Pirtobrutinib (Jaypirca™) as monotherapy for the treatment of relapsed or refractory (R/R) mantle cell lymphoma (MCL)

General information [1]

Drug description	Indication
The active substance of Jaypirca™ is pirtobrutinib (LOXO-305), a protein kinase inhibitor. Pirtobrutinib is a reversible, noncovalent inhibitor of Bruton's tyrosine kinase (BTK), which is involved in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.	Pirtobrutinib (Jaypirca™) as monotherapy is indicated for the treatment of adult patients with R/R MCL who have been previously treated with a BTK inhibitor.

Incidence

With an annual incidence of 2-3 per 100,000 persons, MCL accounts for approximately 6-9% of non-Hodgkin-lymphomas; men are more often affected than women (3:1) [2].
The median onset of disease is at an age of 65 years [3].

Current treatment [3]

- ❖ According to the Onkopedia guideline, in terms of relapse, immune chemotherapy provides a treatment option, particularly when the duration of initial remission is ≥24 months. The selection of the regimen depends on the primary therapy.
- ❖ In case of early relapse, ibrutinib seems to be superior to administration of further chemotherapy.
- ❖ In case of relapse after the administration of a BTK-inhibitor, an aggressive course of disease is common. The recently approved CAR-T-cell therapy achieves ongoing remissions in this population. In elderly patients, venetoclax (which is not approved for MCL) achieves remission in up to 50% of patients; however, the duration of response is limited.
- ❖ In patients with multiple relapses or refractory disease, lenalidomide is also superior to chemotherapy. The combination with rituximab results in higher response rate at similar tolerability.
- ❖ Temsirolimus, a mTOR inhibitor, achieves only a short duration of remission (median 2.9 months) in patients with multiple relapses or refractory disease; possibly, a combination e.g., with bendamustin-rituximab can be considered.
- ❖ Bortezomib, a proteasome inhibitor, also shows short remissions when administered as monotherapy; depending on prior therapy, the VR-CAP-regimen can be discussed.

Regulatory status

EMA [1]

Approval status for this indication: On 26 April 2023, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Jaypirca™.

<u>The full indication is:</u>

- ❖ Jaypirca™ as monotherapy is indicated for the treatment of adult patients with R/R MCL who have been previously treated with a BTK inhibitor.

Other indications: none

- ✓ **Medicine is under additional monitoring**
- ✓ **Medicine received a conditional marketing authorisation[1]**

FDA [4, 5]

Approval status for this indication: On 27 January 2023, the FDA granted accelerated approval to pirtobrutinib (Jaypirca™) for R/R MCL after at least 2 lines of systemic therapy, including a BTK inhibitor. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- ✓ Priority review
- ✓ Fast track designation
- ✓ Orphan drug designation

Other indications: Jaypirca™ is indicated for the treatment of

- ❖ Adult patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. This indication is approved under accelerated approval based on response rate.

Manufacturer

Eli Lilly and Company is the manufacturer of Jaypirca™.

Costs

56 Jaypirca film tablets 100 mg = € 7,930.00 (ex-factory price) [6]

[1] The approval of a medicine that address unmet medical needs of patients based on less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Posology [4]

- Recommended dosage: 200 mg orally once daily; swallow whole with water, with or without food. Do not cut, crush, or chew tablets.
- Manage toxicity using treatment interruption, dosage reduction, or discontinuation.
- Reduce dose in patients with severe renal impairment.

Warnings and precautions [4, 7]

- **Infections**
  - Monitor for signs and symptoms of infection, evaluate promptly, and treat.
- **Haemorrhage**
  - Monitor for bleeding and manage appropriately.
- **Cytopenias**
  - Monitor complete blood counts during treatment.
- **Atrial fibrillation and atrial flutter**
  - Monitor for symptoms of arrhythmias and manage appropriately.
- **Second primary malignancies**
  - Other malignancies have developed, including skin cancers and other carcinomas. Monitor and advise patients to use sun protection.
- **Tumour lysis syndrome (TLS)**
  - TLS has been reported rarely with pircabrutinib therapy.
  - Patients at high risk of TLS are those with high tumour burden prior to treatment. Patients should be assessed for possible risk of TLS and closely monitored as clinically indicated.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of potential risk to a foetus and to use effective contraception.
- **Lactose**
  - Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- **Sodium**
  - This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg daily dose, that is to say essentially 'sodium-free'.

Study characteristics [8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
BRUIN NCT03740529	323[2]	**Phase 1:** Pirtobrutinib orally once daily in 28-day cycles; 7 dose levels were administered: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg once per day[3] **Phase 2:** pirtobrutinib 200 mg once per day	-	maximum tolerated dose (phase 1) + ORR (phase 2)	6.0 months	**ongoing[4]**, multicentre, open-label, phase 1/2 trial	BTK	Loxo Oncology	BRUIN trial [9], [11]

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (n=323)
<u>All Patients:</u> ❖ ECOC PS 0-2; age ≥18 years ❖ Confirmation of availability of tumour sample obtained after most recent treatment	❖ Investigational agent or anticancer therapy within 5 half-lives prior to planned start of LOXO-305	<u>**All patients:**</u> ❖ **Median age**: 68 years (IQR 62–74) ❖ **Male sex:** 66% ❖ **ECOG PS 0**: 50%; **PS 1**:43%; **PS 2:** 6%

[2] N=170 with CLL or SLL, n=61 with MCL, n=26 with Waldenström macroglobulinaemia, and n=66 with other B-cell lymphomas. Of 323 enrolled patients, 203 were assigned to receive pirtobrutinib (25–300 mg once per day; phase 1) and 120 patients received pirtobrutinib (200 mg once per day; phase 2).

[3] Treatment continued until disease progression, unacceptable toxicity, or withdrawal. Patients with disease progression could continue treatment if deriving ongoing clinical benefit per investigator opinion.

[4] The BRUIN trial is currently ongoing; estimated study completion date is 04/2024.

[5] For detailed in- and exclusion criteria, please see supplementary appendix.

- Adequate hepatic and renal function
- Ability to swallow tablets and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation
- Willingness to observe conventional and effective birth control methods

<u>Phase 1/2 LOXO-305 monotherapy</u>

- Histologically confirmed B-cell malignancy failed or intolerant to either ≥ 2 prior SOC regimens given in combination or sequentially OR have received 1 prior BTK-containing regimen when a BTK inhibitor is approved as first line therapy

<u>During dose escalation and dose-limiting toxicity (DLT) assessment</u>

- Adequate hematologic status
- After phase 1 dose escalation and DLT assessment: no hematologic parameters apply but patient must be responsive to transfusion support if given for thrombocytopenia or anaemia
- Patients' refractory to transfusion support are not eligible

<u>Phase 1b LOXO-305 combinations:</u>

- Arm A: (venetoclax + LOXO-305): Histologically confirmed R/R CLL in whom venetoclax is an appropriate salvage treatment
- Arm B: (rituximab +venetoclax+ LOXO-305): Histologically confirmed R/R CLL in whom venetoclax + rituximab is an appropriate salvage treatment; prior antiCD20 therapy is allowed
- Arm C: (rituximab + CHOP + LOXO-305): Histologically confirmed CD20(+) non-GCB-DLBCL, follicular lymphoma, or MCL, who have received ≤1 prior regimen of treatment, with ≥ 1 site of measurable disease, and for which appropriate treatment is the combination of rituximab with standard CHOP chemotherapy

<u>During DLT period</u>

- Adequate hematologic status
- For Arms A and B: ANC ≥ 0.75 × 109/L; the patient may enrol if there is documented bone marrow involvement considered to impair hematopoiesis
- For Arm C: ANC ≥ 1.5× 109/L
- Platelet count ≥ 50 × 109/L not requiring transfusion support; for Arm A and B: the patient may enrol below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis
- Hemoglobin ≥ 8 mg/dL not requiring transfusion support or growth factors; for Arm A and B: the patient may enrol below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis
- Patient must be responsive to transfusion support if given for thrombocytopenia or anaemia; patients refractory to transfusion support are not eligible

- Major surgery within 4 weeks prior to planned start of LOXO-305
- Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment
- Patients requiring therapeutic anticoagulation with warfarin
- Any unresolved toxicities from prior therapy greater than CTCAE (version 5.0) grade 2 at the time of starting study treatment
- History of allogeneic or autologous SCT or CAR-T therapy within the last 60 days or with any of the following: active GVHD; cytopenias from incomplete blood cell count recovery post-transplant; need for anti-cytokine therapy for toxicity from CAR-T therapy; residual symptoms of neurotoxicity > grade 1 from CAR-T therapy; ongoing immunosuppressive therapy
- Known CNS involvement by systemic lymphoma
- Active uncontrolled auto-immune cytopenia
- Clinically significant, uncontrolled cardiac, cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-305, or prolongation of the QT interval corrected for heart rate
- Active uncontrolled systemic bacterial, viral, fungal, or parasitic infection
- Tested positive for HIV
- Clinically significant active malabsorption syndrome or other condition likely to affect GI absorption of the study drug
- Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp inhibitors
- Treatment with PPIs within 7 days of starting LOXO-305
- Pregnancy or lactation
- Active second malignancy
- Patients with a known hypersensitivity to any component or excipient of LOXO-305

- **Median number of previous lines of systemic therapy**: 3 (IQR 2-5)
- **Previous therapy**:
  - BTK inhibitor: 76%
  - Chemotherapy: 87%
  - Anti-CD20 antibody: 94%
  - BCL2 inhibitor: 25%
  - PI3K inhibitor: 16%
  - Lenalidomide: 14%
  - Autologous SCT: 7%
  - Allogenic SCT: 3%
  - CAR T-cell therapy: 7%
- **Reason discontinued any previous BTK inhibitors:**
  - Progressive disease: 71%
  - Toxicity or other[6]: 29%

<u>MCL patients:</u>

- **Median age:** 69 years
- **Male sex**: 77%
- **ECOG PS 0**: 69%; **PS 1**: 28%; **PS 2:** 3%
- **Median number of previous lines of systemic therapy**: 3 (range 2-4)
- **Previous therapy**:
  - BTK inhibitor: 93%
  - Chemotherapy: 92%
  - Anti-CD20 antibody: 98%
  - BCL2 inhibitor: 15%
  - PI3K inhibitor: 2%
  - Lenalidomide: 20%
  - Autologous SCT: 25%
  - Allogenic SCT: 5%
  - CAR T-cell therapy: 5%
- **Reason discontinued any previous BTK inhibitors:**
  - Progressive disease: 77%
  - Toxicity or other: 23%

[6] Includes patients who completed treatment and those who discontinued voluntarily or due to physician's decision.

❖ After the DLT safety assessment is completed for a combination arm: no hematologic parameters apply but patient must be responsive to transfusion support if given for thrombocytopenia or anaemia; patients refractory to transfusion support are not eligible; growth factors may be used as per ASCO guidelines and institutional standard	❖ For patients enrolled to phase 1b Arms B and C: patients with prior significant hypersensitivity to rituximab requiring discontinuation, prior allergic or anaphylactic reaction to rituximab	

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cut-off date: 27 Sept 2020[7] ❖ Pirtobrutinib exhibited linear dose-proportional exposures (maximum concentration in plasma and AUC) and low interpatient variability throughout the entire dosing range of 25 mg- 300 mg daily. ❖ The observed half-life was approximately 20 h. ❖ Efficacy was observed at all dose levels and safety data supported selection of a 300 mg dose. ❖ 200 mg daily, corresponding to unbound pirtobrutinib trough steady-state exposures with BTK plasma concentration corresponding to 96% target inhibition, was selected as the recommended phase 2 dose. ❖ Seven dose levels, 25 mg to 300 mg daily, were evaluated. No dose-limiting toxicities were observed and thus no maximum tolerated dose was established. **ORR in patients with MCL (n=56): 52% (95% CI 38–65), including 14 with CR, 15 with PR, 10 with stable disease,12 with progressive disease, and 5 not evaluable** **ORR in patients with CLL or SLL (n=139)**: 63% (95% CI, 55–71) including 69 patients with PR, 19 with PR with lymphocytosis, 45 with stable disease, 1 with progressive disease, and 5 discontinued before their first response assessment and were considered non-evaluable, but counted as non-responders **ORR in BTK-pre-treated patients (n=121):** 62% (95% CI 53–71) **ORR among patients who had received a previous covalent BTK inhibitor (n=52)**: 52% (95% CI 38–66) **Median time to first response:** 1.8 months (IQR 1.8–1.9) **Median follow-up for efficacy evaluable patients with MCL**: 6 months (IQR 3–9) **ORR in patients with Waldenström Macroglobulinaemia (n=19):** 68%, including 9 patients with PR, 4 with minor response, 3 with stable disease, and 3 with progressive disease. **ORR among patients who had received a previous covalent BTK inhibitor (n=13)**: 69% (5 with PR and 4 with minor response) **Responses in patients with follicular lymphoma who were efficacy evaluable (n=8):** 50% **Data-cutoff date: 29 July 2022 [11]:** ORR among the patients who had previously received a BTK inhibitor: 73.3% (95% CI, 67.3-78.7), including 4 CRs (in 1.6%), 1 nodular PR (in 0.4%), and 176 PRs (in 71.3%) ORR when PR with lymphocytosis was considered: 82.2% (95% CI, 76.8-86.7) ORR in patients who had previously received both a BTK inhibitor and a BCL2 inhibitor: 70.0% (95% CI, 60.0-78.8) and 79.0% (95% CI, 69.7-86.5) when PR with lymphocytosis was included. Patients with a decrease in the size of the target lesions, regardless of the reason for discontinuation of previous BTK inhibitor therapy and regardless of previous BCL2 treatment: 96.9% Median PFS in the overall efficacy cohort (at a median follow-up of 19.4 months): 19.6 months (95% CI, 16.9-22.1) Median PFS in the subgroup of patients who had previously received both a BTK inhibitor and a BCL2 inhibitor:16.8 months (95% CI, 13.2-18.7) Median PFS among patients who had received a BTK inhibitor but not a BCL2 inhibitor: 22.1 months (95% CI, 19.6-27.4) Median PFS among patients who had received all five classes of available CLL or SLL therapy, including BTK,	**Data cut-off date: 27 Sept 2020** **Any TEAEs in CLL/SLL patients**: n=142/170 (84%) **Any TEAES in MCL patients**: n=50/61 (82%) **TRAEs of special interest (any grade):** • Bruising: n=37/323 (12%) • Rash: n=18/323 (6%) • Arthralgia: n=5/323 (2%) • Haemorrhage: n=5/323 (2%) • Hypertension: n=4/323 (1%) • Atrial fibrillation or flutter: n=0 (0%) **Permanent discontinuations for drug-related AEs**: n=5/323 (1%) **Data-cutoff date: 29 July 2022:** Infections: 71.0% Infections grade ≥3: 28.1% Bleeding: 42.6% Neutropenia: 32.5% Neutropenia grade ≥3: 26.8% Treatment discontinuation due to TRAES: 2.8% Patients who died while receiving pirtobrutinib for causes other than disease progression: n=8 (Covid-19 or Covid-19–related pneumonia; n=2 (pneumonia or fungal pneumonia); n=2 (septic shock or shock); n=4 (other causes)

[7] Of the 323 patients treated with pirtobrutinib, 269 patients were efficacy evaluable, including 139 with CLL or SLL, 56 with MCL, 19 with Waldenström macroglobulinaemia, and 55 with other B-cell lymphomas. The 54 (17%) patients who were not included in the efficacy analysis for response were all ongoing on pirtobrutinib, progression-free, and pending their first response assessment at the time of data lock. Patients who withdrew from the protocol before a formal response assessment were efficacy evaluable and considered non-responders.

BCL2, and PI3K inhibitors as well as chemoimmunotherapy: 13.8 months (95% CI, 10.3-NE) 12-month OS among all the patients who had previously received a BTK inhibitor at a median follow-up of 22.6 months: 86.0% (95% CI, 81.0-89.8) 18-month OS: 80.5% (95% CI, 74.8-85.0)	

Patient-reported outcomes; interim analysis data [12]

- PRO data were collected using paper forms at each clinic visit.
- HRQoL was collected using the EORTC QLQ-C30 (Physical Function and QoL subscales)
- Patient-reported MCL symptoms data were from 13 EORTC Item Library (IL) items, and fatigue data were from 6 EORTC IL items.
- All subscales are scored 0-100.
- Pre-defined minimal clinically important difference (MCID) thresholds, defined as a minimum change in PRO scores that is clinically meaningful to patients for improvement or worsening, were used to categorize patients based on their individual change. Higher scores represent better Physical Functioning and QoL on those subscales. For MCL symptoms and fatigue, higher scores represent greater symptoms.
- PRO data were presented from Cycle 1 to 11 since the majority of patients (84.7%) had duration of PFS <12 months.
- Results:
  - A total of 124 patients with MCL were enrolled at the time of this interim analysis, with a mean (standard deviation [SD]) age of 69.4 (8.5) years, range: 46-88 years, at baseline. The majority were male (79.0%) and from the US (60.5%).
  - The mean overall completion rate of PRO instruments was 85.5% at baseline.
  - The proportion of enrolled participants completing subsequent assessments declined over time, at Cycle 11 the overall completion rate was 64.9%.
  - Baseline mean (SD) Physical Function score was 83.6 (18.1) and QoL score was 62.6 (23.4).
  - Mean (SD) MCL Symptoms and Fatigue scores at baseline were 21.2 (17.7) and 29.6 (23.1), respectively.
  - The majority of patients reported stable or clinically meaningful improved outcomes from baseline for Physical Function (>80% of patients), QoL (>80%), MCL symptoms (>75%), and fatigue (>65%) at each of these visits (through Cycle 11), based on the MCID thresholds.
  - HRQoL and symptoms were maintained or improved for the majority of R/R cBTKi exposed MCL patients throughout the first 11 cycles of pirtobrutinib treatment.
  - PRO data should be interpreted with caution due to relatively small numbers of patients in later cycles and relatively low completion rates in some cycles.

ESMO-MCBS for Haematological Malignancies version 1.0

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 52%	-	ORR (PR+CR) ≥40-<60%	2	-	QoL improved	+1[8]	3

Risk of bias - study level (case series) [13]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[9]	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	partial	yes	unclear[10]	yes

[8] QoL upgrade.
[9] Patient characteristics at baseline regarding the number and types of previous therapies were heterogenous.
[10] Since the BRUIN trial is currently ongoing; there is no final analysis data available.

Overall risk of bias: moderate		
Ongoing trials		
NCT number/trial name	Description	Estimated study completion date
NCT03740529/ BRUIN trial	Please see above	04/2024
NCT04662255/BRUIN-MCL-321	A phase 3 open-label, randomised study of LOXO-305 vs. investigator choice of BTK inhibitor in patients with previously treated BTK inhibitor naïve mantle cell lymphoma	04/2025

Available assessments

- A Health Technology Briefing „Pirtobrutinib for mantle cell lymphoma" was published by NIHR in June 2021 [14].
- No further assessments were identified via NICE, CADTH, ICER and G-BA.

Other aspects and conclusions

- In April 2023, the **CHMP adopted a positive opinion,** recommending the granting of a conditional marketing authorisation for pirtobrutinib (Jaypirca™) as monotherapy for the treatment of adult patients with R/R MCL who have been previously treated with a BTK inhibitor. In January 2023, the **FDA granted accelerated approval** to pirtobrutinib (Jaypirca™) for R/R MCL after at least 2 lines of systemic therapy, including a BTK inhibitor.
- The **BRUIN trial (NCT03740529)** evaluates the safety and efficacy of pirtobrutinib in 323 patients with previously treated B-cell malignancies, including **56 patients with MCL**.
- **MCL patients** had a median age of 69 years and 97% had an ECOG PS of 0 or 1. The patients received a median number of 3 previous lines of systemic therapy (93% received a BTK inhibitor); 77% of patients discontinued any previous BTK-inhibitors due to progressive disease.
- The primary end point was an overall response (PR or better) as assessed by independent review. The percentage of patients with an overall response to pirtobrutinib was 73.3% (95% CI, 67.3-78.7), and the percentage was 82.2% (95% CI, 76.8-86.7) when PR with lymphocytosis was included.
- Analyses showed that HRQoL and symptoms were maintained or improved for the majority of R/R cBTKi exposed MCL patients throughout the first 11 cycles of pirtobrutinib treatment. However, PRO
- data should be interpreted with caution due to relatively small numbers of patients in later cycles and relatively low completion rates in some cycles.
- The **RoB** of the BRUIN trial was considered as **moderate,** due to the single-arm and open-label design, the differences in patient characteristics (e.g. number and types of previous therapies) and the involvement of the sponsor.
- The **ESMO-MCBS** for Haematological Malignancies was applied, resulting in a final adjusted magnitude of clinical benefit **grade of 3.**
- The method of the study was not fully transparent, e.g. the simultaneous assignment of patients into the 2 phases of the BRUIN trial and the various treatment arms, drug combinations and dose modifications.
- Besides the BRUIN trial, another phase 3 trial (NCT04662255, BRUIN-MCL-321), evaluating pirtobrutinib vs. investigator choice of BTK inhibitor in MCL patients, is currently ongoing. **Final analysis data** (including final analysis of patient-reported outcomes) from the BRUIN trial, and **robust phase 3 data is required** to extend treatment options for patients affected by this rare disease with poor prognosis.

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Abbreviations: AE=adverse event, AJ=adjustment, ANC=absolute neutrophil count, ASCO=American Society of Clinical Oncology, AUC=area under the curve, BCL2=B-cell Lymphoma 2, BTK=Bruton's tyrosine kinase, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone, CI=confidence interval, CLL=chronic lymphocytic leukaemia, CNS=central nervous system, CTCAE=Common Terminology Criteria for Adverse Events, DLBCL=diffuse large B-cell lymphoma, DLT=dose-limiting toxicity, ECOG PS= Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GCB= germinal center subtype, GVHD=graft versus host disease, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MCL=mantle cell lymphoma, MG=median gain, mTOR=mammalian target of rapamycin, n=number of patients, NICE=National Institute for Health Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI3K=PI3-kinase, PM=preliminary grade, QoL=quality of life, R/R=relapsed/refractory, SAE=serious adverse event, SCT=stem cell transplant, SLL=small lymphocytic lymphoma, SOC=standard of care, ST=standard treatment, TEAE=treatment-emergent adverse event, VR-CAP=rituximab/cyclophosphamide/doxorubicin/bortezomib/prednisone

References:

[1] European Medicines Agency (EMA). Medicines. Jaypirca. [cited 2023-05-04]. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jaypirca.

[2] Deutsche Krebsgesellschaft and ONKO Internetportal. Mantelzell-Lymphom (MCL). [cited 2023-05-04]. Available from: https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/non-hodgkin-lymphome/b-zell-lymphome/hintergrund/basis.html#:~:text=Mit%20einer%20j%C3%A4hrlichen%20Inzidenz%20von,zwischen%2065%20und%2075%20Jahre.

[3] DGHO and Onkopedia. Onkopedia Leitlinien. Mantelzell-Lymphom. [cited 2023-05-04]. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/mantelzell-lymphom/@@guideline/html/index.html#ID0EEGAC.

[4] U.S. Food and Drug Administration (FDA). Jaypirca. Label Information. [cited 2023-05-04]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216059Orig1s000Corrected_lbl.pdf.

[5] U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma. [cited 2023-05-04]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma.

[6] Österreichischer Apotheker-Verlag. Warenverzeichnis Online,. [cited 2023-12-06]. Available from: https://warenverzeichnis.apoverlag.at/.

[7] European Medicines Agency (EMA). Jaypirca: EPAR - Product Information. [cited 2023-12-06]. Available from: https://www.ema.europa.eu/en/documents/product-information/jaypirca-epar-product-information_en.pdf.

[8] Supplement to: Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021; 397: 892–901.

[9] Mato AR, Shah NN, Jurczak W and et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021; 397: 892–901.

[10] U.S. National Library of Medicine and ClinicalTrials.gov. A Study of Oral LOXO-305 in Patients With Previously Treated CLL/SLL or NHL. [cited 2023-05-09]. Available from: https://clinicaltrials.gov/ct2/show/NCT03740529.

[11] Mato AR, Woyach JA, Brown JR and et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. N Engl J Med 2023;389:33-44.

[12] Cohen J and et al. P1112 PATIENT-REPORTED OUTCOMES (PRO) AMONG PATIENTS WITH MANTLE CELL LYMPHOMA RECEIVING PIRTOBRUTINIB AFTER PRIOR COVALENT BTKI: INTERIM PRO ANALYSIS FROM THE BRUIN PHASE 1/2 STUDY. HemaSphere | 2023;7(S3) EHA2023 Hybrid Congress.

[13] Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

[14] National Institute for Health Research (NIHR). Pirtobrutinib for mantle cell lymphoma. [cited 2023-05-09]. Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/27486-Pirtobrutinib-for-Mantle-Cell-Lymphoma-v1.0-JUN21-NON-CONF-.pdf.