Zanubrutinib (Brukinsa®) with obinutuzumab for the treatment of refractory or relapsed follicular lymphoma (FL)

General information

Drug description [1]

Zanubrutinib (Brukinsa®) is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in the activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.

Indication [2]

Zanubrutinib (Brukinsa®) in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed FL who have received at least two prior systemic therapies.

Incidence [3]

In Germany, 3 to 4 per 100,000 persons/year are newly diagnosed with FL. The median age at diagnosis is 60 years.

Current treatment [4]

For the treatment of patients with FL after the second relapse, Onkopedia recommends (depending on prior therapies and duration of remission):

- Participation in clinical trials
- Mosunetuzumab
- Tisacel
- Rituximab-lenalidomide
- Rituximab-chemotherapy
- Allogeneic transplantation (preferably after failure of ASCT and within clinical trials.

Beyond the third relapse, the following is recommended:

- Axi-cel
- Further therapeutical options as mentioned above
- Idelalisib.

Regulatory status

EMA [2]	FDA
Approval status for this indication: On 12 October 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Brukinsa®. The CHMP adopted a new indication as follows: ❖ Brukinsa® in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed FL who have received at least two prior systemic therapies. **Other indications**: Brukinsa® is indicated: ❖ as monotherapy 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. ❖ as monotherapy for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. ❖ as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).	**Approval status for this indication**: not approved According to the manufacturer, the FDA has accepted for review a supplemental new drug application for the combination of zanubrutinib and obinutuzumab for the treatment of adult patients with relapsed or refractory FL after at least 2 prior lines of therapy [5]. **Other indications**: Brukinsa® is indicated for the treatment of adult patients with [1]: ❖ Mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on the overall response rate. ❖ WM ❖ Relapsed or refractory MZL who have received at least one CD20–based regimen. This indication is approved under accelerated approval based on the overall response rate.

✓ **Medicine under additional monitoring**	❖ CLL or small lymphocytic lymphoma (SLL).

Manufacturer

Brukinsa® is manufactured by BeiGene.

Costs

120 Brukinsa® hard capsules 80 mg = **€ 4,936.57** (ex-factory price) [6]

Special warnings and precautions for use [7]

- **Haemorrhage**
  - Serious and fatal haemorrhagic events have occurred in patients treated with Brukinsa® monotherapy.
  - Grade 3 or higher bleeding events including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported in patients.
  - Bleeding events of any grade including purpura and petechiae occurred in patients with haematological malignancies. The mechanism for the bleeding events is not well understood.
  - Brukinsa® may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Dose modification may be necessary for Grade 3 or greater adverse reactions as recommended. Warfarin or other vitamin K antagonists should not be administered concomitantly with Brukinsa®.
  - Patients should be monitored for signs and symptoms of bleeding and monitor complete blood counts. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with Brukinsa®.
  - Consider the benefit-risk of withholding zanubrutinib for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- **Infections**
  - Fatal and non-fatal infections (including bacterial, viral, fungal infections, or sepsis) and opportunistic infections (e.g. herpes viral, cryptococcal, aspergillus and pneumocystis jiroveci infections) have occurred in patients treated with Brukinsa® monotherapy.
  - Grade 3 or higher infections occurred in patients. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have also occurred. Before initiating treatment with Brukinsa®, patients' HBV status should be established. Consultation with a liver disease expert physician is recommended for patients who test positive for HBV or have positive hepatitis B serology, before initiating treatment. Patients should be monitored and managed according to the medical standards to prevent hepatitis B reactivation.
  - Consider prophylaxis according to the standard of care in patients who are at increased risk for infections. Patients should be monitored for signs and symptoms of infection and treated appropriately.
- **Cytopenia**
  - Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anaemia based on laboratory measurements were reported in patients treated with Brukinsa® monotherapy.
  - Monitor complete blood counts monthly during treatment.
- **Second primary malignancies**
  - Second primary malignancies, including non-skin carcinoma, have occurred in patients treated with Brukinsa® monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin). Advise patients to use sun protection.
- **Atrial fibrillation and flutter**
  - Atrial fibrillation and atrial flutter have occurred in patients treated with Brukinsa® monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.
- **Tumour lysis syndrome**
  - Tumour lysis syndrome has been infrequently reported with zanubrutinib therapy, particularly in patients who were treated for CLL. Assess relevant risks (e.g., high tumour burden or blood uric acid level) and take appropriate precautions. Monitor patients closely and treat them as appropriate.
- **Women of childbearing potential**
  - Women of childbearing potential must use a highly effective method of contraception while taking Brukinsa®.
- **Brukinsa® contains sodium**

- This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
ROSEWOOD BGB-3111-212 NCT03332017	217 2:1	zanubrutinib orally 160 mg twice daily[1] + obinutuzumab IV 1,000 mg on days 1, 8, and 15 of cycle 1, then on day 1 of cycles 2-6, then once every 8 weeks up to a total of 20 infusions (2-year maintenance)	obinutuzumab IV 1,000 mg on days 1, 8, and 15 of cycle 1, then on day 1 of cycles 2-6, then once every 8 weeks up to a total of 20 infusions (2-year maintenance)	ORR by PET-CT assessment by ICR	20.2 months	**ongoing**[2], open-label, randomized, phase 2 trial	-	BeiGene	ROSEWOOD trial [11]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=145 vs. n=72)
❖ ≥ 18 years with a histologically confirmed diagnosis of B-cell FL (Grade 1, 2 or 3a) based on the WHO 2008 classification of tumours of hematopoietic and lymphoid tissue. ❖ ≥ 2 prior systemic treatments for FL. ❖ Previously received an anti-CD20 antibody and an appropriate alkylator-based combination therapy, including: • Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone • Rituximab, cyclophosphamide, vincristine, and prednisolone • Bendamustine plus rituximab. ❖ Disease progression after completion of most recent therapy or refractory disease, defined as failure to achieve CR or PR to most recent therapy, and most recent therapy was an appropriate second-line (or later) systemic therapy for FL. ❖ Presence of measurable disease, defined as ≥ 1 nodal lesion that is > 2 cm in longest diameter, or ≥ 1 extranodal lesion that is > 1 cm in longest diameter. ❖ Availability of archival tissue confirming the diagnosis of B-cell FL. ❖ ECOG PS of 0, 1, or 2 ❖ Life expectancy ≥ 6 months ❖ Adequate organ function is defined as: • ANC ≥ 1000/mm3, except when neutropenia is assessed by the investigator to be directly due to active lymphoma, in which case ANC must be ≥ 750/mm3.	❖ Known CNS involvement by leukaemia or lymphoma. ❖ Evidence of transformation from FL to DLBCL or other aggressive histology. ❖ Allogeneic HSCT within 12 months of study enrolment. ❖ Prior exposure to a BTK inhibitor. ❖ Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer. ❖ Clinically significant cardiovascular disease including the following: Myocardial infarction within 6 months before screening, unstable angina within 3 months before screening, New York Heart Association Class III or IV congestive heart failure, history of clinically significant arrhythmias, QTcF > 480 milliseconds based on Fridericia's formula, history of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place, uncontrolled hypertension. ❖ History of severe bleeding disorder such as haemophilia A, haemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention. ❖ History of stroke or intracranial haemorrhage within 6 months before first dose of study drug. ❖ Severe or debilitating pulmonary disease.	❖ Median age: 63.0 vs. 65.5 years ❖ Previous lines of therapy: • Median: 3 vs. 3 • 2-3: 72% vs. 75% • >3: 28% vs. 25% ❖ ECOG PS 0-1: 97% vs. 99% ❖ High FLIPI score: 53% vs. 51% ❖ Ann Arbor stage III-IV: 82% vs. 83% ❖ Target lesion SPD by ICR, mm2, median: 1,614.0 vs. 1,727.0 ❖ Bulky disease (≥7 cm): 16% vs. 17% ❖ High LDH level (>ULN): 34% vs. 40% ❖ High tumour burden per GELF criteria: 57% vs. 56% ❖ Refractory to rituximab: 54% vs. 50% ❖ Refractory to most recent line of therapy: 32% vs. 40% ❖ PD ≤24 months of starting first line of therapy: 34% vs. 42%

[1] Continuously until progressive disease or unacceptable toxicity.
[2] The ROSEWOOD trial is currently ongoing; the estimated study completion date is 11/2023.
[3] For detailed in- and exclusion criteria, please see trial protocol.

• Platelet > 50,000/mm3 (without growth factor support or transfusion within 7 days). • Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault or MDRD equation or as measured by nuclear medicine scan or 24-hour urine collection). • AST/serum glutamic oxaloacetic transaminase, and ALT/serum glutamic pyruvic transaminase ≤ 3.0 x ULN. • Serum total bilirubin < 2.0 x ULN (unless documented Gilbert's syndrome). ❖ Female patients of childbearing potential must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, or 18 months after the last dose of obinutuzumab, whichever is longer. ❖ Male patients are eligible if abstinent, vasectomized, or if they agree to the use of barrier contraception in combination with other methods. ❖ Ability to provide written informed consent and can understand and comply with the requirements of the study.	❖ Unable to swallow capsules or disease significantly affecting gastrointestinal function. ❖ Active fungal, bacterial and/or viral infection requiring systemic therapy. ❖ Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of safety or efficacy results. ❖ Known infection with HIV, or serologic status reflecting active hepatitis B or C infection. ❖ Major surgery within 4 weeks of the first dose of study drug. ❖ Pregnant or lactating women. ❖ Vaccination with a live vaccine within 35 days prior to the first dose of study drug. ❖ Ongoing alcohol or drug addiction. ❖ Hypersensitivity to zanubrutinib or obinutuzumab or any of the other ingredients of the study drugs. ❖ Requires ongoing treatment with a strong CYP3A inhibitor or inducer. ❖ Concurrent participation in another therapeutic clinical trial. ❖ Requires ongoing need for corticosteroid treatment.	

Efficacy (I vs. C, n=145 vs. n=72)	**Safety** (I vs. C, n=143 vs. n=71)
<u>Data cutoff 25 June 2022; median follow-up 20.2 months</u> **ORR per ICR**: 69% vs. 46% (95% CI, 9-37; p= .001) **CR rate by ICR**: 39% vs. 19% **PR by ICR**: 30% vs. 26% **Median time to first response**: 2.8 months (range, 2.0-23.0) vs. 2.8 months (range, 2.5-6.5) **Median DOR by ICR:** NE (95% CI, 25.3-NE) vs. 14.0 months (95%CI, 9.2-25.1); **DOR, 18 -month rate**: 69% cs. 42% **Median duration of CR by ICR**: NE-26.5 months **Median PFS by ICR:** 28.0 (95% CI, 16.1-NE) vs. 10.4 (95% CI, 6.5-13.8); HR 0.50 (95% CI, 0.33-0.75); two-sided p<.001 **Median TTNT**: NE (95% CI, 33.4-NE) vs. 12.2 (95% CI, 8.5-17.3); HR 0.34 (95% CI, 0.22 to 0.52); two-sided p<.001 **Median OS**: NE (NE-NE) vs. 34.6 months (95%CI, 29.3-NE); HR 0.62 (95% CI, 0.35-1.07); two-sided p=0.085 **24-month OS rate**: 77% (95% CI, 68-84) vs. 71% (95% CI, 58-81) **ORR by investigators**: 68% vs. 43%; concordance rate between ICR and investigator: 88%	**≥1 TEAE:** 94% vs. 90% **TEAEs grade ≥3**: 63% vs. 48% **Atrial fibrillation**: 3% vs. 1% **Hypertension**: 3% vs. 6% **Bleeding**: 28% vs. 13% **Infections of any grade**: 55% vs. 41% **≥1 TEAE leading to death[4]:** 8% vs. 10%

Patient-reported outcomes
Patient-reported outcomes are a secondary endpoint of the ROSEWOOD trial; currently, no results are available.

[4] One death was related to study treatment (anaphylactic reaction after obinutuzumab infusion in C).

ESMO-MCBS for Haematological Malignancies version 1.0 [12]											
Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2c	-	ORR: + 23%	-	RR is increased ≥20%	2	-	-	-	2

Risk of bias (RCT) [13]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no[5] high risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing trials [14]		
NCT number/trial name	Description	Estimated study completion date
NCT03332017/ ROSEWOOD	Please see above.	11/2023
NCT05100862/ MAHOGANY	A phase 3 randomized, open-label, multicentre study of zanubrutinib (BGB-3111) plus anti-CD20 antibodies vs. lenalidomide plus rituximab in patients with relapsed/refractory FL or MZL.	06/2029

Available assessments

- In July 2023, NIHR published a Health Technology Briefing "Zanubrutinib plus obinutuzumab for treating relapsed or refractory follicular lymphoma" [15].
- No further assessments were identified via NICE, ICER, CADTH and G-BA.

Other aspects and conclusions

- In October 2023, the **CHMP adopted a new indication** for Brukinsa® in combination with obinutuzumab for the treatment of adult patients with refractory or relapsed FL who have received at least two prior systemic therapies. This indication is currently **not approved by the FDA**.
- **ROSEWOOD (**NCT03332017) is an **ongoing**, phase II, randomized study assessing the efficacy and safety of zanubrutinib plus obinutuzumab vs. obinutuzumab monotherapy in patients with relapsed or refractory FL. Eligible patients had a diagnosis of grade 1, 2, or 3a FL based on the WHO 2008 classification, must have received ≥2 previous systemic therapies for FL, an ECOG PS of 0-2, absence of transformation to aggressive B-cell lymphoma; and no previous BTK inhibitor exposure.
- The **primary endpoint was ORR** by ICR: 69% vs. 46% p=.001.
- Although defined as a secondary endpoint, **patient-reported outcomes are currently not available**.
- The **ESMO-MCBS for Haematological Malignancies** was applied, resulting in a final adjusted magnitude of clinical benefit **grade 2**.
- Since the ROSEWOOD trial is currently ongoing, the **risk of bias was considered unclear**. However, it is **increased** by the open-label design, the industry-funded background, the possibility to crossover and the difference in treatment duration between the two treatment arms.
- Besides the ongoing ROSEWOOD trial, one **phase 3 trial,** evaluating zanubrutinib plus anti-CD20 antibodies vs. lenalidomide plus rituximab in patients with relapsed/refractory FL or MZL, was identified.
- Final analysis data, including **patient-reported outcomes** of the ROSEWOOD trial, as well as **robust phase 3 data** is required to determine the role of zanubrutinib in patients with relapsed or refractory FL.

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, DLBCL=Diffuse large B cell lymphoma, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FLIPI=Follicular Lymphoma International

[5] ROSEWOOD is an open-label trial.
[6] ROSEWOOD trial is ongoing; currently, only primary analysis results are available.
[7] Industry-funded. At the investigator´s discretion, patients in the obinutuzumab arm were eligible to crossover to zanubrutinib + obinutuzumab arm if they experienced progressive disease or stable disease after 12 months. Furthermore, there was a difference in treatment duration between the two arms (median duration of zanubrutinib exposure was 12.2 months; median duration of obinutuzumab exposure in I was 6.5 months).

Prognostic Index, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GELF=Groupe d'Etude des Lymphomes Folliculaires, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, ICR=independent central review, Int.=intention, LDH=lactate dehydrogenase, MDRD=Modification of Diet in Renal Disease, MG=median gain, n=number of patients, NE=not estimable, NICE=National Institute for Health Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, SPD=sum of product of perpendicular diameters, ST=standard treatment, TTNT=time to next treatment, ULN=upper limit of normal

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