case (DKK) |
|---|---|---|---|---|---|
| DRG transplant cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS: Weibull for I, exponential for A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS: log-normal for both I and A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS: generalised gamma for both I and A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FFS: Weibull for I, exponential for A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FFS: log-normal for both I and A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FFS: log-logistic for both I and A | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS instead of FFS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

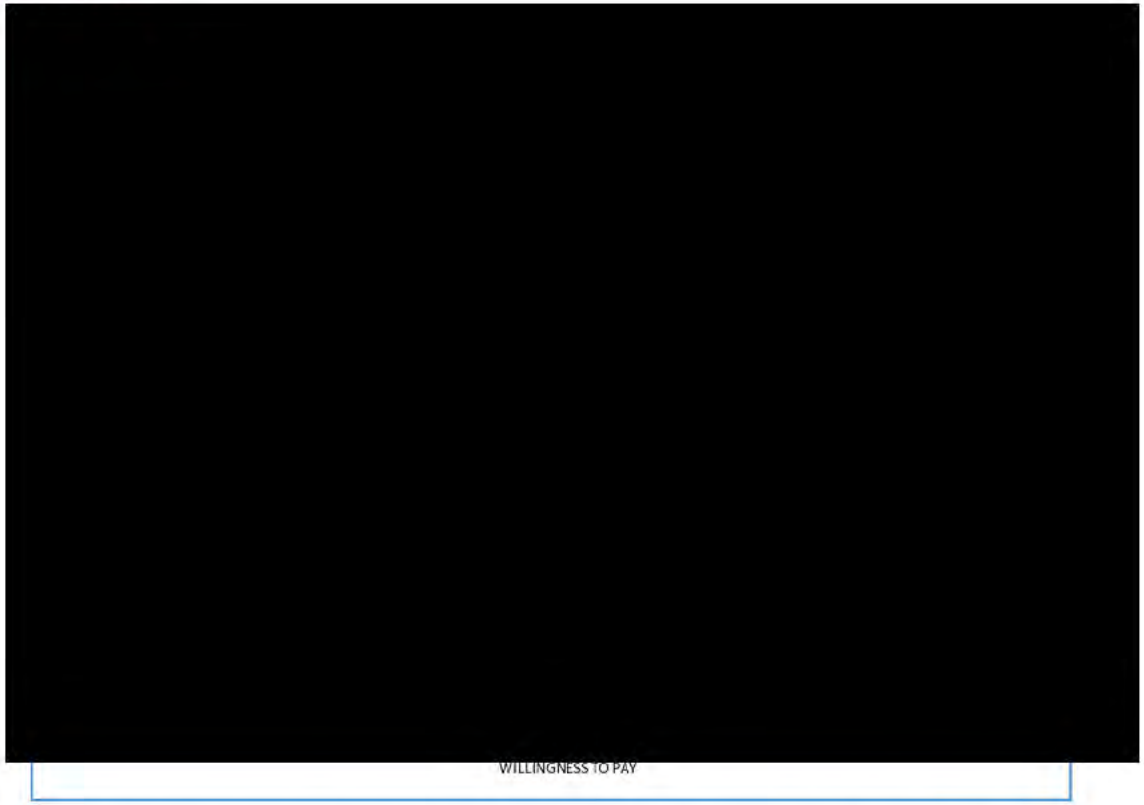
Abbreviations: FFS, failure free survival; OS, overall survival.

### 12.2.2 Probabilistic sensitivity analyses

1000 iterations of probability sensitivity analyses were run. The scatter plot, the cost effectiveness acceptability curves (CEAC) and ICER convergence curve are presented in Figure 18, Figure 19 and Figure 20. The maximum willingness-to-pay threshold for the CEAC is 800,000 DKK. As shown in Figure 18, the majority of the ICER simulations fall tightly in the northeast quadrant of the graph, and by visual inspection, the centre of the cloud also lies in the same quadrant.

**Figure 18 Scatter plot of the probability sensitivity analyses**

**Figure 19 Cost-effectiveness acceptability curves**




Abbreviations: R-CHOP, Rituximab + Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone; R-DHAP, Rituximab + Dexamethasone, High-dose Ara-C (cytarabine), and Platinum (cisplatin).

**Figure 20 Convergence plot of the estimated mean ICER**

Abbreviations: ICER, incremental cost-effectiveness ratio.

# 13. Budget impact analysis

## 13.1 Number of patients (including assumptions of market share)

The estimated number of patients that are eligible for ibrutinib is 45 and is steady throughout the next 5 years. The market share of ibrutinib is estimated to be starting at 80%, then 90% for the second year, then 100% for the next 3 years. These numbers have been validated by Danish clinical experts[33].

**Table 50 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| | | | **Recommendation** | | |
| **Ibrutinib** | 36 | 41 | 45 | 45 | 45 |
| **ASCT** | 9 | 5 | 0 | 0 | 0 |
| | | | **Non-recommendation** | | |
| **Ibrutinib** | 0 | 0 | 0 | 0 | 0 |
| **ASCT** | 45 | 45 | 45 | 45 | 45 |

## 13.2 Budget impact

**Table 51 Expected budget impact of recommending the medicine for the indication [DKK]**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| The medicine under consideration is recommended | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| The medicine under consideration is NOT recommended | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Budget impact of the recommendation** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

# 14. List of experts

[redacted]

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# Appendix A. Main characteristics of studies included

**Table 52 Main characteristics of studies included - TRIANGLE**

| Trial name: TRIANGLE | NCT number: NCT02858258 |
|---|---|
| **Objective** | To establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP+ibrutinib /R-DHAP followed by ASCT and ibrutinib maintenance (experimental arm A+I), and R-CHOP+ibrutinib /R-DHAP followed by ibrutinib maintenance (experimental arm I) as future standard based on the comparison of the investigator-assessed FFS. |
| **Publications – title, author, journal, year** | Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. 2024;403(10441):2293-2306. doi:10.1016/S0140-6736(24)00184-3 |
| **Study type and design** | An open-label, randomised, controlled phase 3 Study of Ibrutinib combined with immunochemotherapy with or without ASCT versus immunochemotherapy and ASCT in previously untreated patients with MCL |
| **Sample size (n)** | Total N = 870<br>Arm A = 288<br>Arm A+I = 292<br>Arm I = 290 |
| **Main inclusion criteria** | All patients must meet the following criteria:<br>• Histologically confirmed diagnosis of MCL according to WHO classification<br>• Suitable for high-dose treatment including high-dose Ara-C<br>• Stage II-IV (Ann Arbor)<br>• Age ≥ 18 years and ≤ 65 years<br>• Previously untreated MCL<br>• At least 1 measurable lesion; in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations. |

| Trial name: TRIANGLE | NCT number: NCT02858258 |
|---|---|
| | • ECOG/WHO performance status ≤ 2<br>• The following laboratory values at screening (unless related to MCL):<br>  ○ ANC ≥1000 cells/µL<br>  ○ Platelets ≥100,000 cells/µL<br>  ○ Transaminases (AST and ALT) ≤3 x ULN<br>  ○ Total bilirubin ≤2 x ULN unless due to known Morbus Meulengracht [Gilbert-Meulengracht-Syndrome])<br>  ○ Creatinine ≤2 mg/dL or calculated creatinine clearance ≥ 50 mL/min<br>• Written informed consent form according to ICH/EU GCP and national regulations<br>• Sexually active men and women of child-bearing potential must agree to use highly effective contraceptives (eg, condoms, implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or sterilised partner) while on study; this should be maintained for 90 days after the last dose of study drug. |
| **Main exclusion criteria** | Any potential subject who meets any of the following criteria will be excluded from participating in the study.<br>• Major surgery within 4 weeks prior to randomization.<br>• Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg phenprocoumon).<br>• History of stroke or intracranial haemorrhage within 6 months prior to randomization.<br>• Requires treatment with strong CYP3A4/5 inhibitors.<br>• Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.<br>• Vaccinated with live, attenuated vaccines within 4 weeks prior to randomisation.<br>• Known CNS involvement of MCL<br>• Clinically significant hypersensitivity (eg, anaphylactic or anaphylactoid reactions to the compound of ibrutinib itself or to the excipients in its formulation)<br>• Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies<br>• Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except prephase therapy according to trial protocol |

| Trial name: TRIANGLE | NCT number: NCT02858258 |
|---|---|
| | • Serious concomitant disease interfering with a regular therapy according to the study protocol:<br>  ○ Cardiac (Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below LLN)<br>  ○ Pulmonary (e.g. chronic lung disease with hypoxemia)<br>  ○ Endocrinological (e.g. severe, not sufficiently controlled diabetes mellitus)<br>  ○ Renal insufficiency (unless caused by the lymphoma): creatinine > 2x normal value and/or creatinine clearance < 50 ml/min)<br>  ○ Impairment of liver function (unless caused by the lymphoma): transaminases > 3x normal or bilirubin > 2,0 mg/dl unless due to Morbus Meulengracht (Gilbert-Meulengracht-Syndrome)<br>• Patients with unresolved hepatitis B or C infection or known HIV positive infection (mandatory test)<br>• Prior organ, bone marrow or peripheral blood stem cell transplantation<br>• Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer or in situ uterine cervix cancer<br>• Pregnancy or lactation<br>• Any psychological, familiar, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule<br>• Subjects not able to give consent<br>• Subjects without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial<br>• Participation in another clinical trial within 30 days before randomisation in this study. |
| **Intervention** | Experimental Arm A+I<br>Drug: R-CHOP/R-DHAP<br>• Drug: R-CHOP/DHAP Alternating 3x R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) / 3x R-DHAP (rituximab, dexamethasone, Ara-C, cisplatine, G-CSF)<br>Drug: Ibrutinib (Induction)<br>• Ibrutinib: only in cycle 1,3,5 on Day 1-19<br>Drug: ASCT conditioning |

| Trial name: TRIANGLE | NCT number: NCT02858258 |
|---|---|
| | • ASCT conditioning THAM or BEAM, stratified per site before trial activation at site<br>THAM (TBI (total body irradiation), Ara-C, Melphalan) or<br>BEAM (BCNU, Etoposide, Cytarabine, Melphalan)<br>Drug: Ibrutinib (Maintenance)<br>• Ibrutinib (Maintenance), daily 560 mg for 2 years<br><br>Experimental Arm I<br>Drug: R-CHOP/R-DHAP<br>• Drug: R-CHOP/DHAP Alternating 3x R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) / 3x R-DHAP (rituximab, dexamethasone, Ara-C, cisplatine, G-CSF)<br>Drug: Ibrutinib (Induction)<br>• Ibrutinib: only in cycle 1,3,5 on Day 1-19<br>Drug: Ibrutinib (Maintenance)<br>• Ibrutinib (Maintenance), daily 560 mg for 2 years |
| **Comparator(s)** | Standard Arm A<br>Drug: R-CHOP/R-DHAP<br>• Drug: R-CHOP/DHAP Alternating 3x R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) / 3x R-DHAP (rituximab, dexamethasone, Ara-C, cisplatine, G-CSF)<br>Drug: ASCT conditioning<br>• ASCT conditioning THAM or BEAM, stratified per site before trial activation at site<br>THAM (TBI (total body irradiation), Ara-C, Melphalan) or<br>BEAM (BCNU, Etoposide, Cytarabine, Melphalan) |
| **Follow-up time** | Median follow-up of 31 months (range: 30.1 to 33.0) |
| **Is the study used in the health economic model?** | Yes |
| **Primary, secondary and exploratory endpoints** | *Primary endpoint*<br>• FFS<br>*Secondary endpoints*<br>• OS |

| Trial name: TRIANGLE | NCT number: NCT02858258 |
|---|---|
| | • PFS<br>• ORR<br>**Other endpoints not included in this application:**<br>*Secondary endpoints*<br>• Number of participants with treatment-related adverse events as assessed by CTC Version 4.03<br>• Number of Adverse Events by CTC grade (Version 4.03) |
| **Method of analysis** | All efficacy analyses were intention-to-treat analyses. The Kaplan–Meier method was used to estimate rates of failure-free survival and overall survival. Hazard ratios were estimated with unstratified Cox proportional hazards regression. The proportional hazards assumption was assessed by looking for trends in the scaled Schoenfeld residuals |
| **Subgroup analyses** | The following pre-specified subgroup analyses of FFS were performed across all three arms:<br>• Sex<br>• MIPI risk group<br>• Ki-67 index<br>• Cytology of MCL<br>• p53 expression<br>• Rituximab maintenance |
| **Other relevant information** | N/A |

Abbreviations: ALT, alanine transaminase; ANC, absolute neutrophil count; ASCT, autologous stem-cell transplantation; AST, aspartate transaminase; BEAM, BCNU, Etoposide, Cytarabine, Melphalan; CHOP, cyclophosphamide, doxorubicine, vincristine, prednisone; CNS, central nervous system; DHAP, dexamethasone, Ara-C, cisplatine, G-CSF; ECOG, Eastern Cooperative Oncology Group; FFS, failure free survival; G-CSF, granulocyte colony-stimulating factor; LLN, lower limit of normal; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; ORR, overall response rate OS, overall survival; PFS, progression-free survival; R, rituximab; TBI, total body irradiation; THAM, TBI, Ara-C, Melphalan; ULN, upper limit of normal

# Appendix B. Efficacy results per study

**Results per study**

Results of the TRIANGLE trial is presented in Table 53, below. All results are based on the latest efficacy data cut.

**Table 53 Results per study – TRIANGLE (CCO May 9, 2024)**

| Results of TRIANGLE (NCT02858258) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | % CI | *P* value | | |
| Median FFS (54.9 months FAS) | Arm I | 268 | N/A | N/A | N/A | N/A | HR: 0.639 | 98.33%; 0.428–0.953 | 0.0068* | FFS is based on KM estimates uncorrected for the sequential design with selected survival probabilities with two-sided 95% CIs. The analysis was done using Cox regression with two-sided 95% CIs for HR | J&J [Data on file] (2024)[8] |
| | Arm A | 269 | N/A | | | | | | | | |
| Median OS (54.9 months FAS) | Arm I | 268 | N/A | N/A | N/A | N/A | HR: 0.522 | 95% CI; 0.341–0.799 | 0.0023* | OS is based on KM estimates uncorrected for the sequential design are calculated and selected survival probabilities with two-sided 95% CIs. The exploratory analysis was done using Cox regression with two-sided 95% CIs for HR. | J&J [Data on file] (2024)[8] |
| | Arm A | 269 | N/A | | | | | | | | |
| PFS (54.9 months FAS) | Arm I | 268 | N/A | N/A | N/A | N/A | HR: 0.633 | 98.33% CI; 0.424–0.946 | 0.0060* | PFS was analysed using the Kaplan-Meier method. Hazard ratios and 95% CIs. The | J&J [Data on file] (2024)[8] |
| | Arm A | 269 | N/A | | | | | | | | |

| Results of TRIANGLE (NCT02858258) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | % CI | *P* value | | |
| | | | | | | | | | | exploratory analysis was done using Cox regression with two-sided 95% CIs for HR. | |
| ORR (54.9 months FAS) | Arm I | 268 | 258 (96.3%) (N/A-N/A) | N/A | N/A | N/A | RR: 1.044 | 95% CI; 1.001–1.089 | 0.0627* | The ORR is the percentage of patients with CR or PR among those with evaluable response. The ORR and PR to CR conversion rates were compared using relative risk with their associated 2-sided 95% CIs using Fisher's exact test. Tests of these endpoints were considered independent from the primary outcome and each other. | J&J [Data on file] (2024)[8] |
| | Arm A | 269 | 248 (92.2%) (N/A-N/A) | | | | | | | | |

Abbreviations: ASCT, autologous stem cell transplantation; Arm A; ASCT; Arm I, ibrutinib without ASCT; CI, confidence interval; CR, complete response; FAS, full analysis set; FFS, failure-free survival; HR, hazard ratio; J&J, Janssen Research & Development; KM, Kaplan-Meier; N/A, not applicable/not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, relative risk.
* Two-sided p-value is from an unstratified log-rank test.

# Appendix C. Comparative analysis of efficacy

Not applicable.

# Appendix D. Extrapolation

## D.1 Extrapolation of overall survival

### D.1.1 Data input

**IMBRUVICA + R-CHOP**

OS was measured in the TRIANGLE trial, a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance therapy was used as a comparator.

**R-DHAP (or R-DHAOx) without IMBRUVICA (followed by IMBRUVICA monotherapy)**

OS was measured in the TRIANGLE trial, a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network.

**ASCT**

The relevant comparator for OS ASCT, induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance therapy.

**Population**

The target population of interest consisted of a total of 537 patients from the TRIANGLE trial.

A total of 33 deaths (12.3%) were reported in the ibrutinib arm, compared to 60 deaths (22.3%) in the ASCT arm. This difference represents a statistically significant and clinically meaningful improvement in OS for the ibrutinib arm. The Cox regression analysis yielded a HR of 0.522 (95% CI: 0.341–0.799; two-sided nominal p=0.0023), indicating a 47.8% reduction in the risk of death for patients receiving ibrutinib compared to those treated with ASCT.

While the median OS was not reached in either treatment arm, KM OS rate estimates at 54 months were 87.3% for the ibrutinib arm and 77.9% for the ASCT arm. Notably, an initial drop in the KM plot of OS for the ASCT arm was observed at approximately six months. This decline is likely attributable to the initiation of high-dose chemotherapy and autologous stem cell transplantation, reflecting the toxicity associated with high-dose chemotherapy.

The KM estimates for OS, comparing the ibrutinib and ASCT arms, are presented in Figure 21.

Figure 21. KM curves of OS (ibrutinib versus ASCT)

### D.1.2 Model

As described previously, standard parametric survival models were used to extrapolate OS. The following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Gamma
- Generalised gamma

### D.1.3 Proportional hazards

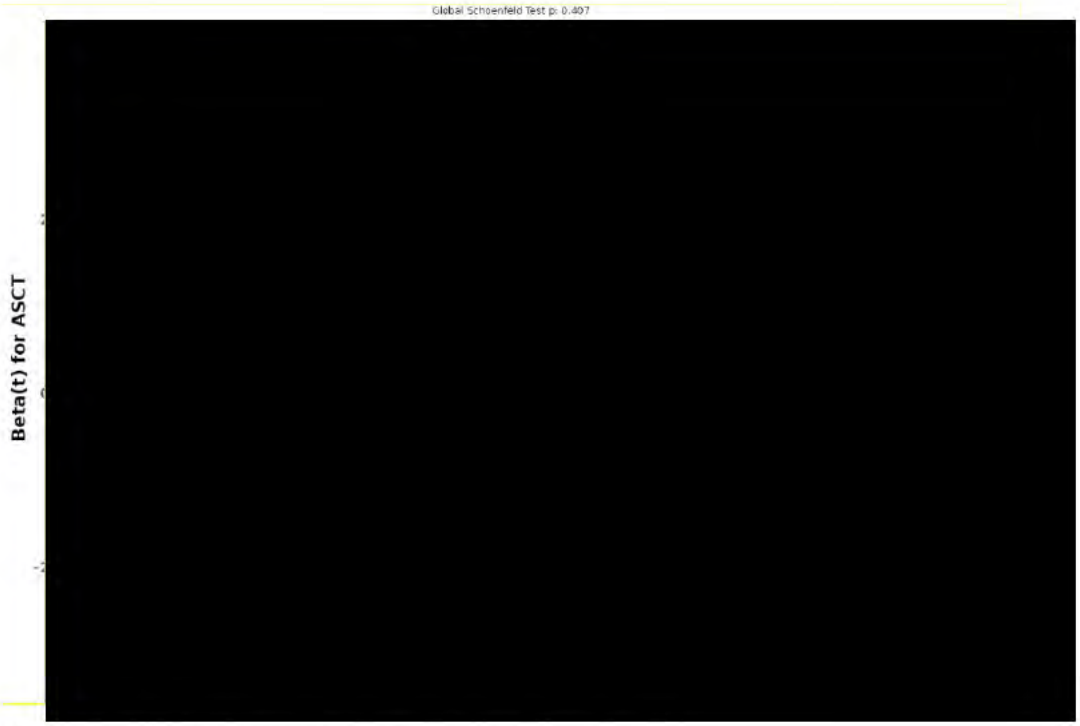
The proportional hazards (PH) assumption was visually assessed using the log-cumulative hazard plot. The parallel nature of the two curves—without convergence or divergence—throughout the time horizon supports the PH assumption. This finding was

further corroborated by the Schoenfeld residuals plot and the associated test, which yielded a non-significant p-value (p=[redacted].

Despite evidence suggesting a constant treatment effect over time, the approach of independent fits was ultimately deemed more appropriate. Independent fits allow for the application of the PH assumption while also providing additional flexibility.

Visual inspection revealed variability in the hazard within each treatment arm over time, as indicated by changing slopes in the hazard plots. A reduced slope over time suggests a decreasing risk as time progresses.

**Figure 22 Schoenfeld residuals plot for OS**




Abbreviations: ASCT, autologous stem cell transplantation; OS, overall survival.

**Figure 23 Log cumulative hazard for OS**

Abbreviations: ASCT, autologous stem cell transplantation; FAS, full analysis set; OS, overall survival.

### D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 54 below presents the re-scaled GoF statistics for OS in the ibrutinib and ASCT arms. For the ASCT arm, the generalized gamma model demonstrated the lowest AIC score, indicating the best fit according to this criterion. Notably, only one other model, the log-normal, had ΔAIC statistics ≤ 2, suggesting it also provides a good fit. Importantly, no model for this arm had an ΔAIC statistic > 10, indicating that all models fit reasonably well. [8]

When considering the BIC, the exponential model provided the best fit for the ASCT arm, followed by the log-normal model, with the generalised gamma model ranking third. This pattern was consistent with the ibrutinib arm, where the exponential model also provided the best fit according to BIC.

Examining the total re-scaled GoF statistics (the sum of the re-scaled GoF for both treatment arms), the generalised gamma model provided the best fit according to total AIC (ΔAIC = 0). In contrast, the exponential model was the best-fitting model according to total BIC (ΔBIC = 0). The log-normal model ranked second-best according to both total AIC and BIC, with ΔAIC statistics ≤ 2 for both treatment arms.

**Table 54 re-scaled AIC and BIC – OS**

| Model | ASCT | | Ibrutinib | | Total | |
|---|---|---|---|---|---|---|
| | ΔAIC | ΔBIC | ΔAIC | ΔBIC | ΔAIC | ΔBIC |
| Exponential | [redacted] | | | | | |
| Weibull | | | | | | |
| Gompertz | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Log-logistic | [redacted] | | | | | |
| Log-normal | [redacted] | | | | | |
| Gamma | [redacted] | | | | | |
| Generalised gamma | [redacted] | | | | | |

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival.

### D.1.5 Evaluation of visual fit

Kaplan-Meier curves of OS for ibrutinib without ASCT and ASCT are presented in Figure 24. Due to the immaturity of the data, it is very hard to determine which parameterisation fits the best. All the distributions fit relatively well up to the point where the clinical data stops being available.

[redacted]

### D.1.6 Evaluation of hazard functions

Plots of the estimated hazard functions for all fitted parametric models (exponential, Weibull, log-normal, log-logistic, generalised gamma, gamma and Gompertz) are presented in Figure 25 (ASCT arm) and Figure 26 (Ibrutinib arm).

For the ASCT arm, the smoothed hazard shows a continuously decreasing trend over time. Models that allow for time-dependent hazards (all except the exponential) exhibit a similar overarching trend of decreasing hazards over time. However, the log-normal, log-logistic, and generalised gamma models initially project an increase in hazard, followed by a continuous decrease. In contrast, the exponential model assumes a constant hazard over time, which does not align with the smoothed hazard observed for the ASCT arm in the TRIANGLE trial.

For the ibrutinib arm, the smoothed hazard was relatively stable during the first 25–30 months but then showed a continuous decline over time. None of the parametric models closely aligned with this hazard shape. However, four models (lognormal, log-logistic, Gompertz, and generalised gamma) projected long-term trends of decreasing hazards over time. Despite this similarity in long-term trends, the hazard functions of these models differed significantly. For example, the generalised gamma model projected steeply increasing hazards during the first 10–15 months, while the Gompertz model projected decreasing hazards already from the start. In contrast, the Weibull and gamma models projected increasing hazards over time, which clearly failed to align with the observed trend of decreasing hazards. Lastly, the exponential model, by definition, projected a constant hazard over time. While this aligned relatively well with the smoothed hazard during the first 25–30 months, it failed to capture the subsequent decreasing trend.

Figure 25 Observed Hazard of OS for ASCT and different parameterisations

Figure 26 Observed Hazard of OS for ibrutinib and different parameterisations

### D.1.7 Validation and discussion of extrapolated curves

Based on the goodness-of-fit (GoF) criteria using AIC and BIC, visual inspection of survival curves and hazard functions, and clinical plausibility, the exponential model was selected for the ibrutinib arm, while the Weibull model was chosen for the ASCT arm.

Disregarding clinical plausibility, the generalised gamma model was deemed the most appropriate for both treatment arms due to its superior GoF (particularly according to AIC), visual fit, alignment with the smoothed hazard, and the advantage of using the same model for both arms, as recommended by NICE guidelines. However, clinical plausibility could not be disregarded, as the long-term projections from the generalised gamma model were considered overly optimistic: the clinical data shows that for ibrutinib the overall survival rate at 1, 3 and 5 years are [redacted] and for ASCT, the overall survival rate at 1, 3 and 5 years are [redacted]

The clinical experts estimated that OS for ASCT decline from year 7 to year 10 by 20%, and that ibrutinib patients fare better than that. The generalised gamma gives [redacted] and [redacted] for ibrutinib and [redacted] and [redacted] for ASCT. The estimates are [redacted] and [redacted] for ibrutinib using exponential model, and [redacted] and [redacted] for ASCT using Weibull, which fit better than the generalised gamma model according to clinical experts[33].

For the ibrutinib arm, the exponential model was an appropriate choice based on its AIC statistics and its superior fit according to BIC. Additionally, its survival curve aligned well with the KM estimates. The primary limitation of the exponential model was the discrepancy between its constant hazard function and the smoothed hazard, which showed a decreasing trend over time. However, models with decreasing hazard functions tended to produce overly optimistic long-term projections. The Weibull and gamma models were not viable alternatives for the ibrutinib arm, as their GoF was notably worse than the exponential model, and their hazard functions indicated increasing hazards, which contradicted the smoothed hazard.

For the ASCT arm, the selection of the Weibull model was less straightforward compared to the exponential model for the ibrutinib arm. While the lognormal, loglogistic, Gompertz and generalised gamma models appeared overly optimistic—especially when paired with the exponential model for the ibrutinib arm—the exponential model demonstrated better GoF than the Weibull model. However, the Weibull model's hazard function aligned more closely with the smoothed hazard observed in the TRIANGLE trial, as both indicated continuously decreasing hazards over time. Furthermore, the Weibull model produced slightly more optimistic long-term predictions compared to the exponential model for the ASCT arm, making its selection conservative from a relative efficacy perspective.

Scenario analyses were performed using alternative curve selections, including the Weibull model for the ibrutinib arm and the exponential model for the ASCT arm. Additionally, the log-normal and generalized gamma models were utilized in scenario analyses due to their superior statistical fit, despite concerns that their long-term projections may be overly optimistic.

### D.1.8 Adjustment of background mortality

As per DMC, all models were adjusted to Danish background mortality.

### D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

### D.1.10 Waning effect

Not applicable.

### D.1.11 Cure-point

Not applicable.

## D.2 Extrapolation of failure-free survival

### D.2.1 Data input

**IMBRUVICA + R-CHOP**

FFS was measured in the TRIANGLE trial, a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network and was used for the base case. Induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance therapy was used as a comparator.

**R-DHAP (or R-DHAOx) without IMBRUVICA (followed by IMBRUVICA monotherapy)**

FFS was measured in the TRIANGLE trial, a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network.

**ASCT**

As described above, the relevant comparator for FFS is ASCT, induction treatment with immunochemotherapy alternating R-maxiCHOP and R-AraC followed by HDT and ASCT, and rituximab maintenance therapy.

**Population**

The target population of interest consisted of a total of 537 patients from the TRIANGLE trial.

Using the protocol-specified truncated sequential probability ratio test (tSPRT) boundary-based approach, and based on a two-sided significance level of 1.67%, the ibrutinib arm demonstrated a statistically significant improvement in FFS compared to the ASCT arm, with an HR (based on an unstratified Cox regression model) of 0.639 (two-sided 98.33% CI: 0.428–0.953; p=0.0068). This represents a statistically significant 36.1%

reduction in the risk of SD at the end of induction, PD, or death for participants in the ibrutinib vs ASCT arm.

KM estimates for FFS comparing ibrutinib and ASCT are presented in Figure 27.

Abbreviations: KM, Kaplan-Meier; FFS, failure free survival; ASCT, autologous stem cell transplant.

### D.2.2 Model

As described previously, standard parametric survival models were used to extrapolate FFS. The following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Gamma
- Generalised gamma

### D.2.3 Proportional hazards

The Schoenfeld residuals (Figure 28) and the log-cumulative hazard plot (Figure 29) for the population are shown below. Visual inspection of the log-cumulative hazard reveals evidence of a potential violation of the PH assumption, as the two curves appear to converge over time. This observation is further supported by the Schoenfeld residuals plot and the statistically significant test score from the corresponding test (p-value = [redacted]. In this context, statistical significance indicates a violation of the PH assumption.

Given the results from both the log-cumulative hazard plot and the Schoenfeld residuals plot, there is no justification for applying joint fits or restricting the analysis. Consequently, independent fits were performed. For both treatment arms, the log-cumulative hazards suggest a change in the hazard over time, with a slight decrease observed as time progresses.

Abbreviation: FAS, full analysis set; FFS, failure-free survival.

### D.2.4 Evaluation of statistical fit (AIC and BIC)

For the IMBRUVICA + R-CHOP, the exponential model demonstrated the best fit, with the lowest ΔAIC (0) and ΔBIC (0) values. The log-normal model ranked second, with ΔAIC = [redacted] and ΔBIC = [redacted] All models, except the generalised gamma, had ΔAIC values ≤ 2, indicating a good fit to the data. The generalised gamma model had the highest ΔAIC [redacted] and ΔBIC [redacted]), making it the least suitable model. Overall, the AIC and BIC rankings were aligned, with the exponential model consistently demonstrating the best performance, while the generalised gamma model ranked the lowest.

The log-normal model demonstrated the best fit for the ASCT arm, with the lowest ΔAIC (0) and ΔBIC (0) values. The second-best fitting models were the generalised gamma (ΔAIC = [redacted] and Gompertz (ΔBIC = [redacted] No other model achieved ΔAIC ≤ 2, although the Gompertz model had a ΔAIC slightly above this threshold [redacted] All models had ΔAIC values ≤ 10, indicating reasonable fit.

When considering the total re-scaled GoF statistics across both treatment arms, the log-normal model provided the best fit according to both ΔAIC and ΔBIC. It was the only model to achieve ΔAIC ≤ 2 for both treatment arms.

**Table 55 Separate fits, rescaled AIC and BIC - FFS**

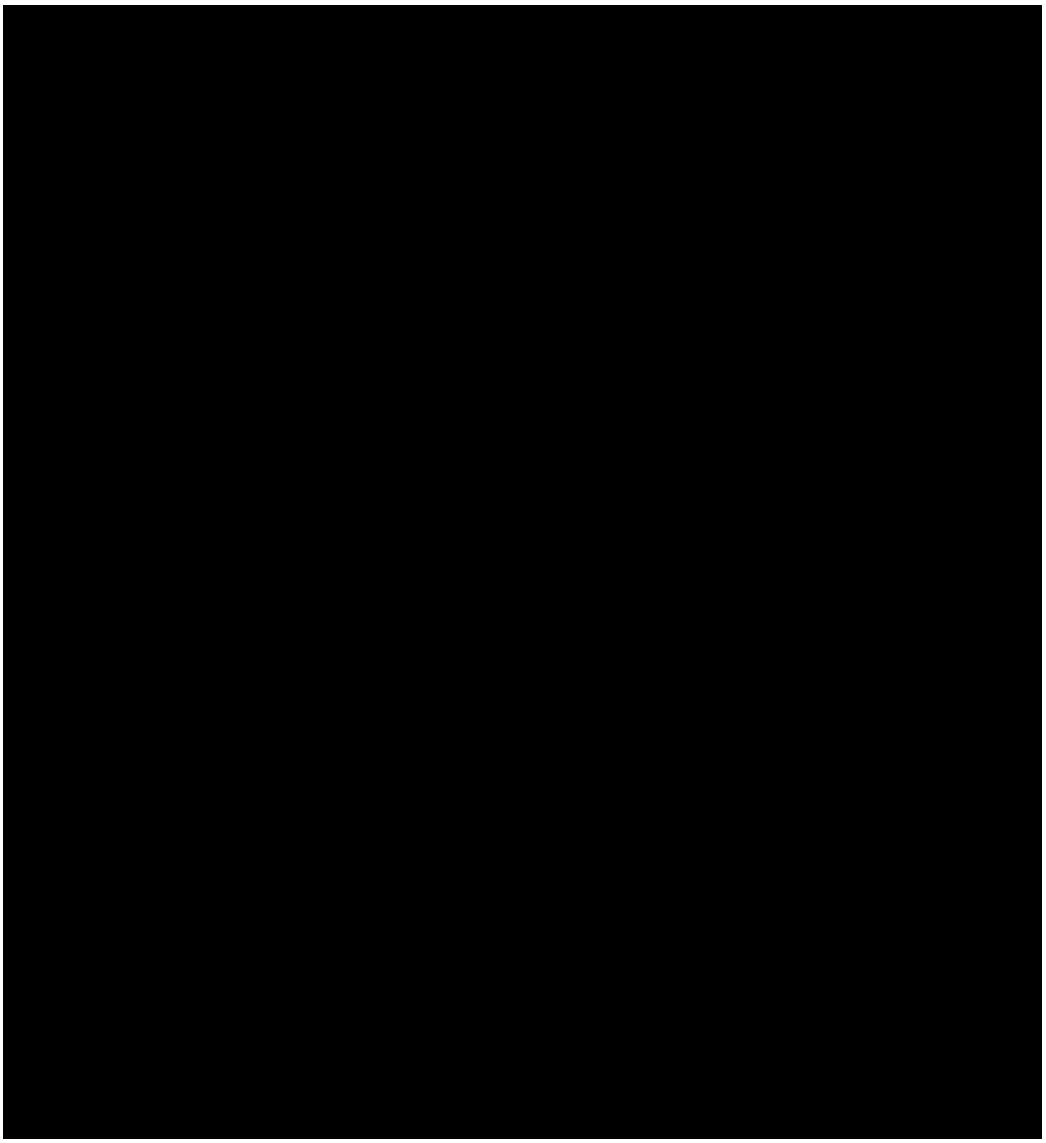
| Model | ASCT | | Ibrutinib | | Total | |
|---|---|---|---|---|---|---|
| | ΔAIC | ΔBIC | ΔAIC | ΔBIC | ΔAIC | ΔBIC |
| Exponential | [redacted] | | | | | |
| Weibull | [redacted] | | | | | |
| Gompertz | [redacted] | | | | | |
| Log-logistic | [redacted] | | | | | |
| Log-normal | [redacted] | | | | | |
| Gamma | [redacted] | | | | | |
| Generalized gamma | [redacted] | | | | | |

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; FFS, failure free survival.

### D.2.5 Evaluation of visual fit

Kaplan-Meier curves ofFF for ibrutinib without ASCT and ASCT are presented in Figure 30. Due to the immaturity of the data, it is very hard to determine which parameterisation fits the best. All the distributions fit relatively well up to the point where the clinical data stops being available.

**Figure 30 Kaplan-Meier curves of FFS (Ibrutinib without ASCT vs. ASCT; FAS)**



### D.2.6 Evaluation of hazard functions

Plots of the hazard functions for the parametric models for FFS are presented in Figure 31 and Figure 32, along with the chosen statistical fits.

For ASCT, the smoothed hazard shows a continuously decreasing trend over time, appearing linear. Models with time-dependent hazards, such as the generalised gamma and log-normal, aligned well with the smoothed hazard after an initial brief period of increasing hazards. The Gompertz model also closely matched the smoothed hazard. In contrast, the Weibull and gamma models predicted decreasing hazards over time but had dissimilar shapes, with their slopes decreasing progressively over time.

For ibrutinib, the smoothed hazard exhibited a complex trend: it initially decreased gently from month 0 to 25, increased slightly for 5–10 months, and then began a continuous but gradual decline until month 50. Beyond month 50, the slope became

steeper. Given this pattern, it is uncertain whether the hazard will continue to decrease indefinitely; it may stabilise or even increase, as observed earlier.

Among the parametric models, none closely aligned with the smoothed hazard function. However, the log-normal, log-logistic, and generalised gamma models shared a broadly decreasing trend, albeit with notable deviations at a granular level. The exponential model may also be a reasonable alternative, given the lack of a clear and consistent trend in the smoothed hazard. Conversely, the Weibull, Gompertz, and gamma models appeared less suitable, as they predicted continuously increasing hazards over time, which was not supported by the observed data.

Abbreviation: FAS, full analysis set; FFS, failure-free survival.

### D.2.7 Validation and discussion of extrapolated curves

Based on the GoF criteria using AIC and BIC, visual inspection of survival curves and hazard functions, and clinical plausibility, the exponential model was selected for the ibrutinib arm, while the Weibull model was chosen for the ASCT arm. These models were also used to extrapolate OS.

The exponential model was a clear choice for the ibrutinib arm for FFS, as it met all selection criteria without violations and it maintained consistency with the parametric distribution chosen for the OS endpoint in the base case. The most challenging criterion was ensuring alignment between the exponential model's hazard function and the observed hazard trends within the trial. Although hazards are rarely completely constant, the within-trial hazard trend was ambiguous, making the assumption of a constant hazard appropriate. The log-logistic model was strongly considered for FFS in the ibrutinib arm due to its favourable GoF based on AIC and its hazard function, which partially aligned with the smoothed hazard. However, it was ultimately rejected because using the log-logistic model for FFS while extrapolating OS with the exponential model would result in the gap between the ibrutinib arm's FFS and OS curves narrowing over time, contradicting the KM estimates. Although this convergence becomes particularly pronounced beyond the 20-year mark, the contradiction might not be overly problematic. Therefore, the log-logistic model should be considered for extrapolating FFS in the ibrutinib arm in a scenario analysis. The log-normal model was also strongly considered for the ibrutinib arm for reasons similar to the log-logistic model, but its use would lead to an even more pronounced convergence of the FFS and OS curves.

For the ASCT arm, the selection of the Weibull model was less straightforward compared to the exponential model for the ibrutinib arm. While the log-normal model demonstrated the best statistical fit (based on AIC and BIC) and showed superior visual alignment with the smoothed hazard, the Weibull model was ultimately preferred due to its clinical plausibility. Although the Weibull model's statistical fit was inferior (ΔAIC=4.9 and ΔBIC=4.9) and its alignment with the smoothed hazard was less optimal compared to the log-normal model, its hazard function still exhibited some degree of alignment with the smoothed hazard, making it a valid option. The primary justification for selecting the Weibull model was its ability to produce clinically plausible FFS estimates. In contrast, the log-normal model generated estimates that were inconsistent with clinical expectations. Weibull also maintained consistency with the parametric distribution chosen for the OS endpoint for the ASCT arm in the base case. Specifically, if the log-normal model were employed for FFS while OS was extrapolated using the Weibull model, the projections would suggest that no patients would experience progression beyond approximately the 15-year mark. Furthermore, the log-normal model implied that patients treated with ASCT would remain failure-free to a greater extent than those treated with ibrutinib from year 14 onwards. Such outcomes are not supported by the observed data, particularly when the exponential model is applied to the ibrutinib arm.

Alternative models were explored in scenario analyses, including the Weibull model for the ibrutinib arm, the exponential model for the ASCT arm, the log-normal model for both treatment arms, and the log-logistic model for both treatment arms.

### D.2.8 Adjustment of background mortality

As per DMC, all models were adjusted to Danish Background mortality.

### D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

### D.2.10 Waning effect

Not applicable.

### D.2.11 Cure-point

Not applicable.

# Appendix E. Serious adverse events

All serious AEs are reported in Table 56. In this application, as stated, safety data (AEs) are presented as treatment-emergent serious adverse events (TESAE).

**Table 56 Incidence of TESAE by preferred term at any toxicity grade; Safety data**

| Preferred term | Intervention (N=265), n (%) | Comparator (N=268), n (%) |
|---|---|---|
| **Subjects with any TESAE** | **171 (64.5)** | **123 (45.9)** |
| Pneumonia | 11 (4.2) | 8 (3.0) |
| COVID-19 | 12 (4.5) | 3 (1.1) |
| Sepsis | 2 (0.8) | 6 (2.2) |
| COVID-19 pneumonia | 10 (3.8) | 1 (0.4) |
| Device related infection | 0 | 1 (0.4) |
| Herpes zoster | 1 (0.4) | 0 |
| Influenza | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Sinusitis | [redacted] | [redacted] |
| Upper respiratory tract infection | [redacted] | [redacted] |
| Appendicitis | [redacted] | [redacted] |
| Catheter site infection | [redacted] | [redacted] |
| Hepatitis E | [redacted] | [redacted] |
| Staphylococcal sepsis | [redacted] | [redacted] |
| Urinary tract infection | [redacted] | [redacted] |
| Viral infection | [redacted] | [redacted] |
| Cellulitis | [redacted] | [redacted] |
| Coronavirus infection | [redacted] | [redacted] |
| Diverticulitis | [redacted] | [redacted] |
| Escherichia sepsis | [redacted] | [redacted] |
| Febrile infection | [redacted] | [redacted] |
| Infection | [redacted] | [redacted] |

| | | |
|---|---|---|
| Oral candidiasis | [redacted] | [redacted] |
| Pneumonia fungal | [redacted] | [redacted] |
| Pseudomonas infection | [redacted] | [redacted] |
| Respiratory tract infection | [redacted] | [redacted] |
| Staphylococcal infection | [redacted] | [redacted] |
| Streptococcal bacteraemia | [redacted] | [redacted] |
| Anal abscess | [redacted] | [redacted] |
| Bacteraemia | [redacted] | [redacted] |
| Candida infection | [redacted] | [redacted] |
| Candida pneumonia | [redacted] | [redacted] |
| Cerebral fungal infection | [redacted] | [redacted] |
| Cholecystitis infective | [redacted] | [redacted] |
| Clostridium colitis | [redacted] | [redacted] |
| Enteritis infectious | [redacted] | [redacted] |
| Enterobacter sepsis | [redacted] | [redacted] |
| Enterococcal infection | [redacted] | [redacted] |
| Enterovirus infection | [redacted] | [redacted] |
| Epididymitis | [redacted] | [redacted] |
| Erysipelas | [redacted] | [redacted] |
| Escherichia bacteraemia | [redacted] | [redacted] |
| Escherichia infection | [redacted] | [redacted] |
| Fungal infection | [redacted] | [redacted] |
| Gastroenteritis | [redacted] | [redacted] |
| Groin abscess | [redacted] | [redacted] |
| Infected cyst | [redacted] | [redacted] |

| | | |
|---|---|---|
| Intervertebral discitis | [redacted] | [redacted] |
| Klebsiella infection | [redacted] | [redacted] |
| Neutropenic sepsis | [redacted] | [redacted] |
| Oral herpes | [redacted] | [redacted] |
| Osteomyelitis | [redacted] | [redacted] |
| Pharyngitis | [redacted] | [redacted] |
| Pneumonia staphylococcal | [redacted] | [redacted] |
| Respiratory syncytial virus infection | [redacted] | [redacted] |
| Serratia infection | [redacted] | [redacted] |
| Soft tissue infection | [redacted] | [redacted] |
| Tracheostomy infection | [redacted] | [redacted] |
| Varicella zoster virus infection | [redacted] | [redacted] |
| Wound infection | [redacted] | [redacted] |
| Febrile neutropaenia | 28 (10.6) | 19 (7.1) |
| Thrombocytopaenia | 2 (0.8) | 6 (2.2) |
| Anaemia | [redacted] | [redacted] |
| Pancytopaenia | [redacted] | [redacted] |
| Leukocytosis | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Splenic infarction | [redacted] | [redacted] |
| Diarrhoea | 2 (0.8) | 3 (1.1) |
| Vomiting | 9 (3.4) | 4 (1.5) |
| Nausea | [redacted] | [redacted] |
| Enteritis | [redacted] | [redacted] |
| Stomatitis | [redacted] | [redacted] |

| | | |
|---|---|---|
| Abdominal pain | [redacted] | [redacted] |
| Gastric haemorrhage | [redacted] | [redacted] |
| Gastrointestinal inflammation | [redacted] | [redacted] |
| Abdominal wall mass | [redacted] | [redacted] |
| Anal haemorrhage | [redacted] | [redacted] |
| Constipation | [redacted] | [redacted] |
| Dental caries | [redacted] | [redacted] |
| Enterocolitis | [redacted] | [redacted] |
| Gastrooesophageal reflux disease | [redacted] | [redacted] |
| Ileus | [redacted] | [redacted] |
| Ileus paralytic | [redacted] | [redacted] |
| Intestinal haemorrhage | [redacted] | [redacted] |
| Intestinal perforation | [redacted] | [redacted] |
| Large intestinal obstruction | [redacted] | [redacted] |
| Rectal haemorrhage | [redacted] | [redacted] |
| Acute kidney injury | 18 (6.8) | 14 (5.2) |
| Renal failure | 5 (1.9) | 4 (1.5) |
| Urinary retention | [redacted] | [redacted] |
| Renal impairment | [redacted] | [redacted] |
| Pyrexia | 8 (3.0) | 8 (3.0) |
| Asthenia | [redacted] | [redacted] |
| Catheter site haemorrhage | [redacted] | [redacted] |
| Chills | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| General physical health deterioration | [redacted] | [redacted] |

| | | |
|---|---|---|
| Mucosal inflammation | [redacted] | [redacted] |
| Catheter site pain | [redacted] | [redacted] |
| Hernia | [redacted] | [redacted] |
| Infusion site extravasation | [redacted] | [redacted] |
| Malaise | [redacted] | [redacted] |
| Sudden death | [redacted] | [redacted] |
| Atrial fibrillation | 12 (4.5) | 1 (0.4) |
| Left ventricular dysfunction | [redacted] | [redacted] |
| Myocardial infarction | [redacted] | [redacted] |
| Pericarditis | [redacted] | [redacted] |
| Acute myocardial infarction | [redacted] | [redacted] |
| Bradycardia | [redacted] | [redacted] |
| Cardiovascular disorder | [redacted] | [redacted] |
| Dilated cardiomyopathy | [redacted] | [redacted] |
| Pericardial effusion | [redacted] | [redacted] |
| Sinus node dysfunction | [redacted] | [redacted] |
| Blood creatinine increased | 5 (1.9) | 4 (1.5) |
| Platelet count decreased | 0 | 6 (2.2) |
| Electrocardiogram T wave inversion | [redacted] | [redacted] |
| Hepatic enzyme abnormal | [redacted] | [redacted] |
| Liver function test increased | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Urine output decreased | [redacted] | [redacted] |
| White blood cell count increased | [redacted] | [redacted] |
| Interstitial lung disease | [redacted] | [redacted] |

| | | |
|---|---|---|
| Acute respiratory distress syndrome | [redacted] | [redacted] |
| Dyspnoea | [redacted] | [redacted] |
| Pneumonitis | [redacted] | [redacted] |
| Pleural effusion | [redacted] | [redacted] |
| Pneumothorax | [redacted] | [redacted] |
| Pulmonary oedema | [redacted] | [redacted] |
| Respiratory failure | [redacted] | [redacted] |
| Clavicle fracture | [redacted] | [redacted] |
| Dialysis related complication | [redacted] | [redacted] |
| Femoral neck fracture | [redacted] | [redacted] |
| Infusion related reaction | [redacted] | [redacted] |
| Jaw fracture | [redacted] | [redacted] |
| Limb injury | [redacted] | [redacted] |
| Shunt stenosis | [redacted] | [redacted] |
| Upper limb fracture | [redacted] | [redacted] |
| Malignant melanoma | [redacted] | [redacted] |
| Follicular thyroid cancer | [redacted] | [redacted] |
| Oesophageal adenocarcinoma | [redacted] | [redacted] |
| Prostate cancer | [redacted] | [redacted] |
| Rectal adenocarcinoma | [redacted] | [redacted] |
| Renal neoplasm | [redacted] | [redacted] |
| Syncope | [redacted] | [redacted] |
| Presyncope | [redacted] | [redacted] |
| Seizure | [redacted] | [redacted] |
| Cerebral infarction | [redacted] | [redacted] |

| | | |
|---|---|---|
| Dizziness | [redacted] | [redacted] |
| Encephalitis autoimmune | [redacted] | [redacted] |
| Epilepsy | [redacted] | [redacted] |
| Facial paralysis | [redacted] | [redacted] |
| Generalised tonic-clonic seizure | [redacted] | [redacted] |
| Haemorrhage intracranial | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Lumbar radiculopathy | [redacted] | [redacted] |
| Neuropathy peripheral | [redacted] | [redacted] |
| Radiculopathy | [redacted] | [redacted] |
| Subarachnoid haemorrhage | [redacted] | [redacted] |
| Transient ischaemic attack | [redacted] | [redacted] |
| Dehydration | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] |
| Hyponatraemia | [redacted] | [redacted] |
| Hyperglycaemia | [redacted] | [redacted] |
| Hypoglycaemia | [redacted] | [redacted] |
| Tumour lysis syndrome | [redacted] | [redacted] |
| Hypotension | [redacted] | [redacted] |
| Hypertensive crisis | [redacted] | [redacted] |
| Embolism | [redacted] | [redacted] |
| Haematoma | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] |
| Peripheral ischaemia | [redacted] | [redacted] |

| | | |
|---|---|---|
| Subclavian vein thrombosis | [redacted] | [redacted] |
| Thrombophlebitis | [redacted] | [redacted] |
| Thrombosis | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Intervertebral disc protrusion | [redacted] | [redacted] |
| Arthritis | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] |
| Myositis | [redacted] | [redacted] |
| Vertebral foraminal stenosis | [redacted] | [redacted] |
| Biliary colic | [redacted] | [redacted] |
| Cholecystitis | [redacted] | [redacted] |
| Gallbladder obstruction | [redacted] | [redacted] |
| Hydrocholecystis | [redacted] | [redacted] |
| Drug hypersensitivity | [redacted] | [redacted] |
| Cytokine release syndrome | [redacted] | [redacted] |
| Engraftment syndrome | [redacted] | [redacted] |
| Delirium | [redacted] | [redacted] |
| Depression | [redacted] | [redacted] |
| Fanconi syndrome | [redacted] | [redacted] |
| Hypoacusis | [redacted] | [redacted] |
| Vertigo | [redacted] | [redacted] |
| Diplopia | [redacted] | [redacted] |

Abbreviations: TESAE, treatment-emergent serious adverse events
Source: Janssen Research & Development [Data on file][8]

# Appendix F. Health-related quality of life

Not relevant.

# Appendix G. Probabilistic sensitivity analyses

**Table 57 Overview of parameters in the PSA**

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| **HSUV** | | | | |
| AE disutility (ibrutinib) | -0.014 | -0.009 | -0.020 | Log-normal |
| AE disutility (ASCT) | -0.019 | -0.013 | -0.027 | Log-normal |
| FFS utility | 0.89 | 0.82 | 0.94 | Beta |
| PD utility | 0.84 | 0.82 | 0.86 | Beta |
| Utility decrement due to IV treatment | 0.04 | 0.03 | 0.06 | Beta |
| Utility decrement due to R-DHAP treatment | 0.28 | 0.18 | 0.40 | Beta |
| Utility decrement due to conditioning | 0.16 | 0.10 | 0.23 | Beta |
| **Costs** | | | | |
| Disease management cost - FFS- Induction | 423 | 360 | 487 | Gamma |
| Disease management cost - FFS - Consolidation | 559 | 476 | 643 | Gamma |
| Disease management cost - FFS - ASCT | 1,097 | 933 | 1,262 | Gamma |
| Disease management cost - FFS - ibrutinib | 1,078 | 916 | 1,240 | Gamma |

| | | | | |
|---|---|---|---|---|
| Disease management cost - FFS off active treatment | 373 | 317 | 429 | Gamma |
| Disease management cost - PD | 527 | 448 | 607 | Gamma |
| Progression cost | 5,947 | 5,055 | 6,838 | Gamma |
| **Patient characteristics** | | | | |
| BSA | 1.99 | 1.68 | 2.28 | Log-normal |
| Weight | 80 | 68 | 92 | Log-normal |
| **Adverse event frequencies** | | | | |
| Group I - Neutropenia | 0.39 | 0.33 | 0.45 | Beta |
| Group I - Anaemia | 0.22 | 0.18 | 0.25 | Beta |
| Group I - Thrombocytopenia | 0.35 | 0.29 | 0.40 | Beta |
| Group I - Febrile neutropenia | 0.14 | 0.12 | 0.16 | Beta |
| Group I - Leukopenia | 0.09 | 0.08 | 0.11 | Beta |
| Group I - Platelet count decreased | 0.29 | 0.25 | 0.34 | Beta |
| Group I - Neutrophil count decreased | 0.24 | 0.21 | 0.28 | Beta |
| Group I - White blood cell count decreased | 0.06 | 0.05 | 0.07 | Beta |

| | | | | |
|---|---|---|---|---|
| Group I - Gamma-glutamyltransferase increased | 0.02 | 0.02 | 0.03 | Beta |
| Group I - Pneumonia | 0.05 | 0.05 | 0.06 | Beta |
| Group I - Sepsis | 0.01 | 0.01 | 0.01 | Beta |
| Group I - Stomatitis | 0.02 | 0.01 | 0.02 | Beta |
| Group I - Nausea | 0.04 | 0.04 | 0.05 | Beta |
| Group I - Diarrhoea | 0.05 | 0.05 | 0.06 | Beta |
| Group I - Mucosal inflammation | 0.02 | 0.02 | 0.02 | Beta |
| Group I - Hypokalaemia | 0.06 | 0.05 | 0.07 | 0.07 |
| Group A - Neutropenia | 0.39 | 0.33 | 0.45 | 0.39 |
| Group A - Anaemia | 0.34 | 0.29 | 0.39 | 0.34 |
| Group A - Thrombocytopenia | 0.43 | 0.36 | 0.49 | 0.43 |
| Group A - Febrile neutropenia | 0.27 | 0.23 | 0.30 | 0.27 |
| Group A - Leukopenia | 0.11 | 0.10 | 0.13 | 0.11 |
| Group A - Platelet count decreased | 0.33 | 0.28 | 0.38 | 0.33 |
| Group A - Neutrophil count decreased | 0.23 | 0.20 | 0.27 | 0.23 |
| Group A - White blood cell count decreased | 0.13 | 0.11 | 0.15 | 0.13 |

| | | | | |
|---|---|---|---|---|
| Group A - Gamma-glutamyltransferase increased | 0.04 | 0.03 | 0.05 | 0.04 |
| Group A - Pneumonia | 0.04 | 0.03 | 0.05 | 0.04 |
| Group A - Sepsis | 0.03 | 0.02 | 0.03 | 0.03 |
| Group A - Stomatitis | 0.08 | 0.07 | 0.09 | 0.08 |
| Group A - Nausea | 0.08 | 0.07 | 0.09 | 0.08 |
| Group A - Diarrhoea | 0.06 | 0.05 | 0.07 | 0.06 |
| Group A - Mucosal inflammation | 0.13 | 0.11 | 0.15 | 0.13 |
| Group A - Hypokalaemia | 0.04 | 0.04 | 0.05 | 0.04 |
| **Dose Intensity – Front line treatment** | | | | |
| Rituximab - Induction | 1 | 0 | 1 | Uniform |
| Cyclophosphamide | 1 | 0 | 1 | Uniform |
| Doxorubicin | 1 | 0 | 1 | Uniform |
| Vincritine | 1 | 0 | 1 | Uniform |
| Prednisone | 1 | 0 | 1 | Uniform |
| Ibrutinib – Induction | 0.95 | 0 | 1 | Uniform |
| Ibrutinib – Consolidation | 0.95 | 0 | 1 | Uniform |
| Ibrutinb – Maintenance | 0.93 | 0 | 1 | Uniform |

| | | | | |
|---|---|---|---|---|
| Rituximab – Maintenance | 1 | 0 | 1 | Uniform |
| Cyclophosphamide - Maintenance | 1 | 0 | 1 | Uniform |
| Doxorubicin - Maintenance | 1 | 0 | 1 | Uniform |
| Vincristine – Maintenance | 1 | 0 | 1 | Uniform |
| Prednisone - Maintenance | 1 | 0 | 1 | Uniform |
| **Dose intensity – subsequent treatment** | | | | |
| Ibrutinib | 1 | 0 | 1 | Uniform |
| Brexu-cel | 1 | 0 | 1 | Uniform |
| **Frequency of MRU in 1L** | | | | |
| Full blood count – Induction | 0.10 | 0.08 | 0.11 | Gamma |
| Imaging – Induction | 0.02 | 0.02 | 0.02 | Gamma |
| Haematologist visit - Induction | 0.08 | 0.07 | 0.09 | Gamma |
| PET Scan – Induction | 0.02 | 0.02 | 0.02 | Gamma |
| Infection Prophylaxis - Induction | 0.06 | 0.05 | 0.07 | Gamma |
| Full blood count – Consolidation | 0.11 | 0.10 | 0.13 | Gamma |
| Haematologist visit - Consolidation | 0.17 | 0.15 | 0.20 | Gamma |

| | | | | |
|---|---|---|---|---|
| PET Scan – Consolidation | 0.06 | 0.05 | 0.07 | Gamma |
| Infection Prophylaxis - Consolidation | 0.06 | 0.05 | 0.07 | Gamma |
| Full blood count – Maintenance, ASCT containing arm | 0.57 | 0.49 | 0.66 | Gamma |
| Haematologist visit – Maintenance, ASCT containing arm | 0.52 | 0.44 | 0.60 | Gamma |
| CT Scan - Maintenance, ASCT containing arm | 0.09 | 0.07 | 0.10 | Gamma |
| Infection Prophylaxis - Maintenance, ASCT containing arm | 0.06 | 0.05 | 0.07 | Gamma |
| Full blood count – Maintenance, Non-ASCT containing arm | 0.52 | 0.44 | 0.60 | Gamma |
| Haematologist visit – Maintenance, Non-ASCT containing arm | 0.52 | 0.44 | 0.60 | Gamma |
| CT Scan - Maintenance, Non-ASCT containing arm | 0.09 | 0.07 | 0.10 | Gamma |
| Infection Prophylaxis - Maintenance, Non-ASCT containing arm | 0.06 | 0.05 | 0.07 | Gamma |
| Full blood count – Off active maintenance | 0.29 | 0.24 | 0.33 | Gamma |

| | | | | |
|---|---|---|---|---|
| Haematologist visit – Off active maintenance | 0.06 | 0.05 | 0.07 | Gamma |
| Infection Prophylaxis - Off active maintenance | 0.06 | 0.05 | 0.07 | Gamma |

Abbreviations: AE, adverse event; ASCT, autologous stem cell transplant; BSA, body surface area; FFS, failure free survival; HSUV, health state utility value; IV, intravenous; PD, progressed disease; PSA, probability sensitivity analysis; R-DHAP, Rituximab + Dexamethasone, High-dose Ara-C (cytarabine), and Platinum (cisplatin).

# Appendix H. Literature searches for the clinical assessment

Not applicable.

# Appendix I. Literature searches for health-related quality of life

## I.1 Health-related quality-of-life search

**Objective**

The objective of this systematic literature review (SLR) was to identify published evidence on the humanistic burden associated with 1L MCL and related conditions. Specifically, the review aimed to capture studies reporting utility or disutility measures. To meet the study objectives, the following research question will be addressed:

"What is the impact of disease and treatment in patients with previously untreated MCL in terms of HRQoL and utilities based on the published literature?"

The SLRs were conducted according to the standards set out in the Cochrane Handbook for Systematic Reviews of Interventions[87] as well as the high-quality standards required by NICE[88].

### I.1.1 Information sources

Systematic searches were first conducted on 7th December 2023 with the subsequent search update on 9th May 2025 via OVID SP in Embase, MEDLINE and PsycINFO for the humanistic SLR (Table 58) database using a pre-defined search strategy.

**Table 58 Bibliographic databases included in the humanistic literature search**

| Database | Platform | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **Embase** | Ovid | 1974 and onwards | 09.05.2025 |
| **Medline** | Ovid | 1946 and onwards | 09.05.2025 |
| **PsycINFO** | Ovid | 1806 and onwards | 09.05.2025 |

Additionally, conference searches were conducted from 2021 (in 2023 SLR) and 2024 (in 2025 update) onwards to capture the most recent and relevant references. This rationale was in line with the recommendations from the NICE guidelines, which mention that good-quality studies often publish full text papers after the conference abstract, and these are identified by routine searches[89]. The conferences included in Table 59 were hand-searched.

**Table 59 Conference material included in the literature search**

| Conference | Platform | Relevant period for the search | Latest date of search completion |
|---|---|---|---|
| American Association for Cancer Research (AACR) | www.aacr.org | 2020-2025 | 09.05.2025 |
| American Society of Clinical Oncology (ASCO) | www.asco.org | 2020-2025 | 09.05.2025 |
| American Society of Hematology (ASH)[a] | www.hematology.org | 2020-2025 | 09.05.2025 |
| European Hematology Association (EHA) | www.ehaweb.org | 2020-2025 | 09.05.2025 |
| European Society for Medical Oncology (ESMO)[a] | www.esmo.org | 2020-2025 | 09.05.2025 |
| International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[b] | www.ispor.org | 2020-2025 | 09.05.2025 |

a. The latest proceedings from the ASH 2025 and the ESMO 2025 were not available at the time of conducting the hand-searches
b. ISPOR was only searched for the 2025 update

To ensure that ongoing clinical intervention trials were also identified, clinicaltrials.gov and the European Union's Clinical Trials Register were screened. Additionally, to complement the electronic database searches for the SLR, searches of HTA websites were conducted (only in the 2025 update) to identify economic evaluation reports (Table 60).

**Table 60 Other sources included in the literature search**

| Source name | Platform | Relevant period for the search | Latest date of search completion |
|---|---|---|---|
| Agency for Healthcare Research and Quality (AHRQ) | www.ahrq.gov | 2020-2025 | 09.05.2025 |
| Agenzia Italiana del Farmaco (AIFA) | www.aifa.gov.it | 2020-2025 | 09.05.2025 |
| All Wales Medicines Strategy Group (AWMSG) | www.gov.wales/all-wales-medicines-strategy-group | 2020-2025 | 09.05.2025 |
| European Medicines Agency (EMA) | www.ema.europa.eu | 2020-2025 | 09.05.2025 |

| Source name | Platform | Relevant period for the search | Latest date of search completion |
|---|---|---|---|
| Canada's Drug Agency (CDA) | www.cda-amc.ca | 2020-2025 | 09.05.2025 |
| Federal Joint Committee (G-BA) | www.g-ba.de | 2020-2025 | 09.05.2025 |
| Haute Autorité de Santé (HAS) | www.has-sante.fr | 2020-2025 | 09.05.2025 |
| Institute for Clinical and Economic Review (ICER) | www.icer.org | 2020-2025 | 09.05.2025 |
| The International Network of Agencies for HTA (INAHTA) | www.inahta.org | 2020-2025 | 09.05.2025 |
| Institute for Quality and Efficiency in Health Care (IQWiG) | www.iqwig.de | 2020-2025 | 09.05.2025 |
| National Centre for Pharmacoeconomics (NCPE) | www.ncpe.ie | 2020-2025 | 09.05.2025 |
| National Health Care Institute (Zorginstituut Nederland, ZIN) | www.zorginstituutnederland.nl | 2020-2025 | 09.05.2025 |
| National Institute for Health and Care Excellence (NICE) | www.nice.org.uk | 2020-2025 | 09.05.2025 |
| Scottish Medicines Consortium (SMC) | www.scottishmedicines.org.uk | 2020-2025 | 09.05.2025 |
| Pharmaceutical Benefits Advisory Committee (PBAC) | www.pbs.gov.au | 2020-2025 | 09.05.2025 |
| Tandvårds och läkemedelsförmånsverket (TLV) | www.tlv.se | 2020-2025 | 09.05.2025 |

### I.1.2 Search strategies

The searches were designed using a combination of free-text search terms and controlled vocabulary terms specific to each database as recommended by search strategy guidelines. The search strings of the humanistic SLR were developed using the health utilities and quality-of-life filter of the Canadian Drug and Health Technology Agency (CADTH). The search strings for the December 2023 and May 2025 humanistic SLRs are reported below.

### I.1.2.1 Humanistic SLR 2023

**Table 61 Search strategy for humanistic SLR: Embase 1974 to 7th December 2023**

| No. | Query | Results |
|---|---|---|
| #1 | mantle cell lymphoma/ | 14704 |
| #2 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti.ab. | 29286 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti.ab. | 170 |
| #4 | or/1-3 | 33942 |
| #5 | first-line treatment/ | 2832 |
| #6 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab<br>ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 2211518 |
| #7 | 5 or 6 | 2211518 |
| #8 | 4 and 7 | 8516 |
| #9 | socioeconomics/ | 162293 |
| #10 | exp Quality of Life/ | 652608 |
| #11 | quality of life.ti.kf. | 181444 |
| #12 | ((instrument or instruments) adj3 quality of life).ab. | 5451 |
| #13 | Quality-Adjusted Life Year/ | 35266 |
| #14 | quality adjusted life.ti.ab.kf. | 26773 |
| #15 | (qaly* or qald* or qale* or qtime* or life year or life years).ti.ab.kf. | 44868 |
| #16 | disability adjusted life.ti.ab.kf. | 6530 |
| #17 | daly*.ti.ab.kf. | 6337 |
| #18 | (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti.ab.kf. | 50208 |
| #19 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti.ab.kf. | 2980 |

| No. | Query | Results |
|---|---|---|
| #20 | (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti.ab.kf. | 1025 |
| #21 | (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti.ab.kf. | 12292 |
| #22 | (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti.ab.kf. | 69 |
| #23 | (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti.ab.kf. | 530 |
| #24 | (hql or hqol or h qol or hrqol or hr qol).ti.ab.kf. | 39329 |
| #25 | (hye or hYes).ti.ab.kf. | 178 |
| #26 | (health* adj2 year* adj2 equivalent*).ti.ab.kf. | 56 |
| #27 | (pqol or qls).ti.ab.kf. | 749 |
| #28 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti.ab.kf. | 891 |
| #29 | exp "named inventories questionnaires and rating scales"/ | 1940337 |
| #30 | nottingham health profile*.ti.ab.kf. | 1675 |
| #31 | sickness impact profile.ti.ab.kf. | 1292 |
| #32 | health status indicator/ | 3514 |
| #33 | (health adj3 (utilit* or status)).ti.ab.kf. | 121750 |
| #34 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti.ab.kf. | 25608 |
| #35 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti.ab.kf. | 19243 |
| #36 | disutilit*.ti.ab.kf. | 1260 |
| #37 | rosser.ti.ab.kf. | 143 |
| #38 | willingness to pay.ti.ab.kf. | 13175 |

| No. | Query | Results |
|---|---|---|
| #39 | standard gamble*.ti.ab.kf. | 1219 |
| #40 | (time trade off or time tradeoff).ti.ab.kf. | 2404 |
| #41 | tto.ti.ab.kf. | 2249 |
| #42 | (hui or hui1 or hui2 or hui3).ti.ab.kf. | 3135 |
| #43 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti.ab.kf. | 38308 |
| #44 | duke health profile.ti.ab.kf. | 119 |
| #45 | functional status questionnaire.ti.ab.kf. | 174 |
| #46 | dartmouth coop functional health assessment*.ti.ab.kf. | 14 |
| #47 | or/9-46 | 2668200 |
| #48 | EORTC.ti.ab.kf. | 22577 |
| #49 | ("european organization for research and treatment of cancer" or "european organisation for research and treatment of cancer").ti.ab.kf. | 8401 |
| #50 | 48 or 49 | 25422 |
| #51 | (c30 or c-30).ti.ab.kf. | 16577 |
| #52 | 50 and 51 | 11472 |
| #53 | (qlq adj2 (c30 or c 30)).ti.ab.kf. | 11584 |
| #54 | Quality of Life Questionnaire Core 30.ti.ab.kf. | 958 |
| #55 | EORTC C30 questionnaire.ti.ab.kf. | 13 |
| #56 | or/52-55 | 12686 |
| #57 | (FACT or FACTG or FACTLym or "functional assessment of cancer therapy" or FACIT or FACTbrm).ti.ab.kf. | 358040 |
| #58 | 47 or 56 or 57 | 2994950 |
| #59 | 8 and 58 | 791 |
| #60 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 1070457 |
| #61 | case reports/ or case study/ or case report$.jx. or case report$.jw. | 368444 |

| No. | Query | Results |
|---|---|---|
| #62 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3638900 |
| #63 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti.ab. | 2871260 |
| #64 | or/60-63 | 7627561 |
| #65 | 59 not 64 | 670 |
| #66 | conference abstract.pt. | 4872067 |
| #67 | 65 not 66 | 221 |
| #68 | limit 65 to (conference abstract and yr="2020-current") | 180 |
| #69 | 67 or 68 | 401 |

**Table 62 Search strategy for humanistic SLR: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to 7th December 2023**

| No. | Query | Results |
|---|---|---|
| #1 | Lymphoma mantle-cell/ | 3776 |
| #2 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti.ab | 17221 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti.ab | 133 |
| #4 | or/1-3 | 17722 |
| #5 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 1405107 |
| #6 | 4 and 5 | 2928 |
| #7 | Value of Life/ | 5809 |
| #8 | Quality of Life/ | 271986 |
| #9 | quality of life.ti.kf. | 117577 |

| No. | Query | Results |
|---|---|---|
| #10 | ((instrument or instruments) adj3 quality of life).ab. | 3942 |
| #11 | Quality-Adjusted Life Years/ | 15823 |
| #12 | quality adjusted life.ti.ab.kf. | 17617 |
| #13 | (qaly* or qald* or qale* or qtime* or life year or life years).ti.ab.kf. | 28539 |
| #14 | disability adjusted life.ti.ab.kf. | 5487 |
| #15 | daly*.ti.ab.kf. | 4962 |
| #16 | (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti.ab.kf. | 30877 |
| #17 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti.ab.kf. | 2666 |
| #18 | (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti.ab.kf. | 623 |
| #19 | (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti.ab.kf. | 7742 |
| #20 | (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti.ab.kf. | 40 |
| #21 | (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti.ab.kf. | 459 |
| #22 | (hql or hqol or h qol or hrqol or hr qol).ti.ab.kf. | 24439 |
| #23 | (hye or hYes).ti.ab.kf. | 76 |
| #24 | (health* adj2 year* adj2 equivalent*).ti.ab.kf. | 48 |
| #25 | (pqol or qls).ti.ab.kf. | 464 |
| #26 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti.ab.kf. | 722 |
| #27 | nottingham health profile*.ti.ab.kf. | 1239 |
| #28 | sickness impact profile.ti.ab.kf. | 1095 |

| No. | Query | Results |
|---|---|---|
| #29 | exp health status indicators/ | 342988 |
| #30 | (health adj3 (utilit* or status)).ti.ab.kf. | 93027 |
| #31 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti.ab.kf. | 16082 |
| #32 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti.ab.kf. | 14544 |
| #33 | disutilit*.ti.ab.kf. | 633 |
| #34 | rosser.ti.ab.kf. | 109 |
| #35 | willingness to pay.ti.ab.kf. | 8764 |
| #36 | standard gamble*.ti.ab.kf. | 917 |
| #37 | (time trade off or time tradeoff).ti.ab.kf. | 1665 |
| #38 | tto.ti.ab.kf. | 1419 |
| #39 | (hui or hui1 or hui2 or hui3).ti.ab.kf. | 1993 |
| #40 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti.ab.kf. | 22986 |
| #41 | duke health profile.ti.ab.kf. | 93 |
| #42 | functional status questionnaire.ti.ab.kf. | 131 |
| #43 | dartmouth coop functional health assessment*.ti.ab.kf. | 14 |
| #44 | or/7-43 | 757555 |
| #45 | EORTC.ti.ab.kf. | 10425 |
| #46 | ("european organization for research and treatment of cancer" or "european organisation for research and treatment of cancer").ti.ab.kf. | 6213 |
| #47 | 45 or 46 | 12853 |
| #48 | (c30 or c 30).ti.ab.kf. | 10387 |
| #49 | 47 and 48 | 5695 |
| #50 | (qlq adj2 (c30 or c 30)).ti.ab.kf. | 5705 |
| #51 | Quality of Life Questionnaire Core 30.ti.ab.kf. | 701 |

| No. | Query | Results |
|---|---|---|
| #52 | EORTC C30 questionnaire.ti.ab.kf. | 8 |
| #53 | or/49-52 | 6394 |
| #54 | (FACT or FACTG or FACTLym or "functional assessment of cancer therapy" or FACIT or FACTbrm).ti.ab.kf. | 267165 |
| #55 | 44 or 53 or 54 | 1015616 |
| #56 | 6 and 55 | 61 |
| #57 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 951643 |
| #58 | case reports/ or case study/ or case report$.jw. | 2387896 |
| #59 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3323407 |
| #60 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti.ab | 2973146 |
| #61 | or/57-60 | 8915253 |
| #62 | 56 not 61 | 56 |

**Table 63 Search strategy for humanistic SLR: PsycInfo - 1806 to November Week 4 2023**

| No. | Query | Results |
|---|---|---|
| #1 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti.ab. | 199 |
| #2 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti.ab. | 0 |
| #3 | or/1-2 | 199 |
| #4 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 129121 |
| #5 | 3 and 4 | 16 |
| #6 | Quality of Life/ | 47921 |

| No. | Query | Results |
|---|---|---|
| #7 | ((instrument or instruments) adj3 quality of life).ab. | 1235 |
| #8 | quality adjusted life.ti.ab. | 1679 |
| #9 | (qaly* or qald* or qale* or qtime* or life year or life years).ti.ab. | 2829 |
| #10 | disability adjusted life.ti.ab. | 523 |
| #11 | daly*.ti.ab. | 795 |
| #12 | (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti.ab. | 5970 |
| #13 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti.ab. | 79 |
| #14 | (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti.ab. | 153 |
| #15 | (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti.ab. | 1735 |
| #16 | (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti.ab. | 5 |
| #17 | (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti.ab. | 65 |
| #18 | (hql or hqol or h qol or hrqol or hr qol).ti.ab. | 6375 |
| #19 | (hye or hYes).ti.ab. | 45 |
| #20 | (health* adj2 year* adj2 equivalent*).ti.ab. | 4 |
| #21 | (pqol or qls).ti.ab. | 243 |
| #22 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti.ab. | 487 |
| #23 | nottingham health profile*.ti.ab. | 270 |
| #24 | sickness impact profile.ti.ab. | 341 |
| #25 | (health adj3 (utilit* or status)).ti.ab. | 26399 |

| No. | Query | Results |
|---|---|---|
| #26 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti.ab. | 5528 |
| #27 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti.ab. | 9074 |
| #28 | disutilit*.ti.ab. | 256 |
| #29 | rosser.ti.ab. | 72 |
| #30 | willingness to pay.ti.ab. | 2518 |
| #31 | standard gamble*.ti.ab. | 235 |
| #32 | (time trade off or time tradeoff).ti.ab. | 437 |
| #33 | tto.ti.ab. | 247 |
| #34 | (hui or hui1 or hui2 or hui3).ti.ab. | 677 |
| #35 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti.ab. | 4039 |
| #36 | duke health profile.ti.ab. | 49 |
| #37 | functional status questionnaire.ti.ab. | 40 |
| #38 | dartmouth coop functional health assessment*.ti.ab. | 9 |
| #39 | or/6-38 | 95819 |
| #40 | EORTC.ti.ab. | 972 |
| #41 | ("european organization for research and treatment of cancer" or "european organisation for research and treatment of cancer").ti.ab. | 611 |
| #42 | 40 or 41 | 1203 |
| #43 | (c30 or c-30).ti.ab. | 1001 |
| #44 | 42 and 43 | 801 |
| #45 | (qlq adj2 (c30 or c-30)).ti.ab. | 811 |
| #46 | Quality of Life Questionnaire Core 30.ti.ab. | 95 |
| #47 | EORTC C30 questionnaire.ti.ab. | 0 |
| #48 | or/44-47 | 922 |

| No. | Query | Results |
|---|---|---|
| #49 | (FACT or FACTG or FACTLym or "functional assessment of cancer therapy" or FACIT or FACTbrm).ti.ab. | 92233 |
| #50 | 39 or 48 or 49 | 186437 |
| #51 | 5 and 50 | 0 |

### I.1.2.2 Humanistic SLR 2025 update

**Table 64 Search strategy for humanistic SLR: Embase 1974 to 8th May 2025**

| No. | Query | Results |
|---|---|---|
| #1 | mantle cell lymphoma/ | 16604 |
| #2 | (((mantle or centrocytic or intermediate) adj3 (lymph* or NHL)) or MCL).ti,ab. | 32558 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti,ab. | 172 |
| #4 | or/1-3 | 37720 |
| #5 | first-line treatment/ | 16896 |
| #6 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 2470218 |
| #7 | 5 or 6 | 2470218 |
| #8 | 4 and 7 | 9730 |
| #9 | socioeconomics/ | 176093 |
| #10 | exp Quality of Life/ | 756970 |
| #11 | quality of life.ti,kf. | 203369 |
| #12 | ((instrument or instruments) adj3 quality of life).ab. | 5818 |
| #13 | Quality-Adjusted Life Year/ | 40138 |
| #14 | quality adjusted life.ti,ab,kf. | 30251 |
| #15 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. | 52104 |

| No. | Query | Results |
|---|---|---|
| #16 | disability adjusted life.ti,ab,kf. | 9181 |
| #17 | daly*.ti,ab,kf. | 8832 |
| #18 | (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf. | 53945 |
| #19 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf. | 3297 |
| #20 | (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf. | 1116 |
| #21 | (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf. | 13543 |
| #22 | (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf. | 77 |
| #23 | (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf. | 566 |
| #24 | (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. | 44674 |
| #25 | (hye or hyes).ti,ab,kf. | 216 |
| #26 | (health* adj2 year* adj2 equivalent*).ti,ab,kf. | 56 |
| #27 | (pqol or qls).ti,ab,kf. | 815 |
| #28 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. | 984 |
| #29 | exp "named inventories, questionnaires and rating scales"/ | 2341676 |
| #30 | nottingham health profile*.ti,ab,kf. | 1723 |
| #31 | sickness impact profile.ti,ab,kf. | 1306 |
| #32 | health status indicator/ | 3641 |
| #33 | (health adj3 (utilit* or status)).ti,ab,kf. | 135697 |

| No. | Query | Results |
|---|---|---|
| #34 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. | 28956 |
| #35 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf. | 21721 |
| #36 | disutilit*.ti,ab,kf. | 1458 |
| #37 | rosser.ti,ab,kf. | 149 |
| #38 | willingness to pay.ti,ab,kf. | 15378 |
| #39 | standard gamble*.ti,ab,kf. | 1258 |
| #40 | (time trade off or time tradeoff).ti,ab,kf. | 2577 |
| #41 | tto.ti,ab,kf. | 2534 |
| #42 | (hui or hui1 or hui2 or hui3).ti,ab,kf. | 3597 |
| #43 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. | 44504 |
| #44 | duke health profile.ti,ab,kf. | 124 |
| #45 | functional status questionnaire.ti,ab,kf. | 187 |
| #46 | dartmouth coop functional health assessment*.ti,ab,kf. | 14 |
| #47 | or/9-46 | 3152001 |
| #48 | EORTC.ti,ab,kf. | 25749 |
| #49 | ("european organization for research and treatment of cancer" or "european organisation for research and treatment of cancer").ti,ab,kf. | 9417 |
| #50 | 48 or 49 | 28843 |
| #51 | (c30 or c-30).ti,ab,kf. | 18879 |
| #52 | 50 and 51 | 13285 |
| #53 | (qlq adj2 (c30 or c 30)).ti,ab,kf. | 13468 |
| #54 | Quality of Life Questionnaire Core 30.ti,ab,kf. | 1159 |
| #55 | EORTC C30 questionnaire.ti,ab,kf. | 18 |
| #56 | or/52-55 | 14705 |

| No. | Query | Results |
|---|---|---|
| #57 | (FACT or FACTG or FACTLym or "functional assessment of cancer therapy" or FACIT or FACTbrm).ti,ab,kf. | 378032 |
| #58 | 47 or 56 or 57 | 3494445 |
| #59 | 8 and 58 | 949 |
| #60 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 1178954 |
| #61 | case reports/ or case study/ or case report$.jx. or case report$.jw. | 417056 |
| #62 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3883157 |
| #63 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab. | 3063153 |
| #64 | or/60-63 | 8187441 |
| #65 | 59 not 64 | 813 |

**Table 65 Search strategy for humanistic SLR: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to 8th May 2025**

| No. | Query | Results |
|---|---|---|
| #1 | Lymphoma mantle-cell/ | 0 |
| #2 | (((mantle or centrocytic or intermediate) adj3 (lymph* or NHL)) or MCL).ti,ab. | 52934 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti,ab. | 133 |
| #4 | or/1-3 | 53064 |
| #5 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 1562823 |
| #6 | 4 and 5 | 6263 |
| #7 | Value of Life/ | 5835 |
| #8 | Quality of Life/ | 305576 |

| No. | Query | Results |
|---|---|---|
| #9 | quality of life.ti,kf. | 136722 |
| #10 | ((instrument or instruments) adj3 quality of life).ab. | 4236 |
| #11 | Quality-Adjusted Life Years/ | 17841 |
| #12 | quality adjusted life.ti,ab,kf. | 20127 |
| #13 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. | 33833 |
| #14 | disability adjusted life.ti,ab,kf. | 7754 |
| #15 | daly*.ti,ab,kf. | 7012 |
| #16 | (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf. | 33606 |
| #17 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf. | 2965 |
| #18 | (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf. | 681 |
| #19 | (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf. | 8714 |
| #20 | (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf. | 43 |
| #21 | (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf. | 482 |
| #22 | (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. | 28296 |
| #23 | (hye or hyes).ti,ab,kf. | 79 |
| #24 | (health* adj2 year* adj2 equivalent*).ti,ab,kf. | 48 |
| #25 | (pqol or qls).ti,ab,kf. | 508 |
| #26 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. | 817 |
| #27 | nottingham health profile*.ti,ab,kf. | 1285 |

| No. | Query | Results |
|---|---|---|
| #28 | sickness impact profile.ti,ab,kf. | 1105 |
| #29 | exp health status indicators/ | 360775 |
| #30 | (health adj3 (utilit* or status)).ti,ab,kf. | 104595 |
| #31 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. | 18386 |
| #32 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf. | 16592 |
| #33 | disutilit*.ti,ab,kf. | 730 |
| #34 | rosser.ti,ab,kf. | 113 |
| #35 | willingness to pay.ti,ab,kf. | 10518 |
| #36 | standard gamble*.ti,ab,kf. | 947 |
| #37 | (time trade off or time tradeoff).ti,ab,kf. | 1794 |
| #38 | tto.ti,ab,kf. | 1652 |
| #39 | (hui or hui1 or hui2 or hui3).ti,ab,kf. | 2215 |
| #40 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. | 27181 |
| #41 | duke health profile.ti,ab,kf. | 96 |
| #42 | functional status questionnaire.ti,ab,kf. | 136 |
| #43 | dartmouth coop functional health assessment*.ti,ab,kf. | 14 |
| #44 | or/7-43 | 834896 |
| #45 | EORTC.ti,ab,kf. | 11741 |
| #46 | ("european organization for research and treatment of cancer" or "european organisation for research and treatment of cancer").ti,ab,kf. | 6928 |
| #47 | 45 or 46 | 14408 |
| #48 | (c30 or c-30).ti,ab,kf. | 11593 |
| #49 | 47 and 48 | 6571 |
| #50 | (qlq adj2 (c30 or c 30)).ti,ab,kf. | 6635 |

| No. | Query | Results |
|---|---|---|
| #51 | Quality of Life Questionnaire Core 30.ti,ab,kf. | 854 |
| #52 | EORTC C30 questionnaire.ti,ab,kf. | 8 |
| #53 | or/49-52 | 7411 |
| #54 | (FACT or FACTG or FACTLym or "functional assessment of cancer therapy" or FACIT or FACTbrm).ti,ab,kf. | 280964 |
| #55 | 44 or 53 or 54 | 1105898 |
| #56 | 6 and 55 | 190 |
| #57 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 1047870 |
| #58 | case reports/ or case study/ or case report$.jw. | 2515331 |
| #59 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3477723 |
| #60 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab. | 3208516 |
| #61 | or/57-60 | 9461201 |
| #62 | 56 not 61 | 170 |

**Table 66 Search strategy for humanistic SLR: PsycInfo - 1806 to May 2025 week 1**

| No. | Query | Results |
|---|---|---|
| #1 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti,ab. | 216 |
| #2 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti,ab. | 0 |
| #3 | or/1-2 | 216 |
| #4 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 139640 |
| #5 | 3 and 4 | 16 |
| #6 | Quality of Life/ | 52501 |

| No. | Query | Results |
|---|---|---|
| #7 | ((instrument or instruments) adj3 quality of life).ab. | 1318 |
| #8 | quality adjusted life.ti,ab. | 1908 |
| #9 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab. | 3266 |
| #10 | disability adjusted life.ti,ab. | 659 |
| #11 | daly*.ti,ab. | 926 |
| #12 | (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. | 6324 |
| #13 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab. | 96 |
| #14 | (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab. | 164 |
| #15 | (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. | 1874 |
| #16 | (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. | 7 |
| #17 | (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. | 68 |
| #18 | (hql or hqol or h qol or hrqol or hr qol).ti,ab. | 7131 |
| #19 | (hye or hYes).ti,ab. | 52 |
| #20 | (health* adj2 year* adj2 equivalent*).ti,ab. | 4 |
| #21 | (pqol or qls).ti,ab. | 257 |
| #22 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab. | 530 |
| #23 | nottingham health profile*.ti,ab. | 283 |
| #24 | sickness impact profile.ti,ab. | 342 |
| #25 | (health adj3 (utilit* or status)).ti,ab. | 28642 |

| No. | Query | Results |
|---|---|---|
| #26 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab. | 6131 |
| #27 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab. | 9864 |
| #28 | disutilit*.ti,ab. | 279 |
| #29 | rosser.ti,ab. | 76 |
| #30 | willingness to pay.ti,ab. | 2865 |
| #31 | standard gamble*.ti,ab. | 242 |
| #32 | (time trade off or time tradeoff).ti,ab. | 477 |
| #33 | tto.ti,ab. | 270 |
| #34 | (hui or hui1 or hui2 or hui3).ti,ab. | 741 |
| #35 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. | 4583 |
| #36 | duke health profile.ti,ab. | 52 |
| #37 | functional status questionnaire.ti,ab. | 40 |
| #38 | dartmouth coop functional health assessment*.ti,ab. | 9 |
| #39 | or/6-38 | 105332 |
| #40 | EORTC.ti,ab. | 1084 |
| #41 | ("european organization for research and treatment of cancer" or "european organisation for research and treatment of cancer").ti,ab. | 680 |
| #42 | 40 or 41 | 1344 |
| #43 | (c30 or c-30).ti,ab. | 1104 |
| #44 | 42 and 43 | 895 |
| #45 | (qlq adj2 (c30 or c-30)).ti,ab. | 903 |
| #46 | Quality of Life Questionnaire Core 30.ti,ab. | 115 |
| #47 | EORTC C30 questionnaire.ti,ab. | 0 |
| #48 | or/44-47 | 1028 |

| No. | Query | Results |
|---|---|---|
| #49 | (FACT or FACTG or FACTLym or "functional assessment of cancer therapy" or FACIT or FACTbrm).ti,ab. | 96044 |
| #50 | 39 or 48 or 49 | 199605 |
| #51 | 5 and 50 | 0 |

### I.1.3 Eligibility criteria

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. Selection of studies for inclusion was determined using the PICOS framework[87] and are presented in Table 67.

**Table 67 Eligibility criteria for the humanistic systematic literature review**

| PICOS | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | • Adult patients (≥18 years) with previously untreated (1L) MCL<br>• Studies with mixed population of lymphoma patients were eligible for inclusion if they reported outcomes in the population of interest, or the population of interest comprises most (≥80%) of the study population | • Paediatric patients<br>• Studies not including MCL patients<br>• Studies not including previously untreated (1L) MCL patients |
| **Intervention/ Comparators** | No restriction | N/A |
| **Outcomes** | **Utilities/disutilities:** Direct and indirect values, e.g., EQ-5D, HUI, TTO, SG<br><br>**Quality-of-life measures, including, but not limited to:** EORTC QLQ-30, FACT-General, FACT-Fatigue, SF-6, SF-12, SF-36<br><br>**Caregiver/family burden measures, including, but not limited to:** ZBI-22, ZBI-12, ZBI-7, CAHPS cancer care survey, CGI | • Outcomes not listed in the inclusion criteria |
| **Study design(s)** | • Interventional studies (phases II or III clinical trials e.g., RCTs, single-arm trials, non-RCTs)<br>• Observational studies (prospective or retrospective, including surveys and questionnaires)<br>• Utility elicitation/validation and economic evaluation studies | • Pharmacodynamic/ pharmacokinetic studies, genetic studies, cellular/molecular studies, in vitro/ex-vivo studies<br>• Case reports or case series (studies including <20 patients)<br>• Economic evaluations |

| | | |
|---|---|---|
| | | • Narrative reviews, SLRs/network meta-analyses[1] |
| **Limits** | • Time limit: Full text publications: No restriction; Conference titles/ abstracts: 2020-2025<br>• Geography: No restriction<br>• Language: English | • Time limit: Conference abstracts published before 2020 |

Abbreviations: CAHPS, Consumer Assessment of Healthcare Providers and Systems; CGI, Caregiver Inventory; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EQ-5D, EuroQol 5-Dimension; FACT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-General, Functional Assessment of Cancer Therapy – General; HUI, Health Utilities Index; MCL, mantle cell lymphoma; RCT, Randomised Controlled Trial; SF, Short Form; SG, Standard Gamble; SLR, Systematic literature review; TTO, Time trade-off; ZBI, Zarit Burden Interview.
[1] SLR/ network meta-analyses were included at abstract review stage to search their reference lists for any missed studies and subsequently excluded during the full text review stage.

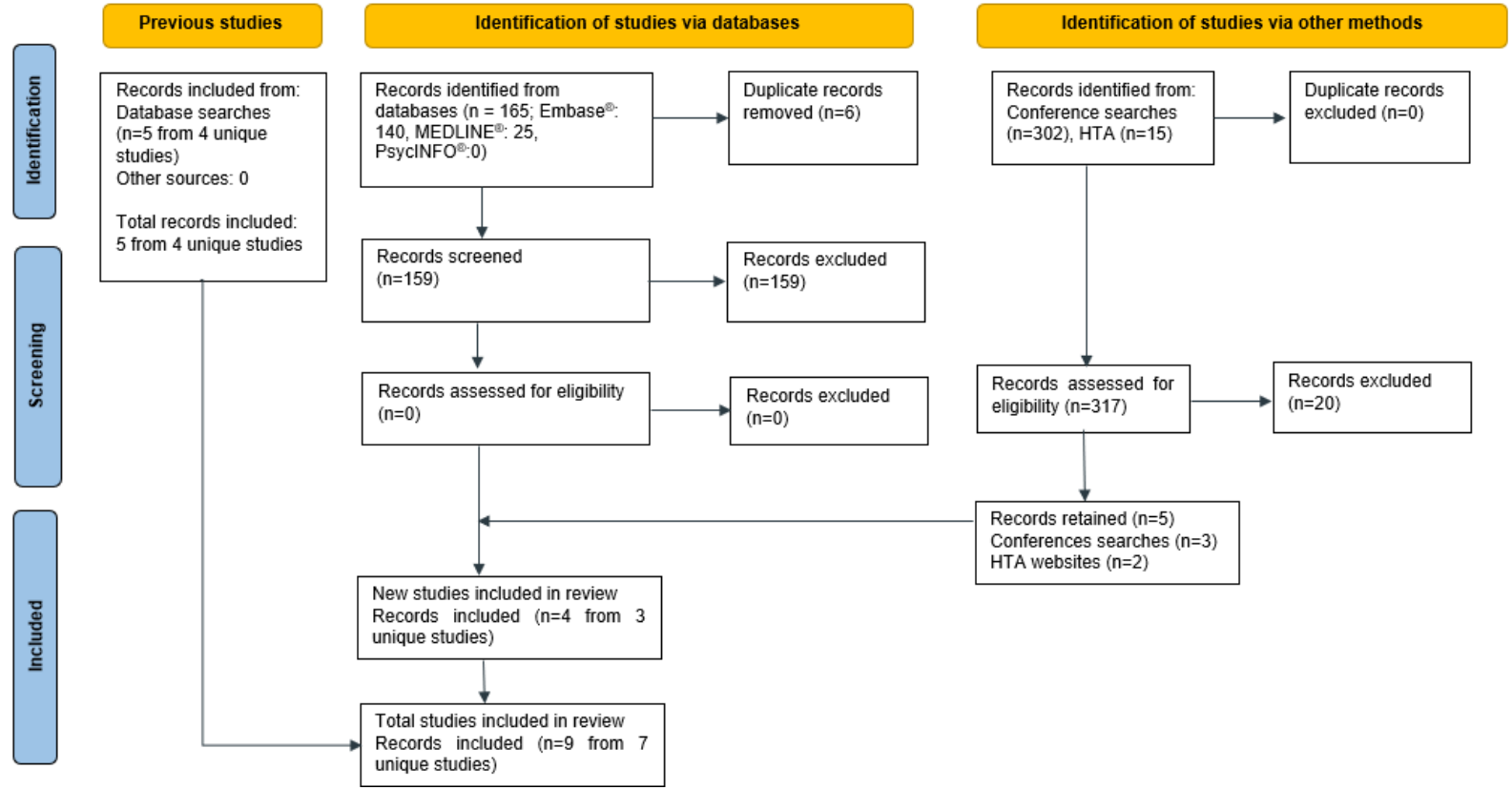
### I.1.4 Systematic selection of studies

A total of 501 references were identified from electronic database searches conducted on 7th December 2023 (Embase: 440; MEDLINE: 61, PsycINFO: 0). After removing duplicates (n=82), titles and abstracts of 419 references were screened against the eligibility criteria. During the screening process, 317 references were excluded, and 102 potentially relevant references were retrieved for full-text assessment. Of these 102 references, 97 references were excluded, resulting in the inclusion of five relevant publications from four unique studies. These four studies on 1L MCL patients were retained for data extraction and are discussed in detail in the below sections. Due to the limited data identified for 1L MCL patients in the SLR, Janssen recommended to include additional data from four studies on broader lymphoma patients in which outcomes specific to the 1L MCL patients were not reported. Although these studies did not meet the eligibility criteria defined in the SLR, these were considered of potential interest.

A SLR update conducted on 9th May 2025 (from 2023-current) identified 165 references from the electronic database searches (Embase: 140; MEDLINE: 25, PsycINFO: 0). The new records were checked against the original SLR and the duplicates were removed (n=6); the remaining 159 publications were screened against the eligibility criteria. After the title and abstract screening, all 159 references were excluded. Additionally, four records were identified through other methods (conference search and HTA reviews), resulting in the inclusion of four publications from three unique studies. In total, nine publications from seven unique studies were included in the combined original (n=5 publications) and updated SLR (n=4 publications). Similar to the original SLR, one study including broader lymphoma patients, in which outcomes specific to the 1L MCL patients were not reported, was also included; therefore, a total of five studies were included the combined original (n=4 publications) and updated SLR (n=1 publication).

The PRISMA diagram in Figure 33 presents the results of the SLR update described above. A detailed PRISMA diagram presenting the results of original SLR is presented in Figure 34.

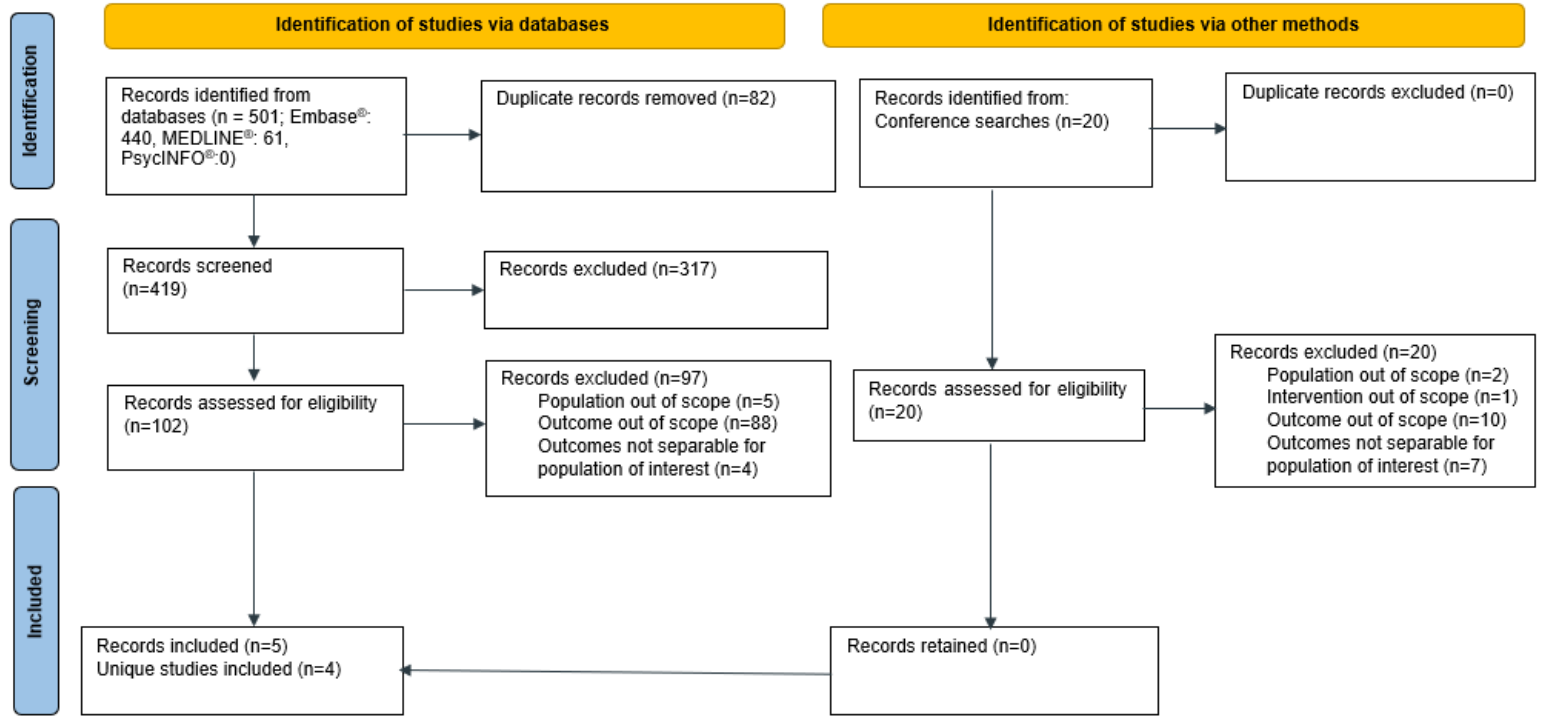
**Figure 33 PRISMA flowchart for study selection of humanistic SLR (original - 7th December 2023 and SLR update - 9th May 2025)**




Source: Adapted from Page et al. (2021)[90].

Note: Additionally, five studies (four from the original SLR and one from the SLR update) on broader lymphoma patients were included in which outcomes specific to the 1L MCL patients were not reported.

**Figure 34 PRISMA flowchart for study selection of humanistic SLR (original SLR - 7th December 2023)**




Source: Adapted from Page et al. (2021)[90].

Note: Because of the limited data identified and included in the humanistic SLR, four studies in which outcomes were not separable for population of interest were also include

### I.1.5 Excluded full text references

The global SLR identified 12 relevant studies. However, as detailed in the local adaptation section above, none of the publications included in the global SLR were used in the current submission, and they are therefore considered 'excluded'. A list of the 12 studies included in the global SLR is provided in Table 68, and a list of studies excluded from all the humanistic SLR is provided in Table 69.

**Table 68 Overview of study design for studies included in the global humanistic SLR**

| Author | Title | Year | Study design |
|---|---|---|---|
| Widmer F, Balabanov S, Soldini D, Samaras P, Gerber B, Manz MG, et al. | R-hyper-CVAD versus R-CHOP/cytarabine with high-dose therapy and autologous haematopoietic stem cell support in fit patients with mantle cell lymphoma: 20 years of single-center experience | 2018 | Retrospective study |
| Krüger WH, Hirt C, Basara N, Sayer HG, Behre G, Fischer T, et al. | Allogeneic stem cell transplantation for mantle cell lymphoma—update of the prospective trials of the East German Study Group Hematology/Oncology (OSHO# 60 and# 74) | 2021 | Pooled analysis of two RCTs |
| Simensen VC, Smeland KB, Kiserud CE, Dahl AA, Bersvendsen HS, Fluge Ø, et al. | Survivors' knowledge of their diagnosis, treatment and possible late adverse effects after autologous stem cell transplantation for lymphoma | 2019 | Cross-sectional study |
| Di M, Ho CI, Smith SD, Shadman M, Ujjani CS, Lynch RC, et al. | Quality of Life during Survivorship Following Autologous Stem Cell Transplant for Mantle Cell Lymphoma | 2024 | Retrospective cohort (survey) |
| Ruan J, Martin P, Shah B, Schuster SJ, Smith SM, Furman RR, et al. | Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma | 2015 | Single-arm trial |
| Burke JM, Van Der Jagt RH, Kahl BS, Wood P, Hawkins TE, MacDonald D, et al. | Differences in quality of life between bendamustine-rituximab and R-CHOP/R-CVP in patients with previously untreated advanced indolent non-Hodgkin lymphoma or mantle cell lymphoma | 2016 | RCT |

| Author | Title | Year | Study design |
|---|---|---|---|
| Witzens-Harig M, Reiz M, Heiß C, Benner A, Hensel M, Neben K, et al. | Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomized controlled trial | 2009 | RCT |
| Wang ML, Jurczak W, Jerkeman M, Trotman J, Zinzani PL, Belada D, et al. | Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma | 2022 | RCT |
| Lindberg Å, Eskelund CW, Albertsson-Lindblad A, Kolstad A, Laurell A, Räty R, et al. | Pre-treatment health-related quality of life parameters have prognostic impact in patients> 65 years with newly diagnosed mantle cell lymphoma: The Nordic Lymphoma Group MCL4 (LENA-BERIT) experience. | 2022 | Single-arm trial |
| Lewis DJ, Jerkeman M, Sorrell L, Wright D, Glimelius I, Pasanen A, et al. | Ibrutinib-Rituximab Is Superior to Rituximab-Chemotherapy in Previously Untreated Older Mantle Cell Lymphoma Patients: Results from the International Randomised Controlled Trial | 2024 | RCT |
| National Institute for Health and Care Excellence | NICE technology appraisal guidance 370 | 2022 | HTA submission |
| Scottish Medicines Consortium | No. (1075/15): Bortezomib (Velcade®) | 2022 | HTA submission |

**Table 69 List of excluded studies at full-text screening stage for global humanistic SLR**

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 1 | Ramsower, 2023 | Evaluation of clinical parameters and biomarkers in older, untreated mantle cell lymphoma patients receiving bendamustine-rituximab | Outcomes |
| 2 | Karmali, 2023 | Ibrutinib Maintenance Following Frontline Treatment in Patients with Mantle Cell Lymphoma | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 3 | Ogura, 2023 | Long-term follow-up after R-High CHOP/CHASER/LEED with Auto-PBSCT in untreated mantle cell lymphoma-Final analysis of JCOG0406 | Outcomes |
| 4 | Yang, 2023 | Real-world treatment and outcome patterns of patients with mantle cell lymphoma in China: A large, multicenter retrospective analysis | Outcomes |
| 5 | Metzner, 2023 | Long-term outcome in patients with mantle cell lymphoma following high-dose therapy and autologous stem cell transplantation | Outcomes |
| 6 | Thurner, 2023 | Radiation and Dose-densification of R-CHOP in Aggressive B-cell Lymphoma With Intermediate Prognosis: The UNFOLDER Study | Outcomes |
| 7 | David, 2023 | Older patients with primary central nervous system lymphoma: Survival and prognostication across 20 U.S. cancer centers | Outcomes |
| 8 | Epperla, 2023 | Impact of diagnosis to treatment interval in patients with newly diagnosed mantle cell lymphoma | Outcomes |
| 9 | Patel, 2023 | Bendamustine/Rituximab Plus Cytarabine/Rituximab, With or Without Acalabrutinib, for the Initial Treatment of Transplant-Eligible Mantle Cell Lymphoma Patients: Pooled Data From Two Pilot Studies | Outcomes |
| 10 | Kalicinska, 2023 | A survey across orbital lymphoma in Poland: Multicenter retrospective study of polish lymphoma research group (PLRG) | Outcomes |
| 11 | Hermine, 2023 | High-Dose Cytarabine and Autologous Stem-Cell Transplantation in Mantle Cell Lymphoma: Long-Term Follow-Up of the Randomised Mantle Cell Lymphoma Younger Trial of the European Mantle Cell Lymphoma Network | Outcomes |
| 12 | Vergote, 2023 | [18F]FDG-PET/CT volumetric parameters can predict outcome in untreated mantle cell lymphoma | Outcomes |
| 13 | Serna, 2022 | Impact of Coronavirus (COVID-19) Pandemic on Maintenance Therapy for Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL) | Outcomes |
| 14 | Rezazadeh, 2022 | Immunoglobulin High Throughput Sequencing (Ig-HTS) Minimal Residual Disease (MRD) Analysis Is an Effective Surveillance Tool in Patients with Mantle Cell Lymphoma | Outcomes |
| 15 | Choquet, 2022 | Use of Ibrutinib in Real Life Settings in France: Results from a Retrospective Observational Study Using the Snds Database (OSIRIS) | Outcomes |
| 16 | Hernandez-Rivas, 2022 | Ibrutinib Plus Bendamustine Plus Rituximab and Rituximab Maintenance (I+BR) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone Regimen (R-CHOP) and Rituximab, Cyclophosphamide, Doxorubicin, Bortezomib, | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| | | Prednisone Regimen (VR-CAP) in First-Line Mantle Cell Lymphoma Patients: An Adjusted Treatment Comparison Using Inverse Probability Weighting | |
| 17 | Erkut, 2022 | Effect of Clinical, Endoscopic, Radiological Findings, and Complications on Survival in Patients with Primary Gastrointestinal Lymphoma | Outcomes |
| 18 | Jain, 2022 | Ibrutinib With Rituximab in First-Line Treatment of Older Patients With Mantle Cell Lymphoma | Outcomes |
| 19 | Villa, 2022 | Bendamustine or high-dose cytarabine-based induction with rituximab in transplant-eligible mantle cell lymphoma | Outcomes |
| 20 | Gine, 2022 | Ibrutinib in Combination With Rituximab for Indolent Clinical Forms of Mantle Cell Lymphoma (IMCL-2015): A Multicenter, Open-Label, Single-Arm, Phase II Trial | Outcomes |
| 21 | Oliveira, 2022 | MANTLE CELL LYMPHOMA IN BRAZIL: FIRST REPORT FROM A REAL-WORLD EVIDENCE STUDY OF A THIRD WORLD COUNTRY | Outcomes |
| 22 | Vergote, 2022 | METABOLIC TUMOR VOLUME IMPROVES OUTCOME PREDICTION IN UNTREATED MANTLE CELL LYMPHOMA | Outcomes |
| 23 | Polyakov, 2022 | THERAPY AND HOSPITAL MORTALITY PREDICTORS IN PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS AND CONCOMITANT COVID-19 INFECTION | Outcomes |
| 24 | Ma, 2022 | Factors associated with death from lymphoma in a single center study | Outcomes |
| 25 | Soumerai, 2021 | Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial | Population |
| 26 | Wu, 2021 | Initial Treatment Patterns and Survival Outcomes of Mantle Cell Lymphoma Patients Managed at Chinese Academic Centers in the Rituximab Era: A Real-World Study | Outcomes |
| 27 | Riedell, 2021 | Outcomes and Utilisation Trends of Front-Line Autologous Haematopoietic Cell Transplantation for Mantle Cell Lymphoma | Outcomes |
| 28 | Zoellner, 2021 | Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial | Outcomes |
| 29 | Yang, 2021 | Treatment patterns and outcomes of older patients with mantle cell lymphoma in an Asian population | Outcomes |
| 30 | Karmali, 2021 | Multi-center analysis of practice patterns and outcomes of younger and older patients with mantle cell lymphoma in the rituximab era | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 31 | Weaver, 2021 | A medicare database analysis of practice patterns in patients with mantle cell lymphoma | Outcomes |
| 32 | Massaro, 2021 | Long-term results of the MCL01 phase II trial of rituximab plus HyperCVAD alternating with high-dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma | Outcomes |
| 33 | Castellino, 2021 | Clinical characteristics and outcomes of primary versus secondary gastrointestinal mantle cell lymphoma | Outcomes |
| 34 | Ma, 2021 | Comparison of clinicopathological features and treatment outcomes in aggressive primary intestinal B- and T/NK-cell lymphomas | Outcomes |
| 35 | Cabirta, 2021 | Early Relapse after First Line Has a Significant Impact on Overall Survival in Patients with Mantle Cell Lymphoma (MCL) | Outcomes |
| 36 | Ruiz, 2021 | Cyclophosphamide, Etoposide, and Intermediate-Dose of Carboplatin; An Efficient Preparative Regimen for Autologous Transplantation for Patients with Lymphoma, a Good Alternative to Those Based on Carmustine. Experience with 108 Patients | Outcomes |
| 37 | Ribrag, 2021 | Rituximab-Lenalidomide(R2) Maintenance Is Superior to Rituximab Maintenance after First Line Immunochemotherapy in Mantle Cell Lymphoma: Results of the MCL R2 Elderly Clinical Trial | Outcomes |
| 38 | Wang, 2021 | Ibrutinib Plus Rituximab and Venetoclax (IRV) Followed By Risk-Stratified Observation or Short Course R-Hypercvad/MTX in Young Patients with Previously Untreated Mantle Cell Lymphoma - Phase-II Window-2 Clinical Trial | Outcomes |
| 39 | Kumar, 2021 | Preliminary Safety and Efficacy from a Multicenter, Investigator-Initiated Phase II Study in Untreated TP53 Mutant Mantle Cell Lymphoma with Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) | Outcomes |
| 40 | Fischer, 2021 | The Addition of Rituximab to Cyclophosphamide, Doxorubicine, Vincristine and Prednisone (CHOP) Prolongs Overall Survival in Previously Untreated Mantle Cell Lymphoma: A Long Term Pooled Trials Analysis | Outcomes |
| 41 | Andrade-Gonzalez, 2021 | Impact of Diagnosis-to-Treatment Interval on Overall Survival in Patients with Mantle Cell Lymphoma: A National Cancer Database Analysis | Outcomes |
| 42 | Delfau, 2021 | Impact of Maintenance Arm on Prognostic Value of MRD after Induction Treatment in MCL R2 Elderly Trial, a Mantle Cell Lymphoma Network Study | Outcomes |
| 43 | Ekberg, 2021 | Late Effects after Treatment in Mantle Cell Lymphoma: No Difference By Intensity of First-Line Regimens with or without Autologous Stem Cell Transplantation | Outcomes |
| 44 | Elhassadi, 2021 | Retrospective study on mantle cell lymphoma (mcl) and treatment out-come-a single center experience | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 45 | Kotchetkov, 2021 | Outcomes of bendamustine + rituximab firstline therapy in patients with indolent non-hodgkin's lymphoma or mantle cell lymphoma: Real world experience | Outcomes |
| 46 | Nolan, 2021 | P53 Immunohistochemistry detects nonpathogenic mutations in mantle cell lymphoma necessitating tp53 ngs for clinical decision making | Outcomes |
| 47 | Martin, 2021 | Real-world treatment patterns and outcomes of 3455 previously untreated mantle cell lymphoma patients in us routine clinical practice | Outcomes |
| 48 | Salles, 2021 | Role of maintenance rituximab (mr) after first-line (1l) bendamustine + rituximab (br) or r-chop in patients (pts) with mantle cell lymphoma (mcl) from a large us real-world (rw) cohort | Outcomes |
| 49 | Kotchetkov, 2021 | First-line treatment with Bendamustine plus Rituximab for patients with indolent nonHodgkin's lymphoma or Mantle cell lymphoma: Real-world experience | Outcomes |
| 50 | Martin, 2021 | Real-world (RW) treatment (tx) patterns and outcomes of 3,455 previously untreated mantle cell lymphoma (MCL) patients (pts) in U.S. routine clinical practice | Outcomes |
| 51 | Smith, 2021 | ECOG-ACRIN E1411 randomised phase 2 trial of bendamustinerituximab (BR)-based induction followed by rituximab (R) +/- lenalidomide (L) consolidation for Mantle cell lymphoma: Effect of adding bortezomib to front-line BR induction on PFS | Outcomes |
| 52 | Roy, 2021 | Cachexia is an independent factor for negative clinical and functional outcomes in lymphoma patients receiving CART therapy | Outcomes |
| 53 | Wang, 2021 | Stem Cell Transplantation in Mantle Cell Lymphoma: Post-Transplant Outcomes of Taiwan Blood and Marrow Transplantation Registry | Outcomes |
| 54 | Wang, 2021 | Role of maintenance rituximab after first-line bendamustine + rituximab or R-CHOP in patients with mantle cell lymphoma from a large us real-world cohort | Outcomes |
| 55 | Kumar, 2021 | Real-world treatment patterns and outcomes of 3455 previously untreated mantle cell lymphoma patients in us routine clinical practice | Population |
| 56 | Kruger, 2021 | Allogeneic stem cell transplantation for mantle cell lymphoma-update of the prospective trials of the East German Study Group Haematology/Oncology (OSHO#60 and #74). | Outcomes |
| 57 | Brasil, 2020 | Non-indolent mantle cell lymphoma at a single public hospital in Brazil: real world first-line treatment cohort study data | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 58 | Villa, 2020 | Bendamustine and rituximab as induction therapy in both transplant-eligible and -ineligible patients with mantle cell lymphoma | Outcomes |
| 59 | Ogul, 2020 | Efficacy of prephase treatment for the prevention of tumor lysis syndrome in lymphoma cases with high tumor burden: A cross-sectional study | Outcomes |
| 60 | Ng, 2019 | A multicenter retrospective comparison of induction chemoimmunotherapy regimens on outcomes in transplant-eligible patients with previously untreated mantle cell lymphoma | Outcomes |
| 61 | Kumar, 2019 | Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse | Population |
| 62 | Simensen, 2019 | Survivors' knowledge of their diagnosis, treatment and possible late adverse effects after autologous stem cell transplantation for lymphoma | Outcomes |
| 63 | Flinn, 2019 | First-line treatment of patients with indolent non-hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: Results of the BRIGHT 5-year follow-up study | Outcomes |
| 64 | Gressin, 2019 | A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for first-line treatment of older patients with mantle cell lymphoma | Outcomes |
| 65 | Ruan, 2018 | Five-year follow-up of lenalidomide plus rituximab as initial treatment of mantle cell lymphoma | Outcomes |
| 66 | Greenwell, 2018 | Complex karyotype in patients with mantle cell lymphoma predicts inferior survival and poor response to intensive induction therapy | Outcomes |
| 67 | Calzada, 2018 | Deferred treatment is a safe and viable option for selected patients with mantle cell lymphoma. | Outcomes |
| 68 | Smith, 2017 | Mantle cell lymphoma initial therapy with abbreviated R-CHOP followed by 90Y-ibritumomab tiuxetan: 10-year follow-up of the phase 2 ECOG-ACRIN study E1499 | Outcomes |
| 69 | Vergote, 2017 | Results from the Belgian mantle cell lymphoma registry | Outcomes |
| 70 | Visco, 2017 | Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: a multicentre, phase 2 trial from Fondazione Italiana Linfomi | Outcomes |
| 71 | Berger, 2016 | Zevalin and BEAM (Z-BEAM) versus rituximab and BEAM (R-BEAM) conditioning chemotherapy prior to autologous stem cell transplantation in patients with mantle cell lymphoma | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 72 | Hermine, 2016 | Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network | Outcomes |
| 73 | Eskelund, 2016 | 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau | Outcomes |
| 74 | Mondello, 2016 | 90Y-Ibritumomab-Tiuxetan Consolidation Therapy for Advanced-Stage Mantle Cell Lymphoma after First-Line Autologous Stem Cell Transplantation: Is It Time for a Step Forward? | Outcomes |
| 75 | Lamar, 2016 | Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (EPOCH) with or Without Rituximab as First-Line Therapy for Aggressive Non-Hodgkin Lymphoma | Outcomes |
| 76 | Till, 2016 | Phase II trial of R-CHOP plus bortezomib induction therapy followed by bortezomib maintenance for newly diagnosed mantle cell lymphoma: SWOG S0601 | Population |
| 77 | Burke, 2016 | Differences in Quality of Life Between Bendamustine-Rituximab and R-CHOP/R-CVP in Patients With Previously Untreated Advanced Indolent Non-Hodgkin Lymphoma or Mantle Cell Lymphoma. | Outcomes |
| 78 | Nastoupil, 2015 | Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma | Outcomes |
| 79 | Becker, 2015 | Bendamustine as first-line treatment in patients with advanced indolent non-Hodgkin lymphoma and mantle cell lymphoma in German routine clinical practice | Outcomes |
| 80 | Hosein, 2015 | Updated survival analysis of two sequential prospective trials of R-MACLO-IVAM followed by maintenance for newly diagnosed mantle cell lymphoma | Outcomes |
| 81 | Kang, 2014 | Clinical features and treatment outcomes in patients with mantle cell lymphoma in Korea: Study by the consortium for improving survival of lymphoma | Outcomes |
| 82 | Leux, 2014 | Mantle cell lymphoma epidemiology: A population-based study in France | Outcomes |
| 83 | Bernstein, 2013 | A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213 | Outcomes |
| 84 | Delarue, 2013 | CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: A phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 85 | Budde, 2011 | Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation | Outcomes |
| 86 | Ruan, 2011 | Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma | Outcomes |
| 87 | Recher, 2011 | Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. | Outcomes |
| 88 | Romaguera, 2010 | Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma | Outcomes |
| 89 | Gressin, 2010 | Evaluation of the (R)VAD+C regimen for the treatment of newly diagnosed mantle cell lymphoma. combined results of two prospective phase ii trials from the French GOELAMS group | Outcomes |
| 90 | Smith, 2010 | Validation of the Mantle Cell Lymphoma International Prognostic Index: A single-center retrospective analysis. | Population |
| 91 | Witzens-Harig, 2009 | Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomised controlled trial. | Outcomes |
| 92 | Akutsu, 2008 | Long-term results of dose-intensive chemotherapy with G-CSF support (TCC-NHL-91) for advanced intermediate-grade non-Hodgkin's lymphoma: A review of 59 consecutive cases treated at a single institute | Population |
| 93 | Ghielmini, 2005 | Single agent rituximab in patients with follicular or mantle cell lymphoma: Clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: A study of the Swiss Group for Clinical Cancer Research (SAKK) | Outcomes |
| 94 | Thieblemont, 2005 | Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. | Outcomes |
| 95 | Visco, 2001 | Non-Hodgkin's lymphoma affecting the testis: Is it curable with doxorubicin-based therapy? | Population |
| 96 | Picozzi, 2001 | Patterns of chemotherapy administration in patients with intermediate-grade non-Hodgkin's lymphoma. | Population |
| 97 | Palmieri, 1998 | Tailored therapy for aggressive non-Hodgkin's lymphoma: results of a phase II study with a long-term follow-up. | Population |

### I.1.6 Local adaptation

To support this submission for ibrutinib for the treatment of MCL in Denmark, the global SLR was adapted by excluding all studies not relevant to a Danish setting. The objective of this SLR was to identify published evidence on the humanistic burden associated with 1L MCL and related conditions. As no sources identified Table 68 aligned with the Danish setting, all sources from the global SLR were excluded as inputs for the health economic model. The local adaptation is illustrated in Figure 35.

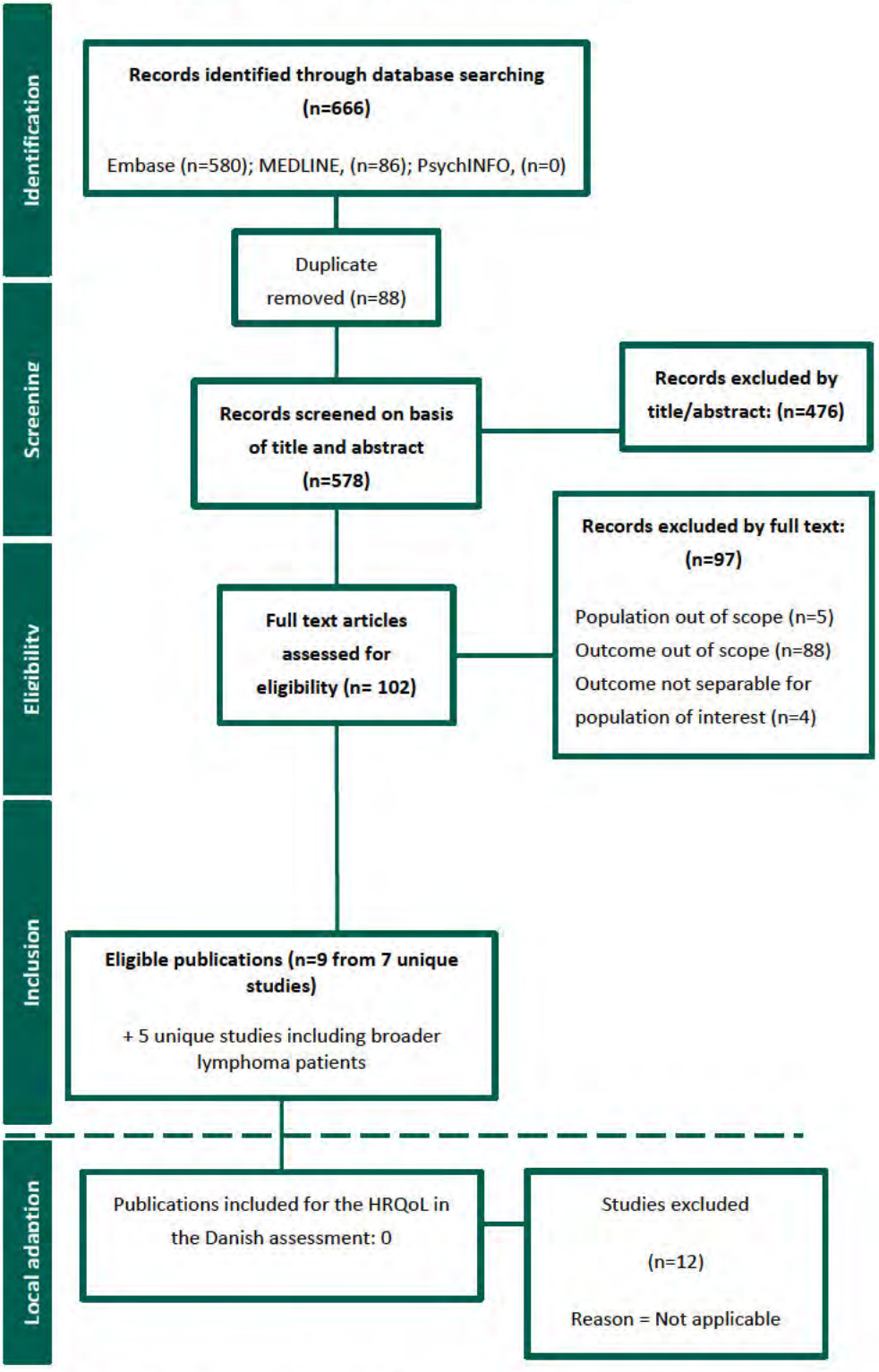
**Targeted literature review – humanistic studies**

In addition to the SLR, a targeted literature review (TLR) was conducted to identify and collect relevant inputs for the HSUV model. The TLR was conducted pragmatically, focusing only on disutility values not already covered by the SHINE and RAY trials. Three sources were identified and used in the HSUV model

**Table 70 List of studies included to identify relevant inputs for the HSUV model, TLR**

| Source name/database | Location/source | Search strategy | Date of search |
|---|---|---|---|
| Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G.[75] | Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia | Hand search | 16.07.2025 |
| NICE TA343 | Technology appraisal guidance: Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia - TA343: www.nice.org.uk | Hand search | 16.07.2025 |
| NICE TA891[74] | Technology appraisal guidance: Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia - TA891: www.nice.org.uk | Hand search | 16.07.2025 |

Figure 35 PRISMA diagram including local adaptation (humanistic SLR)




Abbreviations: HRQoL, health-related quality of life

### I.1.7 Quality assessment and generalizability of estimates

N/A

### I.1.8 Unpublished data

N/A

# Appendix J. Literature searches for input to the health economic model

## J.1 External literature for input to the health economic model

**Objective**

The objective of this SLR was to identify published evidence on the economic burden associated with 1L MCL patients. To meet the study objectives, the following research questions will be addressed:

"What is the economic burden of previously untreated MCL in terms of the following:

- Health resource use and costs?
- Characteristics and results of health economic evaluations of interventions for treating MCL in this patient group?"

The SLRs were conducted according to the standards set out in the Cochrane Handbook for Systematic Reviews of Interventions[87] as well as the high-quality standards required by the NICE[88].

### J.1.1 Information sources

Systematic searches were first conducted on 7th December 2023 with the subsequent search update on 9th May 2025 via OVID SP in Embase, MEDLINE, EconLit and INAHTA (Table 71) database using a pre-defined search strategy.

**Table 71 Bibliographic databases included in the economic literature search**

| Database | Platform | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **Embase** | Ovid | 1974 and onwards | 09.05.2025 |
| **Medline** | Ovid | 1946 and onwards | 09.05.2025 |
| **EconLit** | Ovid | 1886 and onwards | 09.05.2025 |
| **INAHTA**[a] | Ovid | | 09.05.2025 |

a. INAHTA was included in the May 2025 SLR update (was not included in the original SLR)

Additionally, conference searches were conducted from 2021 (in 2023 SLR) and 2024 (in 2025 update) onwards to capture the most recent and relevant references. This rationale was in line with the recommendations from the NICE guidelines, which mention that good-quality studies often publish full text papers after the conference abstract, and these are identified by routine searches[89]. The conferences included in Table 72 were hand-searched.

**Table 72 Conference material included in the literature search**

| Conference | Platform | Relevant period for the search | Latest date of search completion |
|---|---|---|---|
| American Association for Cancer Research (AACR) | www.aacr.org | 2020-2025 | 09.05.2025 |
| American Society of Clinical Oncology (ASCO) | www.asco.org | 2020-2025 | 09.05.2025 |
| American Society of Hematology (ASH)[a] | www.hematology.org | 2020-2025 | 09.05.2025 |
| European Hematology Association (EHA) | www.ehaweb.org | 2020-2025 | 09.05.2025 |
| European Society for Medical Oncology (ESMO)[a] | www.esmo.org | 2020-2025 | 09.05.2025 |
| International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[b] | www.ispor.org | 2020-2025 | 09.05.2025 |

a. The latest proceedings from the ASH 2025 and the ESMO 2025 were not available at the time of conducting the hand-searches
b. ISPOR was only searched for the 2025 update

To ensure that ongoing clinical intervention trials were also identified, clinicaltrials.gov and the European Union's Clinical Trials Register were screened. Additionally, to complement the electronic database searches for the SLR, searches in the HTA websites were conducted (only in the 2025 update) to identify economic evaluation reports (Table 73).

**Table 73 Other sources included in the literature search**

| Source name | Platform | Relevant period for the search | Latest date of search completion |
|---|---|---|---|
| Agency for Healthcare Research and Quality (AHRQ) | www.ahrq.gov | 2020-2025 | 09.05.2025 |
| Agenzia Italiana del Farmaco (AIFA) | www.aifa.gov.it | 2020-2025 | 09.05.2025 |
| All Wales Medicines Strategy Group (AWMSG) | www.gov.wales/all-wales-medicines-strategy-group | 2020-2025 | 09.05.2025 |
| European Medicines Agency (EMA) | www.ema.europa.eu | 2020-2025 | 09.05.2025 |

| Source name | Platform | Relevant period for the search | Latest date of search completion |
|---|---|---|---|
| Canada's Drug Agency (CDA) | www.cda-amc.ca | 2020-2025 | 09.05.2025 |
| Federal Joint Committee (G-BA) | www.g-ba.de | 2020-2025 | 09.05.2025 |
| Haute Autorité de Santé (HAS) | www.has-sante.fr | 2020-2025 | 09.05.2025 |
| Institute for Clinical and Economic Review (ICER) | www.icer.org | 2020-2025 | 09.05.2025 |
| The International Network of Agencies for HTA (INAHTA) | www.inahta.org | 2020-2025 | 09.05.2025 |
| Institute for Quality and Efficiency in Health Care (IQWiG) | www.iqwig.de | 2020-2025 | 09.05.2025 |
| National Centre for Pharmacoeconomics (NCPE) | www.ncpe.ie | 2020-2025 | 09.05.2025 |
| National Health Care Institute (Zorginstituut Nederland, ZIN) | www.zorginstituutnederland.nl | 2020-2025 | 09.05.2025 |
| National Institute for Health and Care Excellence (NICE) | www.nice.org.uk | 2020-2025 | 09.05.2025 |
| Scottish Medicines Consortium (SMC) | www.scottishmedicines.org.uk | 2020-2025 | 09.05.2025 |
| Pharmaceutical Benefits Advisory Committee (PBAC) | www.pbs.gov.au | 2020-2025 | 09.05.2025 |
| Tandvårds och läkemedelsförmånsverket (TLV) | www.tlv.se | 2020-2025 | 09.05.2025 |

### J.1.2 Search strategies

The search strings for the December 2023, and May 2025 SLRs are reported below.

### J.1.2.1 Economic SLR 2023

**Table 74 Search strategy for economic SLR: Embase 1974 to 7th December 2023**

| No. | Query | Results |
|---|---|---|
| #1 | mantle cell lymphoma/ | 14704 |
| #2 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti.ab. | 29286 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti.ab. | 170 |
| #4 | or/1-3 | 33942 |
| #5 | first-line treatment/ | 2832 |
| #6 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 2211518 |
| #7 | 5 or 6 | 2211518 |
| #8 | 4 and 7 | 8516 |
| #9 | Economics/ | 244860 |
| #10 | Cost/ | 63300 |
| #11 | exp health economics/ | 1032129 |
| #12 | Budget/ | 33585 |
| #13 | budget*.ti.ab.kw. | 47542 |
| #14 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti<br>kw. | 315279 |
| #15 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 | 536012 |
| #16 | absenteeism/ | 19904 |
| #17 | presenteeism/ | 2373 |
| #18 | medical leave/ | 8646 |

| No. | Query | Results |
|---|---|---|
| #19 | (disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti.ab. | 1085168 |
| #20 | (healthcare resource$ or medical resource$ or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitali?ation or hospital admission$ or icu admission$ or emergency department visit$ or emergency room visit$ or er visit$ or ed visit$ or inpatient visit$ or outpatient visit$ or specialist visit$ or unscheduled doctor visit$ or unscheduled physician visit$ or general practitioner visit$).ti.ab. | 472766 |
| #21 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.kw. | 286095 |
| #22 | (value adj2 (money or monetary)).ti.ab.kw. | 4113 |
| #23 | Statistical Model/ | 174744 |
| #24 | economic model*.ab.kw. | 6235 |
| #25 | Probability/ | 146098 |
| #26 | markov.ti.ab.kw. | 36643 |
| #27 | monte carlo method/ | 51118 |
| #28 | monte carlo.ti.ab.kw. | 61756 |
| #29 | Decision Theory/ | 1842 |
| #30 | Decision Tree/ | 21790 |
| #31 | (decision* adj2 (tree* or analy* or model*)).ti.ab.kw. | 51344 |
| #32 | or/9-31 | 3354808 |
| #33 | 8 and 32 | 687 |
| #34 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 1070457 |
| #35 | case reports/ or case study/ or case report$.jx. or case report$.jw. | 368444 |
| #36 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3638900 |

| No. | Query | Results |
|---|---|---|
| #37 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti.ab. | 2871260 |
| #38 | or/34-37 | 7627561 |
| #39 | 33 not 38 | 561 |
| #40 | conference abstract.pt. | 4872067 |
| #41 | 39 not 40 | 101 |
| #42 | limit 39 to (conference abstract and yr="2020-current") | 240 |
| #43 | 41 or 42 | 341 |

**Table 75 Search strategy for economic SLR: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to 7th December 2023**

| No. | Query | Results |
|---|---|---|
| #1 | Lymphoma mantle-cell/ | 3776 |
| #2 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti.ab. | 17221 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti.ab. | 133 |
| #4 | or/1-3 | 17722 |
| #5 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab.ti. or ((front or first) and line).ab.ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 1405107 |
| #6 | 4 and 5 | 2928 |
| #7 | Economics/ | 27508 |
| #8 | exp "Costs and Cost Analysis"/ | 266073 |
| #9 | Economics Nursing/ | 4013 |
| #10 | Economics Medical/ | 9253 |
| #11 | Economics Pharmaceutical/ | 3109 |

| No. | Query | Results |
|---|---|---|
| #12 | exp Economics Hospital/ | 25740 |
| #13 | Economics Dental/ | 1921 |
| #14 | exp "Fees and Charges"/ | 31403 |
| #15 | exp Budgets/ | 14139 |
| #16 | budget*.ti.ab.kf. | 36388 |
| #17 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.kf. | 284085 |
| #18 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 | 385566 |
| #19 | absenteeism/ | 9784 |
| #20 | presenteeism/ | 596 |
| #21 | (healthcare resource$ or medical resource$ or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitali?ation or hospital admission$ or icu admission$ or emergency department visit$ or emergency room visit$ or er visit$ or ed visit$ or inpatient visit$ or outpatient visit$ or specialist visit$ or unscheduled doctor visit$ or unscheduled physician visit$ or general practitioner visit$).ti.ab. | 278878 |
| #22 | (disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti.ab. | 785607 |
| #23 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.kf. | 211935 |
| #24 | (value adj2 (money or monetary)).ti.ab.kf. | 3078 |
| #25 | exp models<br>economic/ | 16234 |
| #26 | economic model*.ab.kf. | 4262 |
| #27 | markov chains/ | 16007 |

| No. | Query | Results |
|---|---|---|
| #28 | markov.ti.ab.kf. | 29380 |
| #29 | monte carlo method/ | 32341 |
| #30 | monte carlo.ti.ab.kf. | 60617 |
| #31 | exp Decision Theory/ | 13373 |
| #32 | (decision* adj2 (tree* or analy* or model*)).ti.ab.kf. | 38630 |
| #33 | or/7-32 | 1872641 |
| #34 | 6 and 33 | 54 |
| #35 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 951643 |
| #36 | case reports/ or case study/ or case report$.jw. | 2387896 |
| #37 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3323407 |
| #38 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti.ab. | 2973146 |
| #39 | or/35-38 | 8915253 |
| #40 | 34 not 39 | 46 |

**Table 76 Search strategy for economic SLR: Econlit - 1886 to 23rd November 2023**

| No. | Query | Results |
|---|---|---|
| #1 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti.ab. | 15 |
| #2 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti.ab. | 0 |
| #3 | or/1-2 | 15 |

### J.1.2.2 Economic SLR 2025 update

**Table 77 Search strategy for economic SLR: Embase 1974 to 8th May 2025**

| No. | Query | Results |
|---|---|---|
| #1 | mantle cell lymphoma/ | 16604 |
| #2 | (((mantle or centrocytic or intermediate) adj3 (lymph* or NHL)) or MCL).ti,ab. | 32558 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti,ab. | 172 |
| #4 | or/1-3 | 37720 |
| #5 | first-line treatment/ | 16896 |
| #6 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 2470218 |
| #7 | 5 or 6 | 2470218 |
| #8 | 4 and 7 | 9730 |
| #9 | Economics/ | 246096 |
| #10 | Cost/ | 65727 |
| #11 | exp health economics/ | 1126948 |
| #12 | Budget/ | 36117 |
| #13 | budget*.ti,ab,kw. | 52223 |
| #14 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. | 343235 |
| #15 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 | 608450 |
| #16 | absenteeism/ | 21173 |
| #17 | presenteeism/ | 2930 |
| #18 | medical leave/ | 9590 |

| No. | Query | Results |
|---|---|---|
| #19 | (disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab. | 1217639 |
| #20 | (healthcare resource$ or medical resource$ or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitali?ation or hospital admission$ or icu admission$ or emergency department visit$ or emergency room visit$ or er visit$ or ed visit$ or inpatient visit$ or outpatient visit$ or specialist visit$ or unscheduled doctor visit$ or unscheduled physician visit$ or general practitioner visit$).ti,ab. | 543608 |
| #21 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. | 327337 |
| #22 | (value adj2 (money or monetary)).ti,ab,kw. | 4505 |
| #23 | Statistical Model/ | 180500 |
| #24 | economic model*.ab,kw. | 7015 |
| #25 | Probability/ | 165591 |
| #26 | markov.ti,ab,kw. | 40965 |
| #27 | monte carlo method/ | 57330 |
| #28 | monte carlo.ti,ab,kw. | 68363 |
| #29 | Decision Theory/ | 1912 |
| #30 | Decision Tree/ | 28463 |
| #31 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. | 63922 |
| #32 | or/9-31 | 3733890 |
| #33 | 8 and 32 | 922 |
| #34 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 1178954 |
| #35 | case reports/ or case study/ or case report$.jx. or case report$.jw. | 417056 |
| #36 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3883157 |

| No. | Query | Results |
|---|---|---|
| #37 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab. | 3063153 |
| #38 | or/34-37 | 8187441 |
| #39 | 33 not 38 | 747 |

**Table 78 Search strategy for economic SLR: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to 8th May 2025**

| No. | Query | Results |
|---|---|---|
| #1 | Lymphoma mantle-cell/ | 0 |
| #2 | (((mantle or centrocytic or intermediate) adj3 (lymph* or NHL)) or MCL).ti,ab. | 52934 |
| #3 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti,ab. | 133 |
| #4 | or/1-3 | 53064 |
| #5 | (first line or first-line or front line or front-line or 1st line or 1st-line or induction therapy or primary therapy or primary treatment).mp. or ((primary or initial or induction or naive) and (therapy or treatment)).ab,ti. or ((front or first) and line).ab,ti. or untreated.mp. or un-treated.mp. or treatment naive.mp. or treatment-naive.mp. | 1562823 |
| #6 | 4 and 5 | 6263 |
| #7 | Economics/ | 27544 |
| #8 | exp "Costs and Cost Analysis"/ | 278977 |
| #9 | Economics, Nursing/ | 4013 |
| #10 | Economics, Medical/ | 9304 |
| #11 | Economics, Pharmaceutical/ | 3160 |
| #12 | exp Economics, Hospital/ | 26207 |
| #13 | Economics, Dental/ | 1922 |
| #14 | exp "Fees and Charges"/ | 31678 |
| #15 | exp Budgets/ | 14343 |

| No. | Query | Results |
|---|---|---|
| #16 | budget*.ti,ab,kf. | 40285 |
| #17 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. | 313217 |
| #18 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 | 439824 |
| #19 | absenteeism/ | 10102 |
| #20 | presenteeism/ | 744 |
| #21 | (healthcare resource$ or medical resource$ or health resource consumption or health care consumption or 'healthcare resource use' or medical resource consumption or hospitali?ation or hospital admission$ or icu admission$ or emergency department visit$ or emergency room visit$ or er visit$ or ed visit$ or inpatient visit$ or outpatient visit$ or specialist visit$ or unscheduled doctor visit$ or unscheduled physician visit$ or general practitioner visit$).ti,ab. | 321175 |
| #22 | (disability or functional status or physical function or impairment or disabilities or productivity or employment or retirement or work disability or absenteeism or presenteeism or sick leave or sick day or worktime loss or opportunity loss or job performance or (work adj2 loss)).ti,ab. | 889659 |
| #23 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. | 248281 |
| #24 | (value adj2 (money or monetary)).ti,ab,kf. | 3424 |
| #25 | exp models, economic/ | 16850 |
| #26 | economic model*.ab,kf. | 4752 |
| #27 | markov chains/ | 17078 |
| #28 | markov.ti,ab,kf. | 32970 |
| #29 | monte carlo method/ | 34208 |
| #30 | monte carlo.ti,ab,kf. | 66867 |
| #31 | exp Decision Theory/ | 14323 |
| #32 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. | 49962 |

| No. | Query | Results |
|---|---|---|
| #33 | or/7-32 | 2110403 |
| #34 | 6 and 33 | 299 |
| #35 | (case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti. | 1047870 |
| #36 | case reports/ or case study/ or case report$.jw. | 2515331 |
| #37 | (Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or mice or rat or mouse or animal or murine).ti. | 3477723 |
| #38 | review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab. | 3208516 |
| #39 | or/35-38 | 9461201 |
| #40 | 34 not 39 | 256 |

**Table 79 Search strategy for economic SLR: Econlit - 1986 to 1st May 2025**

| No. | Query | Results |
|---|---|---|
| #1 | (((mantle or centrocytic or intermediate) adj3 lymph*) or MCL).ti,ab. | 17 |
| #2 | ((diffuse adj3 "poorly differentiated" adj2 lymph*) or DPDL).ti,ab. | 0 |
| #3 | or/1-2 | 17 |

**Table 80 Search strategy for economic SLR: INAHTA - 1989 to 8th May 2025**

| No. | Query | Results |
|---|---|---|
| #1 | ("Lymphoma, Mantle-Cell"[mhe]) | 19 |
| #2 | ("mantle cell lymphoma")[Title] | 13 |
| #3 | 1 or 2 | 19 |

### J.1.3 Eligibility criteria

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. Selection of studies for inclusion was determined using the PICOS framework[87] and are presented in Table 81.

**Table 81 Eligibility criteria for the economic systematic literature review**

| PICOS | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | • Adult patients (≥18 years) with previously untreated (1L) MCL<br>• Studies with mixed population of lymphoma patients were eligible for inclusion if they reported outcomes in the population of interest, or the population of interest comprises most (≥80%) of the study population | • Paediatric patients<br>• Studies not including MCL patients<br>• Studies not including previously untreated (1L) MCL patients |
| **Intervention/ Comparators** | No restriction | N/A |
| **Outcomes** | **Economic evaluations:** QALYs, LYs, incremental costs, ICERs<br><br>**Healthcare costs:** Total costs (direct + indirect), direct costs, indirect costs (i.e., productivity losses [patient/caregiver], absenteeism, presenteeism, work productivity and activity impairment questionnaire score)<br><br>**HCRU:** General practitioner/family doctor visits, specialist visits, ER visits, hospitalisations (rate, length of stay), laboratory tests and procedures | • Outcomes not listed in the inclusion criteria |
| **Study design(s)** | • Cross-sectional interventional or observational studies<br>• Databases/registry studies<br>• Economic evaluations (cost-effectiveness analyses, cost-utility analyses; cost-minimisation analyses; cost-benefit analyses) | • Clinical trials<br>• Pharmacodynamic/pharmacokinetic studies, genetic studies, cellular/molecular studies, in vitro/ex-vivo studies<br>• Case reports or case series (studies including <20 patients)<br>• Narrative reviews, SLRs/network meta-analyses[1] |

| | | |
|---|---|---|
| **Limits** | • **Time limit:** Full text publications: 2013 to current; Conference abstracts: 2020-2025<br>• **Geography:** No restriction<br>• **Language:** English | • **Time limit:** Full text publications before 2013; Conference abstracts published before 2020 |

Abbreviations: ER, Emergency Room; GP, General Practitioner; HCRU, Healthcare resource utilisation; ICER, Incremental cost-effectiveness ratio; LY, Life-years; MCL, Mantle cell lymphoma; N/A, Not applicable; QALY, Quality-adjusted life-years; SLR, Systematic literature review.

Notes: SLR/ network meta-analyses were included at abstract review stage to search their reference lists for any missed studies and subsequently excluded during the full text review stage.

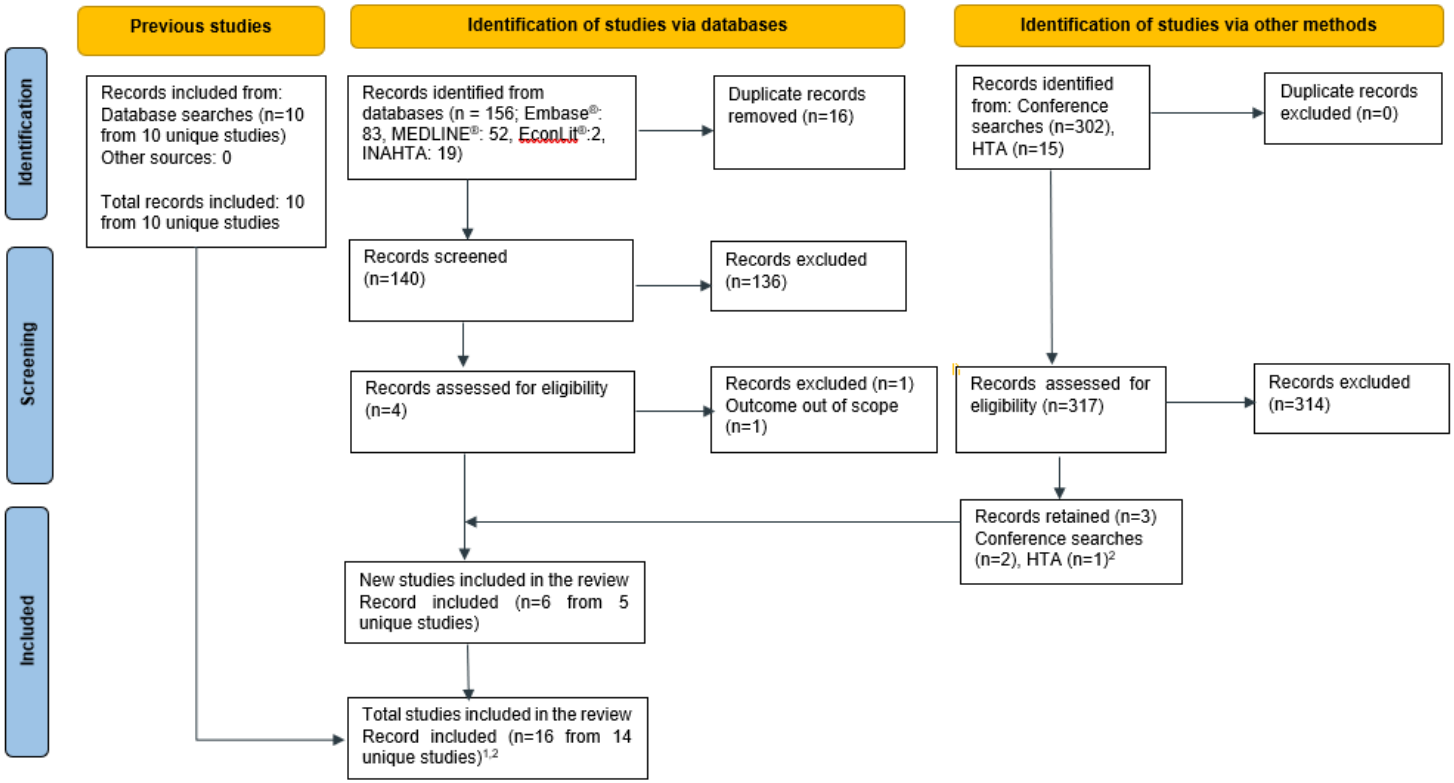
### J.1.4 Systematic selection of studies

A total of 443 references were identified from electronic database searches conducted on 7th December 2023 (Embase®: 397; MEDLINE®: 40, EconLit®: 6). After removing duplicates (n=71), titles and abstracts of 372 references were screened against the eligibility criteria. During the screening process, 329 references were excluded, and 43 potentially relevant references were retrieved for full-text assessment. Of these 43 references, 33 references were excluded, resulting in the inclusion of 10 relevant publications. Overall, 10 included publications on full-text assessment were retained for data extraction and are discussed in detail in the sections below.

A SLR update conducted on 9th May 2025 (from 2023-current) identified 156 references from the electronic database searches (Embase®: 83; MEDLINE®: 52; EconLit®: 2; and INAHTA: 19). The new records were checked against the original SLR, and the duplicates were removed (n=16); the remaining 140 publications were screened against the eligibility criteria. After the title and abstract screening, 136 references were excluded and four potentially relevant references were retrieved for full-text review. During the full-text review, one record was excluded, and three records was included. Additionally, three records were identified through other methods (conference search and HTA reviews), resulting in the inclusion of six publications from five unique studies. In total, 16 publications from 14 unique studies were included in the combined original (n=10 publications) and updated SLR (n=6 publications).

The PRISMA diagram in Figure 36 presents the results of the search described above. A detailed PRISMA diagram presenting the results of original SLR is presented in Figure 37.

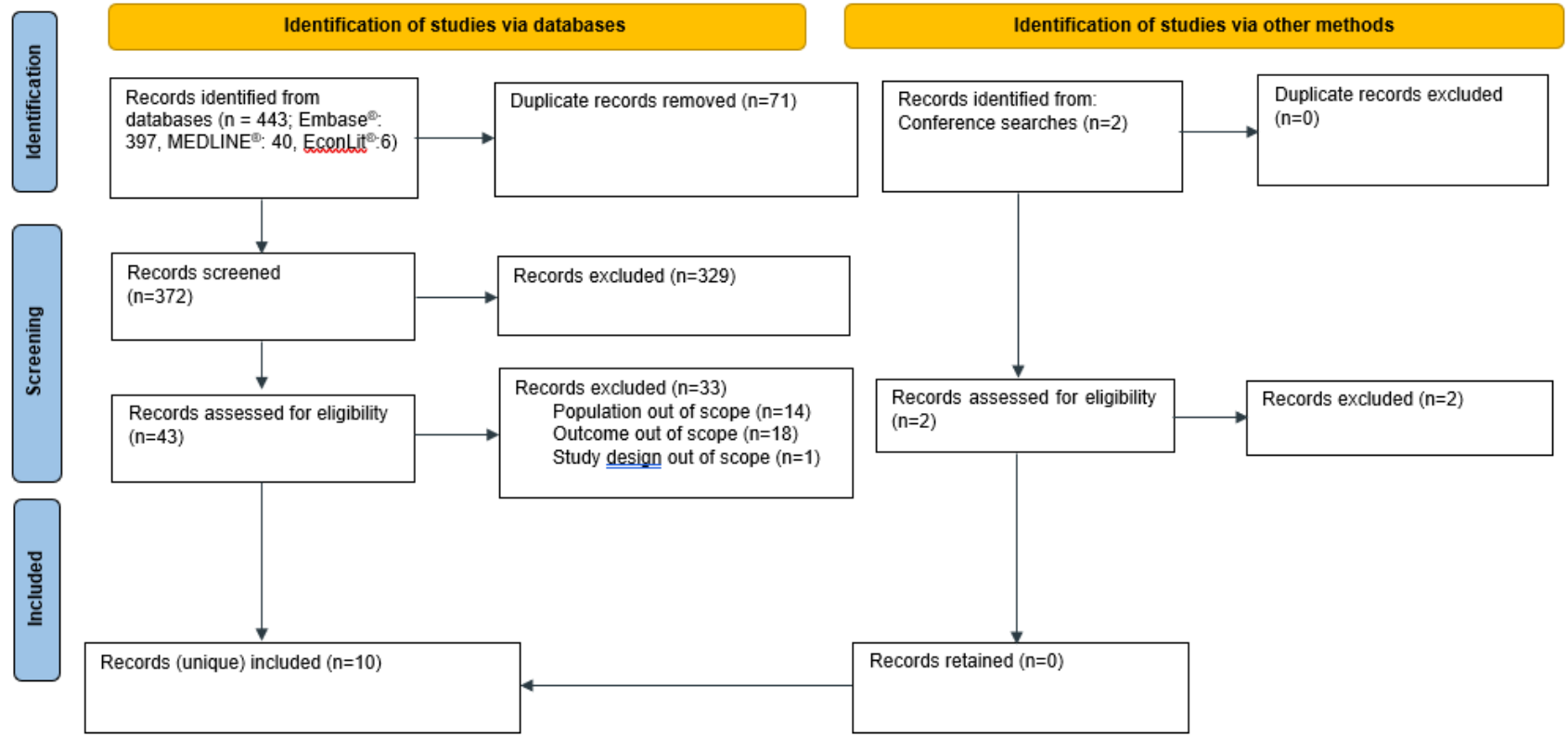
**Figure 36 PRISMA flowchart for study selection of the economic SLR (original - 7th December 2023 and SLR update - 9th May 2025)**




Source: Adapted from Page et al. (2021)[90].

Note: 1) Two references included in the current SLR update were linked to the one identified in the previous SLR;[2] Two additional HTA documents, HAS[91] and CDA-AMC[92] were identified. In the HAS reassessment, only clinical data was reported; therefore, it was not included in the report[91]. Additionally, we identified an HTA report from CDA-AMC, where a submission for acalabrutinib is currently in progress. As this submission is not yet finalised, it has also not been included in the report[92]

**Figure 37 PRISMA flowchart for study selection of economic SLR (original SLR - 7th December 2023)**




Source: Adapted from Page et al. (2021)[90].

### J.1.5 Excluded full text references

The global SLR identified 13 relevant studies. However, as detailed in the local adaptation section above, none of the publications included in the global SLR were used in the current submission, and they are therefore considered 'excluded'. A list of the 13 studies included in the global SLR is provided in Table 82, and a list of studies excluded from all the humanistic SLR is provided in Table 83.

**Table 82 Overview of study design for studies included in the global economic SLR**

| Author | Title | Year | Study design |
|---|---|---|---|
| Widmer F, Balabanov S, Soldini D, Samaras P, Gerber B, Manz MG, et al. | R-hyper-CVAD versus R-CHOP/cytarabine with high-dose therapy and autologous haematopoietic stem cell support in fit patients with mantle cell lymphoma: 20 years of single-center experience | 2018 | Retrospective observational study |
| Izutsu K, Suzumiya J, Takizawa J, Fukase K, Nakamura M, Jinushi M, et al. | Real world treatment practices for9 mantle cell lymphoma in Japan: an observational database research study (CLIMBER-DBR) | 2021 | Retrospective observational study |
| Ratnasingam S, Casan J, Shortt J, Hawkes E, Gilbertson M, McQuilten Z, et al. | Cytarabine-based induction immunochemotherapy in the front-line treatment of older patients with mantle cell lymphoma | 2019 | Retrospective observational study |
| Keating S, Qian J, Inguva S, Shah R | Patient characteristics, treatment patterns, health care resource utilization, and costs associated with treatment of mantle cell lymphoma | 2022 | Retrospective observational study |
| Keating SJ, Rege S, McBride A, Shah R, Qian J, Chirikov V | Real-world treatment (tx) patterns, cost, and overall survival (OS) by line of therapy among patients (pt) with mantle cell lymphoma (MCL): A SEER-Medicare (SM) analysis. | 2022 | Retrospective observational study |
| Keating SJ, Inguva S, Qian J, Shah R, Chirikov V. | Real-world treatment patterns, healthcare resource utilization and total cost of care in mantle cell lymphoma from US commercial claims. | 2023 | Retrospective observational study |

| Author | Title | Year | Study design |
|---|---|---|---|
| Garg M, Satija A, Song Y, Sarpong E, Meade B, Lemus-Wirtz E, et al. | Economic burden and treatment patterns among patients with mantle cell lymphoma in the US: a retrospective claims analysis. | 2022 | Retrospective observational study |
| Goyal RK, Jain P, Nagar SP, Le H, Kabadi SM, Davis K, et al. | Real-world evidence on survival, adverse events, and health care burden in Medicare patients with mantle cell lymphoma | 2021 | Retrospective observational study |
| Anglin P, Elia-Pacitti J, Eberg M, Muratov S, Kukaswadia A, Sharma A, et al. | Estimating the Associated Burden of Illness and Healthcare Utilization of Newly Diagnosed Patients Aged≥ 65 with Mantle Cell Lymphoma (MCL) in Ontario, Canada. | 2023 | Retrospective observational study |
| Squires P, Huntington SF, Puckett J, Ryland KE, Kamal-Bahl S, Raut M, et al. | Treatment Utilization Patterns, Health Resource Use, Costs, and Survival in Mantle Cell Lymphoma: A Real-World Analysis of a National Sample of Medicare Beneficiaries | 2022 | Retrospective observational study |
| Suleman A, Ante Z, Liu N, Crump M, Chan KK, Cheung MC, et al | Outcomes of Transplant-Eligible and Transplant-Ineligible Patients with Mantle Cell Lymphoma in Ontario, Canada | 2023 | Retrospective observational study |
| Alencar AJ, Xue M, Chaung P-Y, Furnback W, editors. | REAL-WORLD BURDEN OF DISEASE, TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) | 2025 | Retrospective observational study |
| Ghosh N, Jawaid D, Emechebe N, Manzoor BS. | Real World Healthcare Resource Utilization (HRU) and Costs Associated With Mantle Cell Lymphoma (MCL) Therapies in the Frontline (1L) and Relapsed/Refractory (R/R) Setting | 2025 | Retrospective observational study |

**Table 83 List of excluded studies at full-text screening stage for global economic SLR**

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| **Original SLR** | | | |
| 1 | Yamshon, 2023 | Nine-year follow-up of lenalidomide plus rituximab as initial treatment for mantle cell lymphoma | Outcomes |
| 2 | Rai, 2022 | Outcomes for Recurrent Mantle Cell Lymphoma Post-Ibrutinib Therapy: A Retrospective Cohort Study from a Japanese Administrative Database | Population |
| 3 | Pei, 2021 | A comprehensive retrospective cohort study of the journey of B-cell lymphoma in Taiwan. | Outcomes |
| 4 | Kabadi, 2019 | Treatment patterns, adverse events, healthcare resource use and costs among commercially insured patients with mantle cell lymphoma in the United States. | Population |
| 5 | Kropp, 2018 | The novel deubiquitinase inhibitor b-AP15 induces direct and NK cell-mediated antitumor effects in human mantle cell lymphoma. | Outcomes |
| 6 | Bellesso, 2022 | Retrospective Evaluation of Real-World Treatment Patterns in Patients with Mantle Cell Lymphoma - REALM in a Single Brazilian Center | Outcomes |
| 7 | Xu, 2022 | A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multi-Center Study Evaluating the Efficacy and Safety of Orelabrutinib Plus R-CHOP Versus Placebo Plus R-CHOP in Treatment-Naive Patients with Mcd Subtype Diffuse Large B-Cell Lymphoma | Study Design |
| 8 | Reves, 2022 | Impact of First-Line Consolidative Autologous Haematopoietic Stem Cell Transplantation (ASCT) in Mantle Cell Lymphoma (MCL): A 'Real-World' Study of Treatment Patterns and Outcomes at a Safety-Net Versus a Tertiary Academic Hospital | Outcomes |
| 9 | Bhave, 2022 | Effectiveness and Safety of Rituximab Biosimilar in Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia: Results from a Prospective, Multicentre, Real-World Registry Study | Population |
| 10 | Serna, 2022 | Impact of Coronavirus (COVID-19) Pandemic on Maintenance Therapy for Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL) | Population |
| 11 | Rezazadeh, 2022 | Immunoglobulin High Throughput Sequencing (Ig-HTS) Minimal Residual Disease (MRD) Analysis Is an Effective Surveillance Tool in Patients with Mantle Cell Lymphoma | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 12 | Di, 2022 | Real-World Practice Patterns and Outcomes Following Bruton Tyrosine Kinase Inhibitors (BTKi) in Older Patients with Mantle Cell Lymphoma (MCL): A Population-Based Analysis | Outcomes |
| 13 | Choquet, 2022 | Use of Ibrutinib in Real Life Settings in France: Results from a Retrospective Observational Study Using the Snds Database (OSIRIS) | Population |
| 14 | Gordon, 2022 | Association of Non-Hodgkin Lymphoma (NHL), Comorbidity and Death Due to Other Cancers in 30,000 Older Adults from SEER-Medicare | Population |
| 15 | Tam, 2022 | 205MO Patterns of treatment and outcomes in MCL patients in Australia: An analysis of the population-wide pharmaceutical benefits scheme dataset | Outcomes |
| 16 | Brizova, 2022 | Comparison of git toxicity of the beam vs team conditioning before autologous transplantation in patients with lymphomas | Outcomes |
| 17 | Marafioti, 2022 | Outcomes of reduced dose team (thiotepa, etoposide, cytarabine, melphalan) prior to autologous stem cell transplantation for hodgkin and non-hodgkin lymphoma: A monocentric experience | Population |
| 18 | Shah, 2022 | Real-world treatment patterns and comparative effectiveness of Bruton tyrosine kinase inhibitors in patients with mantle cell lymphoma | Outcomes |
| 19 | Polyakov, 2022 | Therapy and hospital mortality predictors in patients with lymphoproliferative disorders and concomitant covid-19 infection | Population |
| 20 | Di Folca, 2022 | Outcomes of reduced dose team (thiotepa, etoposide, cytarabine, melphalan) prior to autologous stem cell transplantation for hodgkin and non-hodgkin lymphoma: a monocentric experience | Population |
| 21 | Di, 2022 | Treatment patterns and real-world effectiveness of rituximab maintenance in older patients with mantle cell lymphoma: A population-based analyses | Outcomes |
| 22 | De Pouvourville, 2022 | POSB107 A Retrospective Observational Study of Ibrutinib in Real-Life Settings in France, Using the SNDS Database (OSIRIS) | Population |
| 23 | Weaver, 2021 | A medicare database analysis of practice patterns in patients with mantle cell lymphoma | Outcomes |
| 24 | Shah, 2021 | Real-World Bruton Tyrosine Kinase Inhibitor Treatment Patterns, Compliance, Costs, and Hospitalisations in Patients with Mantle Cell Lymphoma in the United States | Population |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 25 | Ilhan, 2021 | The Outcome of Autologous Haematopoietic Cell Transplantation in Elderly Patients with Aggressive Non-Hodgkin Lymphoma | Outcomes |
| 26 | Rangel-Patino, 2021 | Improvement Diagnosis and Treatment of Mantle Cell Lymphoma in a Middle-Income Country: A Time-Dependent Analysis in Mexico | Outcomes |
| 27 | Kumar, 2021 | Evaluation of the Incidence and Risk Factors Associated with Bleeding Events in Patients Receiving Acalabrutinib Therapy | Population |
| 28 | Obr, 2021 | Ibrutinib in Mantle Cell Lymphoma Patients: Analysis of the Czech Lymphoma Study Group | Outcomes |
| 29 | Bega, 2021 | Rituximab, bendamustine, and cytarabine (r-bac) compared with rituximab and bendamustine (br) in previously untreated elderly patients with mantle cell lymphoma (be-ve-bac study) | Outcomes |
| 30 | Olszewski, 2020 | Outcomes of bendamustine- or cyclophosphamide-based first-line chemotherapy in older patients with indolent B-cell lymphoma | Population |
| 31 | Shah, 2019 | Racial and Socioeconomic Disparities in Mantle Cell Lymphoma | Outcomes |
| 32 | Fu, 2019 | Comparative Effectiveness of Chemotherapy, Rituximab, and Bendamustine in Medicare Beneficiaries With Mantle-Cell Lymphoma | Outcomes |
| 33 | Kerhuel, 2015 | Clinical features of life-threatening complications following autologous stem cell transplantation in patients with lymphoma | Population |
| **Updated SLR** | | | |
| 34 | Ramsower, 2023 | Evaluation of clinical parameters and biomarkers in older, untreated mantle cell lymphoma patients receiving bendamustine-rituximab | Outcomes |
| 35 | Karmali, 2023 | Ibrutinib Maintenance Following Frontline Treatment in Patients with Mantle Cell Lymphoma | Outcomes |
| 36 | Ogura, 2023 | Long-term follow-up after R-High CHOP/CHASER/LEED with Auto-PBSCT in untreated mantle cell lymphoma-Final analysis of JCOG0406 | Outcomes |
| 37 | Yang, 2023 | Real-world treatment and outcome patterns of patients with mantle cell lymphoma in China: A large, multicenter retrospective analysis | Outcomes |
| 38 | Metzner, 2023 | Long-term outcome in patients with mantle cell lymphoma following high-dose therapy and autologous stem cell transplantation | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 39 | Thurner, 2023 | Radiation and Dose-densification of R-CHOP in Aggressive B-cell Lymphoma With Intermediate Prognosis: The UNFOLDER Study | Outcomes |
| 40 | David, 2023 | Older patients with primary central nervous system lymphoma: Survival and prognostication across 20 U.S. cancer centers | Outcomes |
| 41 | Epperla, 2023 | Impact of diagnosis to treatment interval in patients with newly diagnosed mantle cell lymphoma | Outcomes |
| 42 | Patel, 2023 | Bendamustine/Rituximab Plus Cytarabine/Rituximab, With or Without Acalabrutinib, for the Initial Treatment of Transplant-Eligible Mantle Cell Lymphoma Patients: Pooled Data From Two Pilot Studies | Outcomes |
| 43 | Kalicinska, 2023 | A survey across orbital lymphoma in Poland: Multicenter retrospective study of polish lymphoma research group (PLRG) | Outcomes |
| 44 | Hermine, 2023 | High-Dose Cytarabine and Autologous Stem-Cell Transplantation in Mantle Cell Lymphoma: Long-Term Follow-Up of the Randomised Mantle Cell Lymphoma Younger Trial of the European Mantle Cell Lymphoma Network | Outcomes |
| 45 | Vergote, 2023 | [18F]FDG-PET/CT volumetric parameters can predict outcome in untreated mantle cell lymphoma | Outcomes |
| 46 | Serna, 2022 | Impact of Coronavirus (COVID-19) Pandemic on Maintenance Therapy for Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL) | Outcomes |
| 47 | Rezazadeh, 2022 | Immunoglobulin High Throughput Sequencing (Ig-HTS) Minimal Residual Disease (MRD) Analysis Is an Effective Surveillance Tool in Patients with Mantle Cell Lymphoma | Outcomes |
| 48 | Choquet, 2022 | Use of Ibrutinib in Real Life Settings in France: Results from a Retrospective Observational Study Using the Snds Database (OSIRIS) | Outcomes |
| 49 | Hernandez-Rivas, 2022 | Ibrutinib Plus Bendamustine Plus Rituximab and Rituximab Maintenance (I+BR) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone Regimen (R-CHOP) and Rituximab, Cyclophosphamide, Doxorubicin, Bortezomib, Prednisone Regimen (VR-CAP) in First-Line Mantle Cell Lymphoma Patients: An Adjusted Treatment Comparison Using Inverse Probability Weighting | Outcomes |
| 50 | Erkut, 2022 | Effect of Clinical, Endoscopic, Radiological Findings, and Complications on Survival in Patients with Primary Gastrointestinal Lymphoma | Outcomes |
| 51 | Jain, 2022 | Ibrutinib With Rituximab in First-Line Treatment of Older Patients With Mantle Cell Lymphoma | Outcomes |
| 52 | Villa, 2022 | Bendamustine or high-dose cytarabine-based induction with rituximab in transplant-eligible mantle cell lymphoma | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 53 | Gine, 2022 | Ibrutinib in Combination With Rituximab for Indolent Clinical Forms of Mantle Cell Lymphoma (IMCL-2015): A Multicenter, Open-Label, Single-Arm, Phase II Trial | Outcomes |
| 54 | Oliveira, 2022 | MANTLE CELL LYMPHOMA IN BRAZIL: FIRST REPORT FROM A REAL-WORLD EVIDENCE STUDY OF A THIRD WORLD COUNTRY | Outcomes |
| 55 | Vergote, 2022 | METABOLIC TUMOR VOLUME IMPROVES OUTCOME PREDICTION IN UNTREATED MANTLE CELL LYMPHOMA | Outcomes |
| 56 | Polyakov, 2022 | THERAPY AND HOSPITAL MORTALITY PREDICTORS IN PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS AND CONCOMITANT COVID-19 INFECTION | Outcomes |
| 57 | Ma, 2022 | Factors associated with death from lymphoma in a single center study | Outcomes |
| 58 | Soumerai, 2021 | Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial | Population |
| 59 | Wu, 2021 | Initial Treatment Patterns and Survival Outcomes of Mantle Cell Lymphoma Patients Managed at Chinese Academic Centers in the Rituximab Era: A Real-World Study | Outcomes |
| 60 | Riedell, 2021 | Outcomes and Utilisation Trends of Front-Line Autologous Haematopoietic Cell Transplantation for Mantle Cell Lymphoma | Outcomes |
| 61 | Zoellner, 2021 | Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial | Outcomes |
| 62 | Yang, 2021 | Treatment patterns and outcomes of older patients with mantle cell lymphoma in an Asian population | Outcomes |
| 63 | Karmali, 2021 | Multi-center analysis of practice patterns and outcomes of younger and older patients with mantle cell lymphoma in the rituximab era | Outcomes |
| 64 | Weaver, 2021 | A medicare database analysis of practice patterns in patients with mantle cell lymphoma | Outcomes |
| 65 | Massaro, 2021 | Long-term results of the MCL01 phase II trial of rituximab plus HyperCVAD alternating with high-dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma | Outcomes |
| 66 | Castellino, 2021 | Clinical characteristics and outcomes of primary versus secondary gastrointestinal mantle cell lymphoma | Outcomes |
| 67 | Ma, 2021 | Comparison of clinicopathological features and treatment outcomes in aggressive primary intestinal B- and T/NK-cell lymphomas | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 68 | Cabirta, 2021 | Early Relapse after First Line Has a Significant Impact on Overall Survival in Patients with Mantle Cell Lymphoma (MCL) | Outcomes |
| 69 | Ruiz, 2021 | Cyclophosphamide, Etoposide, and Intermediate-Dose of Carboplatin; An Efficient Preparative Regimen for Autologous Transplantation for Patients with Lymphoma, a Good Alternative to Those Based on Carmustine. Experience with 108 Patients | Outcomes |
| 70 | Ribrag, 2021 | Rituximab-Lenalidomide(R2) Maintenance Is Superior to Rituximab Maintenance after First Line Immunochemotherapy in Mantle Cell Lymphoma: Results of the MCL R2 Elderly Clinical Trial | Outcomes |
| 71 | Wang, 2021 | Ibrutinib Plus Rituximab and Venetoclax (IRV) Followed By Risk-Stratified Observation or Short Course R-Hypercvad/MTX in Young Patients with Previously Untreated Mantle Cell Lymphoma - Phase-II Window-2 Clinical Trial | Outcomes |
| 72 | Kumar, 2021 | Preliminary Safety and Efficacy from a Multicenter, Investigator-Initiated Phase II Study in Untreated TP53 Mutant Mantle Cell Lymphoma with Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) | Outcomes |
| 73 | Fischer, 2021 | The Addition of Rituximab to Cyclophosphamide, Doxorubicine, Vincristine and Prednisone (CHOP) Prolongs Overall Survival in Previously Untreated Mantle Cell Lymphoma: A Long Term Pooled Trials Analysis | Outcomes |
| 74 | Andrade-Gonzalez, 2021 | Impact of Diagnosis-to-Treatment Interval on Overall Survival in Patients with Mantle Cell Lymphoma: A National Cancer Database Analysis | Outcomes |
| 75 | Delfau, 2021 | Impact of Maintenance Arm on Prognostic Value of MRD after Induction Treatment in MCL R2 Elderly Trial, a Mantle Cell Lymphoma Network Study | Outcomes |
| 76 | Ekberg, 2021 | Late Effects after Treatment in Mantle Cell Lymphoma: No Difference By Intensity of First-Line Regimens with or without Autologous Stem Cell Transplantation | Outcomes |
| 77 | Elhassadi, 2021 | Retrospective study on mantle cell lymphoma (mcl) and treatment out-come-a single center experience | Outcomes |
| 78 | Kotchetkov, 2021 | Outcomes of bendamustine + rituximab firstline therapy in patients with indolent non-hodgkin's lymphoma or mantle cell lymphoma: Real world experience | Outcomes |
| 79 | Nolan, 2021 | P53 Immunohistochemistry detects nonpathogenic mutations in mantle cell lymphoma necessitating tp53 ngs for clinical decision making | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 80 | Martin, 2021 | Real-world treatment patterns and outcomes of 3455 previously untreated mantle cell lymphoma patients in us routine clinical practice | Outcomes |
| 81 | Salles, 2021 | Role of maintenance rituximab (mr) after first-line (1l) bendamustine + rituximab (br) or r-chop in patients (pts) with mantle cell lymphoma (mcl) from a large us real-world (rw) cohort | Outcomes |
| 82 | Kotchetkov, 2021 | First-line treatment with Bendamustine plus Rituximab for patients with indolent nonHodgkin's lymphoma or Mantle cell lymphoma: Real-world experience | Outcomes |
| 83 | Martin, 2021 | Real-world (RW) treatment (tx) patterns and outcomes of 3,455 previously untreated mantle cell lymphoma (MCL) patients (pts) in U.S. routine clinical practice | Outcomes |
| 84 | Smith, 2021 | ECOG-ACRIN E1411 randomised phase 2 trial of bendamustinerituximab (BR)-based induction followed by rituximab (R) +/- lenalidomide (L) consolidation for Mantle cell lymphoma: Effect of adding bortezomib to front-line BR induction on PFS | Outcomes |
| 85 | Roy, 2021 | Cachexia is an independent factor for negative clinical and functional outcomes in lymphoma patients receiving CART therapy | Outcomes |
| 86 | Wang, 2021 | Stem Cell Transplantation in Mantle Cell Lymphoma: Post-Transplant Outcomes of Taiwan Blood and Marrow Transplantation Registry | Outcomes |
| 87 | Wang, 2021 | Role of maintenance rituximab after first-line bendamustine + rituximab or R-CHOP in patients with mantle cell lymphoma from a large us real-world cohort | Outcomes |
| 88 | Kumar, 2021 | Real-world treatment patterns and outcomes of 3455 previously untreated mantle cell lymphoma patients in us routine clinical practice | Population |
| 89 | Kruger, 2021 | Allogeneic stem cell transplantation for mantle cell lymphoma-update of the prospective trials of the East German Study Group Haematology/Oncology (OSHO#60 and #74). | Outcomes |
| 90 | Brasil, 2020 | Non-indolent mantle cell lymphoma at a single public hospital in Brazil: real world first-line treatment cohort study data | Outcomes |
| 91 | Villa, 2020 | Bendamustine and rituximab as induction therapy in both transplant-eligible and -ineligible patients with mantle cell lymphoma | Outcomes |
| 92 | Ogul, 2020 | Efficacy of prephase treatment for the prevention of tumor lysis syndrome in lymphoma cases with high tumor burden: A cross-sectional study | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 93 | Ng, 2019 | A multicenter retrospective comparison of induction chemoimmunotherapy regimens on outcomes in transplant-eligible patients with previously untreated mantle cell lymphoma | Outcomes |
| 94 | Kumar, 2019 | Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse | Population |
| 95 | Simensen, 2019 | Survivors' knowledge of their diagnosis, treatment and possible late adverse effects after autologous stem cell transplantation for lymphoma | Outcomes |
| 96 | Flinn, 2019 | First-line treatment of patients with indolent non-hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: Results of the BRIGHT 5-year follow-up study | Outcomes |
| 97 | Gressin, 2019 | A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for first-line treatment of older patients with mantle cell lymphoma | Outcomes |
| 98 | Ruan, 2018 | Five-year follow-up of lenalidomide plus rituximab as initial treatment of mantle cell lymphoma | Outcomes |
| 99 | Greenwell, 2018 | Complex karyotype in patients with mantle cell lymphoma predicts inferior survival and poor response to intensive induction therapy | Outcomes |
| 100 | Calzada, 2018 | Deferred treatment is a safe and viable option for selected patients with mantle cell lymphoma. | Outcomes |
| 101 | Smith, 2017 | Mantle cell lymphoma initial therapy with abbreviated R-CHOP followed by 90Y-ibritumomab tiuxetan: 10-year follow-up of the phase 2 ECOG-ACRIN study E1499 | Outcomes |
| 102 | Vergote, 2017 | Results from the Belgian mantle cell lymphoma registry | Outcomes |
| 103 | Visco, 2017 | Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: a multicentre, phase 2 trial from Fondazione Italiana Linfomi | Outcomes |
| 104 | Berger, 2016 | Zevalin and BEAM (Z-BEAM) versus rituximab and BEAM (R-BEAM) conditioning chemotherapy prior to autologous stem cell transplantation in patients with mantle cell lymphoma | Outcomes |
| 105 | Hermine, 2016 | Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 106 | Eskelund, 2016 | 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau | Outcomes |
| 107 | Mondello, 2016 | 90Y-Ibritumomab-Tiuxetan Consolidation Therapy for Advanced-Stage Mantle Cell Lymphoma after First-Line Autologous Stem Cell Transplantation: Is It Time for a Step Forward? | Outcomes |
| 108 | Lamar, 2016 | Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (EPOCH) with or Without Rituximab as First-Line Therapy for Aggressive Non-Hodgkin Lymphoma | Outcomes |
| 109 | Till, 2016 | Phase II trial of R-CHOP plus bortezomib induction therapy followed by bortezomib maintenance for newly diagnosed mantle cell lymphoma: SWOG S0601 | Population |
| 110 | Burke, 2016 | Differences in Quality of Life Between Bendamustine-Rituximab and R-CHOP/R-CVP in Patients With Previously Untreated Advanced Indolent Non-Hodgkin Lymphoma or Mantle Cell Lymphoma. | Outcomes |
| 111 | Nastoupil, 2015 | Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma | Outcomes |
| 112 | Becker, 2015 | Bendamustine as first-line treatment in patients with advanced indolent non-Hodgkin lymphoma and mantle cell lymphoma in German routine clinical practice | Outcomes |
| 113 | Hosein, 2015 | Updated survival analysis of two sequential prospective trials of R-MACLO-IVAM followed by maintenance for newly diagnosed mantle cell lymphoma | Outcomes |
| 114 | Kang, 2014 | Clinical features and treatment outcomes in patients with mantle cell lymphoma in Korea: Study by the consortium for improving survival of lymphoma | Outcomes |
| 115 | Leux, 2014 | Mantle cell lymphoma epidemiology: A population-based study in France | Outcomes |
| 116 | Bernstein, 2013 | A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213 | Outcomes |
| 117 | Delarue, 2013 | CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: A phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte | Outcomes |
| 118 | Budde, 2011 | Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation | Outcomes |

| No. | Author, year | Title | Exclusion reason |
|---|---|---|---|
| 119 | Ruan, 2011 | Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma | Outcomes |
| 120 | Recher, 2011 | Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. | Outcomes |
| 121 | Romaguera, 2010 | Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma | Outcomes |
| 122 | Gressin, 2010 | Evaluation of the (R)VAD+C regimen for the treatment of newly diagnosed mantle cell lymphoma. combined results of two prospective phase ii trials from the French GOELAMS group | Outcomes |
| 123 | Smith, 2010 | Validation of the Mantle Cell Lymphoma International Prognostic Index: A single-center retrospective analysis. | Population |
| 124 | Witzens-Harig, 2009 | Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomised controlled trial. | Outcomes |
| 125 | Akutsu, 2008 | Long-term results of dose-intensive chemotherapy with G-CSF support (TCC-NHL-91) for advanced intermediate-grade non-Hodgkin's lymphoma: A review of 59 consecutive cases treated at a single institute | Population |
| 126 | Ghielmini, 2005 | Single agent rituximab in patients with follicular or mantle cell lymphoma: Clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: A study of the Swiss Group for Clinical Cancer Research (SAKK) | Outcomes |
| 127 | Thieblemont, 2005 | Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. | Outcomes |
| 128 | Visco, 2001 | Non-Hodgkin's lymphoma affecting the testis: Is it curable with doxorubicin-based therapy? | Population |
| 129 | Picozzi, 2001 | Patterns of chemotherapy administration in patients with intermediate-grade non-Hodgkin's lymphoma. | Population |
| 130 | Palmieri, 1998 | Tailored therapy for aggressive non-Hodgkin's lymphoma: results of a phase II study with a long-term follow-up. | Population |

### J.1.6 Local adaptation

To support this submission for ibrutinib for the treatment of MCL in Denmark, the global SLR was adapted by excluding all studies not relevant to a Danish setting. The objective of this SLR was to identify published evidence on the economic burden associated with 1L MCL and related conditions. As no sources were identified that aligned with the Danish setting, all sources from the global SLR were excluded as inputs for the health economic model.

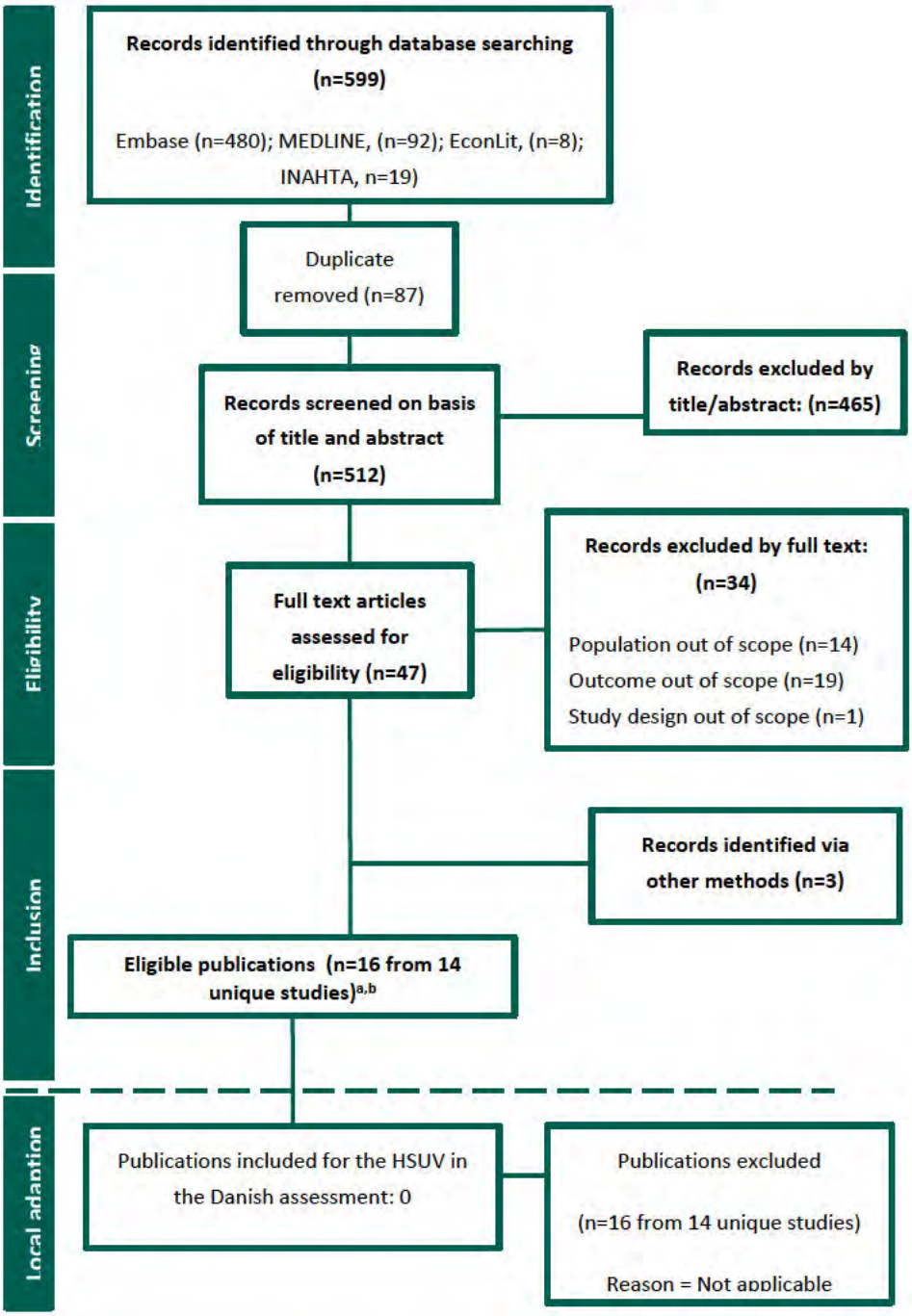
**Targeted literature review – economic studies**

In addition to the SLR, a targeted literature review (TLR) was conducted to identify and collect relevant inputs for the HSUV model. One source was identified and used in the HSUV model

**Table 84 List of studies included to identify relevant inputs for the HSUV model, TLR**

| Source name/database | Location/source | Search strategy | Date of search |
|---|---|---|---|
| Petersohn S, Salles G, Wang M, Wu J, Wade SW, Simons CL, Bennison C, Siddiqi R, Peng W, Kloos I, Castaigne G, Hess G.[76] | Cost-effectiveness analysis of KTE-X19 CAR T therapy versus real-world standard of care in patients with relapsed/refractory mantle cell lymphoma post BTKi in England | Hand search | 16.07.2025 |

Figure 38 PRISMA diagram including local adaptation (economic SLR)




a. Two references included in the current SLR update were linked to the one identified in the previous SLR.

b. Two additional HTA documents, HAS [91] and CDA-AMC [92] were identified. In the HAS reassessment, only clinical data was reported; therefore, it was not included in the report [91]. Additionally, we identified an HTA report from CDA-AMC, where a submission for acalabrutinib is currently in progress. As this submission is not yet finalised, it has also not been included in the report [92].

### J.1.7 Quality assessment and generalizability of estimates

N/A

### J.1.8 Unpublished data

N/A

# Appendix K. Descriptive information of BEAM/THAM

An overview of the BEAM/THAM regimen is presented in Table 85 and Table 86.

**Table 85 Key descriptive information of BEAM regimen**

| Overview of BEAM regimen | |
|---|---|
| **Generic name** | The BEAM regimen includes the drugs carmustine, etoposide, cytarabine, and melphalan |
| **ATC code** | • Carmustine (L01AD01)<br>• Etoposide (L01CB01)<br>• Cytarabine (L01BC01)<br>• Melphalan (L01AA03) |

| Overview of BEAM regimen | |
|---|---|
| **Mechanism of action** | Carmustine is a cell-cycle phase nonspecific antineoplastic agent of the nitrosourea type, which exerts tumour cytotoxicity via multiple mechanisms. As an alkylating agent, it can alkylate reactive sites on nucleoproteins, thus interfering with DNA and RNA synthesis and DNA repair. It is able to form interstrand crosslinks in DNA, which prevents DNA replication and transcription. In addition, carmustine is known to carbamoylate lysine residues on proteins causing irreversible inactivation of enzymes including glutathione reductase. The carbamoylating activity of carmustine is generally considered less significant than the alkylating activity in its action on tumours, but carbamoylation may serve to inhibit DNA repair.[93]<br><br>The main effect of etoposide appears to be at the late S and early G2 portion of the cell cycle in mammalian cells. Two dose-dependent responses are seen: At high concentrations (10 mcg/mL or more), cells entering mitosis are lysed; at low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase. Microtubule assembly is not affected. The predominant macromolecular effect of etoposide seems to be the rupture of the double strand by an interaction with DNA-topoisomerase II or by the formation of free radicals. Etoposide has been shown to cause metaphase arrest in chick fibroblasts.[94]<br><br>Cytarabine (ARA-C) is metabolised *in vivo* to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA. Cytarabine has no effect on non-proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug.[59]<br><br>Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chlorethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication.[95] |
| **Method of administration** | Intravenous infusion (carmustine and melphalan); pump infusion through CVK (cytarabine and etoposide). |
| **Dosing** | Combined chemotherapy administered the week leading up to ASCT (starting day -7).<br><br>Carmustine 300 mg/m$^2$ (Day -7), cytarabine 2×200 mg/m$^2$, every 12 hours (Day -6 to Day -3), etoposide 2×100 mg/m$^2$, every 12 hours (Day -6 to Day -3), and melphalan 140 mg/m$^2$ (Day -2) |
| **Dosing in the health economic model (including relative dose intensity)** | Same as above, relative dose intensity 100%. |

| Overview of BEAM regimen | |
|---|---|
| **Should the medicine be administered with other medicines?** | No |
| **Treatment duration/ criteria for end of treatment** | Described above, or until unacceptable toxicity or disease progression. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Monitoring of blood counts |

Abbreviations: BEAM, carmustine, etoposide, cytarabine, and melphalan; CVK, Central Venous Catheter; ASCT, autologous stem cell transplantation; ARA-C, cytarabine.
Source: EMA[93] , EMC[59,94,95], Janssen Research & Development [Data on file][8], Promedicin.dk[4,96-99], Rigshospitalet.dk[100]

**Table 86 Key descriptive information of THAM regimen**

| Overview of THAM regimen | |
|---|---|
| **Generic name** | The THAM regimen includes the TBI (total body irradiation) and the drugs cytarabine and melphalan |
| **ATC code** | • TBI<br>• Cytarabine (L01BC01)<br>• Melphalan (L01AA03) |

| Overview of THAM regimen | |
|---|---|
| **Mechanism of action** | TBI acts primarily by directly damaging and killing cells, especially rapidly dividing cells like cancer cells and immune cells in the bone marrow, through inducing DNA double-strand breaks. At lower doses, TBI can also exert its effects by suppressing the recipient's existing immune system, which prevents rejection of transplanted bone marrow, and potentially enhancing the host immune response to promote engraftment of donor cells.[101]<br><br>Cytarabine (ARA-C) is metabolised *in vivo* to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA. Cytarabine has no effect on non-proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug.[59]<br><br>Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chlorethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication.[95] |
| **Method of administration** | External beam radiation (TBI); intravenous infusion (melphalan); pump infusion through CVK (cytarabine). |
| **Dosing** | Administered the week leading up to ASCT (starting day -7).<br><br>TBI 10 Gy (Day –7 to Day –5), cytarabine 2×1.5 g/m² every 12 hours, 30-minute IV infusion (Day –4 to Day –3), and melphalan 140 mg/m², 1-hour IV infusion (Day –2). |
| **Dosing in the health economic model (including relative dose intensity)** | Not included in the model, as its rare use (see Appendix K) results in minimal impact on the ICER |
| **Should the medicine be administered with other medicines?** | No |
| **Treatment duration/ criteria for end of treatment** | Described above, or until unacceptable toxicity or disease progression. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Monitoring of blood counts |

Abbreviations: ASCT, autologous stem cell transplantation; TBI, total body irradiation.
Source: EMC[59,95], Janssen Research & Development [Data on file][8], Promedicin.dk[96,98], Sabloff[101], Tseng et al.[53]

# Appendix L. Discontinued study participation (TRIANGLE)

Reasons for discontinuation in the TRIANGLE trial are reported in Table 87 and Table 88.

**Table 87 Subject disposition; Full Analysis Set (TRIANGLE)**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) | Total (N=537) |
|---|---|---|---|
| Discontinued study participation, n (%) | [redacted] | [redacted] | [redacted] |
| **Reason for discontinuation** | | | |
| Withdrawal of consent, n (%) | [redacted] | [redacted] | [redacted] |
| Lost to follow-up, n (%) | [redacted] | [redacted] | [redacted] |
| Other reason, n (%) | [redacted] | [redacted] | [redacted] |

Abbreviations: ASCT, autologous stem cell transplant.

Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.

**Table 88 Treatment disposition; Full Analysis Set (TRIANGLE)**

| | Ibrutinib without ASCT (N=268) | ASCT (N=269) | Total (N=537) |
|---|---|---|---|
| Subjects who discontinued study treatment | [redacted] | [redacted] | [redacted] |
| **Reason for discontinuation** | | | |
| Adverse event, n (%) | [redacted] | [redacted] | [redacted] |
| Asservation failure, n (%) | [redacted] | [redacted] | [redacted] |
| Death, n (%) | [redacted] | [redacted] | [redacted] |
| Investigator or sponsor decision, n (%) | [redacted] | [redacted] | [redacted] |
| Non compliance, n (%) | [redacted] | [redacted] | [redacted] |
| Other [a], n (%) | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| Progressive disease, n (%) | [redacted] | [redacted] | [redacted] |
| Stable disease at end of induction, n (%) | [redacted] | [redacted] | [redacted] |
| Subject refuses treatment, n (%) | [redacted] | [redacted] | [redacted] |
| Withdrawal of consent, n (%) | [redacted] | [redacted] | [redacted] |

Abbreviations: ASCT, autologous stem cell transplant; MCL, Mantle Cell Lymphoma.

a Other includes e.g., non-MCL diagnosis at baseline and errors.

Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.

# Appendix M. Treatment duration, rituximab maintenance therapy

The extent of exposure for rituximab during maintenance period for the ibrutinib without ASCT arm and the ASCT arm is reported in Table 89, below.

**Table 89 Extent of exposure for rituximab during maintenance period; safety analysis set**

| | Ibrutinib without ASCT (N=265) | ASCT (N=268) |
|---|---|---|
| Total treatment duration (months) | | |
| N | [redacted] | [redacted] |
| Mean (SD) | | |
| Median | | |
| Q1; Q3 | | |
| Range | | |

Abbreviations: ASCT, autologous stem cell transplant; SD, standard deviation; Q1, first quartile; Q3=third quartile.

Note: Treatment duration is calculated as (date of last dose of Rituximab - date of first dose of Rituximab +1)/30.4375 during maintenance period.

Source: Janssen Research & Development [Data on file][8]

# Appendix N. Distribution of BEAM and THAM treatment in TRIANGLE

Table 90 and Table 91 summarise the distribution of patients who received BEAM or THAM. In the TRIANGLE trial, some centres experienced carmustine shortages; consequently, TEAM was substituted for BEAM, supported by evidence from a retrospective EBMT comparison showing no differences in survival or safety versus BEAM[102]. This substitution is reflected in the summaries below.

**Table 90 Extent of Exposure for BEAM (or TEAM); Safety Analysis Set**

| | ASCT (N=268) |
|---|---|
| **Thiotepa (TEAM)** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |
| **Carmustine (BEAM)** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |
| **Etoposide** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |
| **Cytarabine** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |
| **Melphalan** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |

Abbreviations: ASCT, autologous stem cell transplant; SD, standard deviation; Q1, first quartile; Q3, third quartile.
Source: Janssen Research & Development [Data on file][8]

**Table 91 Extent of Exposure for THAM; Safety Analysis Set**

| | ASCT (N=268) |
|---|---|
| **Total Body Irradiation (TBI)** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |
| **Cytarabine** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |
| **Melphalan** | |
| N | |
| Mean (SD) | |
| Median | |
| Q1; Q3 | |
| Range | |

Abbreviations: ASCT, autologous stem cell transplant; SD, standard deviation; Q1, first quartile; Q3, third quartile.
Source: Janssen Research & Development [Data on file][8]

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