Zanubrutinib (Brukinsa®) as monotherapy for the treatment of marginal zone lymphoma (MZL)

General information

Drug description [1]	Indication [2]
Zanubrutinib (Brukinsa®) is a potent, highly specific, and irreversible next-generation Bruton tyrosine kinase (BTK) inhibitor.	Zanubrutinib (Brukinsa®) as monotherapy is indicated for the treatment of adult patients with MZL who have received at least one prior anti-CD20-based therapy.

Current treatment [3]

- Currently there are no treatment options recommended by NICE for the treatment of relapsed or refractory MZL.
- The ESMO management guidelines recommend that all patients with gastric MZL be treated with an anti H. pylori antibiotic regimen to eradicate the infection.
- For patients with non-gastric MZL or patients who do not achieve lymphoma regression following antibiotic therapy, irradiation and systemic oncological therapies are recommended.
- The most likely treatment option offered to patients with advanced stage MZL is an antibody therapy such as rituximab either as a monotherapy or in combination with chemotherapy (chemo-immunotherapy).

Regulatory status

EMA [2, 4]

Approval status for this indication: On 15 September 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Brukinsa®.

<u>The CHMP adopted a new indication:</u>

Brukinsa® as monotherapy is indicated for the treatment of adult patients with MZL who have received at least one prior anti-CD20-based therapy.

Other indications:

- Brukinsa® as monotherapy 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.
- Brukinsa® as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).

✓ **Medicine under additional monitoring**

FDA [5, 6]

Approval status for this indication: On 14 September 2021, the FDA granted accelerated approval to zanubrutinib (Brukinsa®) for adult patients with relapsed or refractory MZL who have received at least one anti-CD20-based regimen. This indication is approved under accelerated approval based on overall response rate.

Other indications: Brukinsa® is indicated for the treatment of adult patients with

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (indication approved under accelerated approval based on overall response rate).
- WM
- CLL or small lymphocytic lymphoma (SLL)

Costs

120 Brukinsa® hard capsules 80 mg = € 4,936.57 (ex-factory price) [7].

Warnings and precautions [4, 6]

- **Haemorrhage**
  - Monitor for bleeding and manage appropriately.
- **Infections**
  - Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed.
- **Cytopenias**
  - Monitor complete blood counts during treatment.
- **Second primary malignancies**

- Other malignancies have occurred in patients including skin cancers. Advise patients to use sun protection.

❖ **Cardiac arrhythmias**
- Monitor for atrial fibrillation and atrial flutter and manage appropriately.

❖ **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 as appropriate.

❖ **Embryo-foetal toxicity**
- Can cause foetal harm. Advise women of the potential risk to a foetus and to avoid pregnancy.

Study characteristics: MAGNOLIA trial (BGB-3111–214) [1, 8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
MAGNOLIA, BGB-3111–214 NCT03846427	66[1]	zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity	-	ORR as determined by an IRC	single arm, open-label, phase 2 study	-	BeiGene (Beijing) Co., Ltd	[1]

Efficacy (n=66)

ORR (IRC-assessed): 68.2% (95% CI, 55.56–79.11)
ORR for extranodal (n=25), **nodal** (n=25), **splenic** (n=12), and **unknown** (n=4) **subtypes**: 64%, 76%, 66.7%, and 50%, respectively
Median time to response: 2.8 months (range, 1.7-11.1)
PR: 42.4%
CR: 25.8%
CR rates (IRC-assessed) for each MZL subtype: 40% (extranodal), 20% (nodal), 8.3% (splenic), and 25% (unknown subtype)
Median DOR: NR
Estimated DOR rate at 12 months after first response: 93%
At a median study follow-up of 15.7 months, 89% of the responders were **free from progression or death** with 76% continuing on zanubrutinib.
Median PFS: NR
Estimated PFS rates at 12 and 15 months: 82.5%
Median DOR in any of the subgroups: not reached
Median PFS: NR in all subgroups (except in the subgroup of patients with above normal LDH (n=15; median PFS: 15.5 months)
Median OS: NR
Median 12-month OS: 95.3%
Median 15-month OS: 92.9%

Safety (n=68)

At least one AE of any grade: n=65/68 (95.6%)
At least one grade ≥ 3 AE: n=27/68 (39.7%)
Serious AEs: n=26/68 (38.2%)
Infections: n=31/68 (45.6%)
Grade ≥ 3 infections: n=11/68 (16.2%)
Any-grade neutropenia: n=9 /68 (13.2%)
Bleeding events (all were grade 1 or 2): n=25/68 (36.8%)
Second primary malignancies: n= 5/68[3]
Permanent discontinuation of zanubrutinib: n=4/68[4]
Deaths: n=7/68[5]

UPDATE: Final analysis of the MAGNOLIA Trial [13] (cutoff date 4 May 2022, n=66 evaluable for efficacy):
Any TEAEs: n=68/68 (100%)
Grade ≥3 TEAEs: n=33/68 (48.5%)
Drug-related grade ≥3 TEAEs: n=10/68 (14.7%)
TEAEs leading to dose interruption: n=25/68 (36.8%)
Drug-related TEAEs leading to dose interruption: n=8/68 (11.8%)

[1] 68 patients were enrolled; 66 patients were evaluable for efficacy (2 patients were excluded as central pathology showed transformation of MZL to diffuse large B-cell lymphoma).
[3] Basal cell carcinoma, squamous cell carcinoma, recurrent bladder cancer, papillary thyroid cancer and acute myeloid leukaemia. None of these events led to treatment discontinuation.
[4] Fatal COVID-19 pneumonia (n=2), pyrexia (n=1; attributed to disease progression), and fatal myocardial infarction (in a patient with a pre-existing cardiovascular disease). All four events were assessed by the investigators as unrelated to study treatment.
[5] Disease progression (n=4) and AEs (COVID-19 pneumonia n= 2; and myocardial infarction n=1).

IRC-assessed response rate in a subgroup of 18 patients ≥ 75 years of age (4 of the 18 patients were previously treated with rituximab as their only prior line of therapy): 94.4%
ORR in patients with at least one target lesion of more than 5 cm, refractory disease, and NMZL subtype: 79.2%, 66.7%, and 76.0%, respectively
Concordance rate for IRC and investigator-assessed ORR: 87.9%

UPDATE: Final analysis of the MAGNOLIA Trial [13] (cutoff date 4 May 2022, n=66 evaluable for efficacy):
Median follow-up: 28.0 months (range 1.6-32.9); median treatment duration: 24.2 months (range 0.9-32.9)
ORR (CR + PR; IRC-assessed): 68.2% (CR 25.8%)
SD: 19.7%
PD: 9.1%
ORR: 64.0%, 76.0%, 66.7%, and 50.0% in extranodal, nodal, splenic, and unknown subtypes, respectively
CR rate: 40.0% for extranodal, 20.0% for nodal, 8.3% for splenic, and 25.0% for unknown subtypes
Median DOR, PFS, and OS: not reached
DOR rate at 24 months: 72.9%
PFS rate at 24 months: 70.9%
OS rate at 24 months: 85.9%
Patients who were alive or progression-free at the 2-year landmark by independent review: >70.0%

Sensitivity analysis using only CT-based criteria (n=66) by IRC assessment
ORR: 66.7%
CR: 24.2%
Median DOR and median PFS: not reached

At study completion, 45.6% of patients deriving benefit rolled over to a long-term extension study (NCT04170283[2]); 35.3% of patients discontinued owing to disease progression (investigator assessed); 7.4% due to AEs, 2.9% required prohibited medications, and 1.5% withdrew consent.

TEAEs leading to dose reduction: 0
Patients who died due to unrelated AEs: n=5/68 (7.4%)[6]

ESMO-MCBS version 1.1 [10]

Disclaimer: Though not finally validated, but feasibility tested in [11], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, the original ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR (PR+CR): 68.2%	-	ORR≥60%	3	48.5% grade ≥3 TEAEs	NA	-1	2

Risk of bias - study level (case series) [12]

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?

[2] The estimated study completion date for NCT04170283 is 12/2025.
[6] COVID-19 pneumonia (n=2), acute myeloid leukaemia (n=1, prior alkylating agent exposure), myocardial infarction (n=1, pre-existing coronary artery disease), and septic encephalopathy (n=1, patient in CR).

yes	yes	yes	yes	partial	yes	unclear	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	yes	yes	yes	partial[7]	yes
Overall risk of bias: moderate								

Study characteristics: BGB-3111-AU-003 [13, 14]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
BGB-3111-AU-003 NCT02343120	20[8]	zanubrutinib 160 mg twice daily or 320 mg once daily[9]	-	TEAEs and clinically significant laboratory and vital sign abnormalities	open-label, multicentre, single-agent, phase 1/2 study	-	BeiGene	[13]

Efficacy (n=20)

Median relative dose intensity: 97.9% (range 77.4%-100%)
ORR (assessed by the IRC): 80.0% (95% CI, 56.3-94.3)
CR rate: 20.0% (95% CI, 5.7-43.7)
ORR by subtypes: 88.9% for extranodal, 100% for NMZL, and 50.0% for SMZL
Median time to response: 2.8 months (range, 2.6-23.1)
Median DOR and PFS: not reached
Estimated PFS rate (with a median follow-up of 33.8 months): 84% at 12 months and 72% at both 24 and 36 months
Median OS: NR
OS rates: 100% at 12 months and 83.9% at both 24 and 36 months

Safety (n=20)

Discontinuation of study treatment (at a follow-up of 35.2 months): n=8/20 (40%)[10]
≥1 TEAE of any grade: n=20/20 (100%)
≥1 TEAE of grade ≥3: n=11/20 (55.0%)
Infections: n=15/20 (75.0%)
Bleeding events: n=12/20 (60.0%)
AE leading to death: n=0

ESMO-MCBS version 1.1 [10]

Disclaimer: Though not finally validated, but feasibility tested in [11], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, the original ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The original ESMO-MCBS could not be assessed for this single-arm study due to the primary outcome TEAEs.											

Risk of bias - study level (case series) [12]

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	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?

[7] Data from predefined secondary endpoints, such as QoL assessment data are currently not available.
[8] The BGB-3111-AU-003 study of zanubrutinib in B-cell malignancies enrolled a total of 385 patients to histology-specific disease cohorts. 20 patients with relapsed/refractory MZL were enrolled.
[9] 160 mg twice daily (n=17); 320 mg once daily (n=3). 2 patients switched from 320 mg once daily to 160 mg twice daily.
[10] Discontinuations due to progressive disease (n=5); withdrawn consent (n=2); TEAE (n=1).

			entry into the study clearly stated?					
yes	yes	yes	yes	partial	yes	unclear	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	no	yes	yes	yes	yes
Overall risk of bias: moderate								
First published: 10/2022 **Last updated:** 02/2023								

Abbreviations: AE=adverse event, AJ=adjustment, BTK=Bruton tyrosine kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukemia, COVID=Coronavirus disease, CR=complete response, DOR=duration of response, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, IRC=independent review committee, LDH=lactate dehydrogenase, MCL=mantle cell lymphoma, MG=median gain, MZL=marginal zone lymphoma, n=number of patients, NICE=National Institute for Health and Care Excellence, NMZL=nodal marginal zone lymphoma, NR=not reached, ORR=overall response rate, OS=overall survival, PD=progressive disease, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, SD=stable disease, SLL=small lymphocytic lymphoma, ST=standard treatment, TEAE=treatment-emergent AE, WM=Waldenström macroglobulinemia

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