HOT NEWS

NELLE SINDROMI LINFOPROLIFERATIVE:
la storia continua

Il linfoma della zona marginale: Caso Clinico

Roberta Presicci

Scuola di Specializzazione in Ematologia, Università degli Studi di Cagliari

CAGLIARI

10 Luglio 2023
T Hotel

Disclosures of Roberta Presicci

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No dislosures to declare							

♀

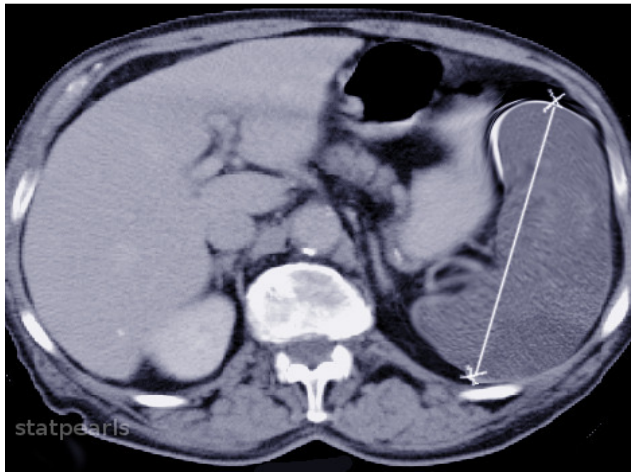
56 aa ECOG 0 CIRS 6

APR: APS, connettivite indifferenziata, fibromialgia, osteoporosi lombare, esofagite grado A, pregressa TVP, pregresso Herpes Zoster

Farmaci in uso: Acenocumarolo, Pregabalin, Idrossiclorochina

- Hb 8.9 g/dl
- WBC 1670/mmc
- N 1010/mmc
- L 500/mmc
- PLTs 127000/mmc
- B2 microglobulina 4.2 mg/L
- VES 72
- LDH 313 U/L
- CM assente
- HCV neg
- Non sintomi B

Aprile 2021



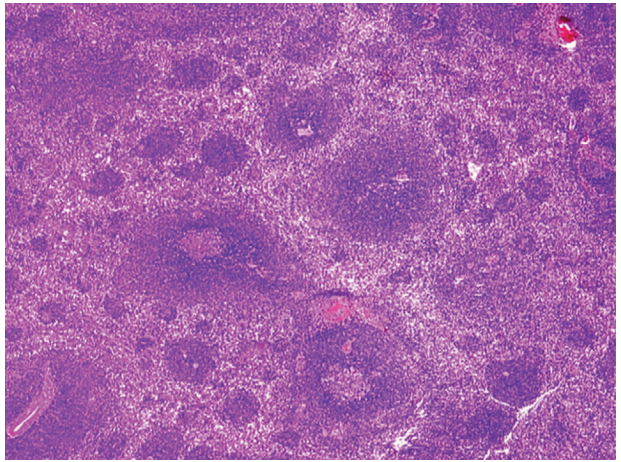
- Margine inferiore splenico palpabile a 4 cm dall'arco
- TC total body: linfonodi del collo di 0.7 cm, splenomegalia di 20.4 cm, area di osteorarefazione nel soma D12

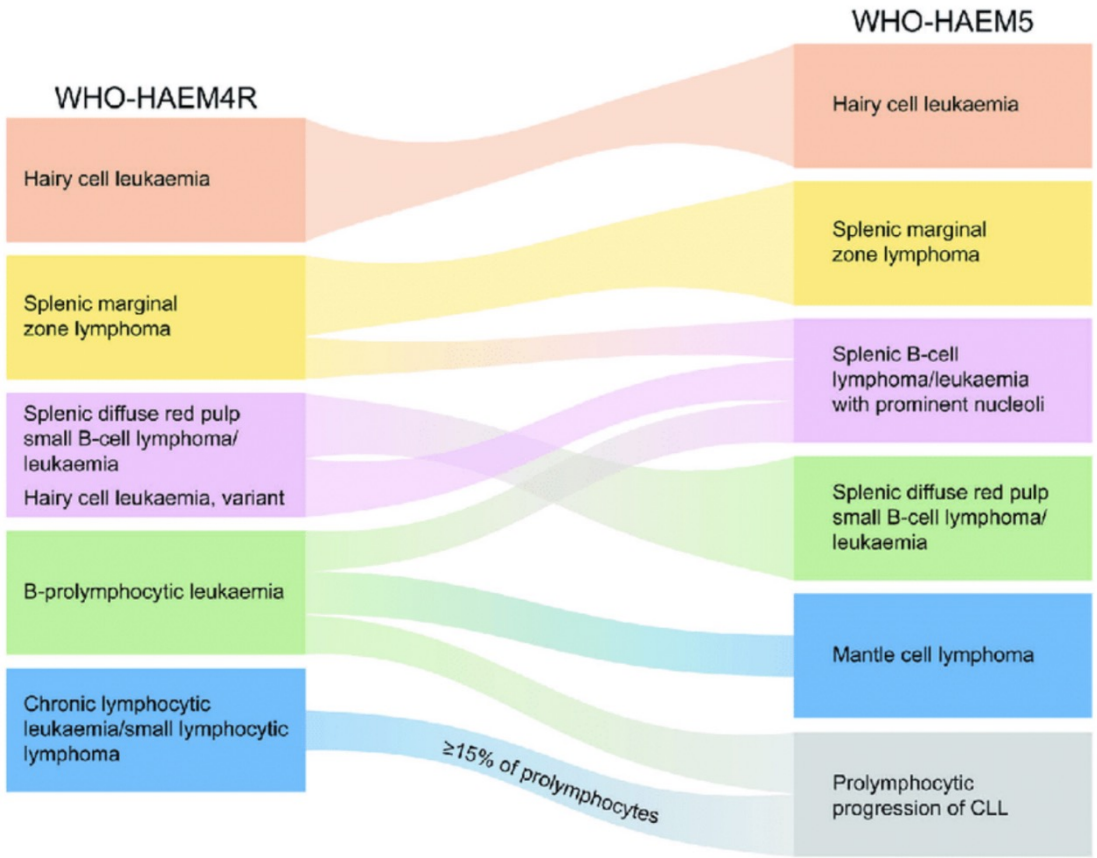
- **Immunofenotipo su sangue midollare**: linfociti CD19+ monoclonali per la catena leggera k con fenotipo CD45+ CD20+ CD79a+ CD5- CD23+ CD10-

- **BOM**: cellularità 40%; infiltrato pari al 15% di piccoli linfociti con IF CD20+ CD23 rare BCL1- CD10- BCL6- ki67 4% che depone per localizzazione midollare di linfoma marginale

Table 1. Immunohistochemical and molecular markers in MZL

Molecule	Type of test	Expected result	Level of recommendation
CD20	IHC	Positive	Mandatory
CD5	IHC	Negative[a]	Mandatory
CD23	IHC	Negative/positive	Suggested[b]
CD10	IHC	Negative	Mandatory
IgD	IHC	Negative[c]	Suggested
Cyclin D1	IHC	Negative	Mandatory[d]
MYD88 mutation	PCR	Negative	Suggested[e]





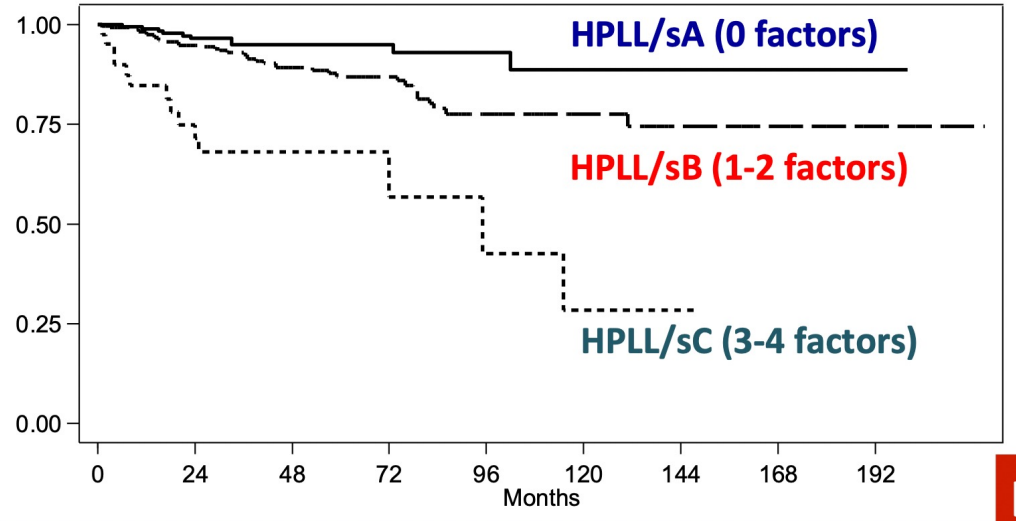
Linfoma splenico della zona marginale stadio IV

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Summary-of-the-relationship-between-splenic-B-cell-lymphoma-entities-as-named-and-defined_fig1_361491239 [accessed 28 Jun, 2023]

Score prognostico HPLL

- Hb < 9.5 g/dl
- PLTs < 80000/mmc
- LDH elevato
- Linfoadenopatie extra-ilari

2 fattori di rischio
gruppo B LLS 87%



LSS

Global p=0.000;
HPLLs/A vs. HPLLs/B: p=0.0159; HPLLs/B vs. HPLLs/C: p=0.000;
HPLLs/A vs. HPLLs/C: p=0.000

Point score simplification for practical use of the risk stratification for SMZ lymphoma: HPLL/sABC
Montalban & SMZLSG. Leukemia Lymphoma. 2014; 55:929

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

E. Zucca[1,2,3], L. Arcaini[4,5], C. Buske[6], P. W. Johnson[7], M. Ponzoni[8], M. Raderer[9], U. Ricardi[10], A. Salar[11], K. Stamatopoulos[12], C. Thieblemont[13], A. Wotherspoon[14] & M. Ladetto[15], on behalf of the ESMO Guidelines Committee*

For SMZL, the recognized therapeutic options are splenectomy, CHT, rituximab alone or rituximab plus CHT. Chemo-immunoterapy is particularly indicated for fit patients with symptomatic disseminated disease, constitutional symptoms and/or signs of high-grade transformation.

NCCN Guidelines Version 4.2023
Marginal Zone Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]
An FDA-approved biosimilar is an appropriate substitute for rituximab.[c]

FIRST-LINE THERAPY[b]

Preferred regimens (in alphabetical order)
- Bendamustine + rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab
- Rituximab (375 mg/m^2 weekly for 4 doses) for SMZL[b]

Other recommended regimens
- Lenalidomide + rituximab (category 2B)
- Rituximab (375 mg/m^2 weekly for 4 doses) for EMZL and nodal MZL

FIRST-LINE THERAPY FOR ELDERLY OR INFIRM[b]
(if none of the above are expected to be tolerable in the opinion of treating physician)

Preferred regimen
- Rituximab (375 mg/m^2 weekly for 4 doses)

Other recommended regimens
- Chlorambucil ± rituximab
- Cyclophosphamide ± rituximab

FIRST-LINE EXTENDED THERAPY (optional)
- Consolidation with rituximab 375 mg/m^2 one dose every 8–12 weeks for up to 2 years

See Second-line and Subsequent Therapy on MZL-A 2 of 4

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens (MZL-A 4 of 4).
[b] The choice of therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with ASCR). Therefore, treatment selection is highly individualized.
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Avviata a 6 cicli di Rituximab-Bendamustina (Luglio-Dicembre 2021)

- Profilassi: Aciclovir 400 mg x 2, Pentamidina 1 fl/28 gg, shift di Acenocumarolo con Fondaparinux
- AEs: Neutropenia febbrile di grado IV con sospetta flogosi polmonare trattata con ab per os, G-CSF e antifungino di profilassi;
  neutropenia di grado III trattata con GCSF che ha determinato il ritardo nell'inizio del III ciclo;
  infezione paucisintomatica da SARS-CoV2

Febbraio 2022
Emocromo: Hb 11.4 g/dl
WBC 2520/mmc
N 1220/mmc
PLTs 142000/mmc
TC: non linfoadenopatie a livello del collo, milza 11.7 cm, reperti ossei invariati
BOM: negativa

Complete response	Resolution of organomegaly (spleen longitudinal diameter <13 cm) Hb >12 g/dl, platelets >100 × 10^9/l and neutrophils >1.5 × 10^9/l No evidence of circulating clonal B cells by flow cytometry (light chain-restricted B cells) No evidence of bone marrow infiltration detected by IHC Negative DAT and PET (if positive at diagnosis)
Partial response	Regression ≥50% in all the measurable disease manifestations No new sites of disease Improvement of cytopaenias Decrease of infiltration and improvement of haematopoietic reserve at bone marrow biopsy
No change	<10% Improvement on the disease manifestations Colonoscopy and EGD
Progression	>50% measurable signs of the disease from nadir
Relapse	Reappearance of any measurable sign of the disease

1.Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆
2.Zucca, E. et al. 3.Annals of Oncology, Volume 31, Issue 1, 17 - 29

Gennaio 2023 (+13 mesi dal termine Rituximab-Bendamustina)

Sudorazioni notturne, sensazione di ingombro addominale
ECOG 0 CIRS 7

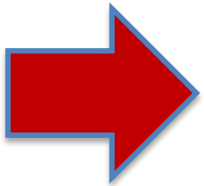
Emocromo: 11.2 g/dl WBC 3650/mmc N 2400/mmc PLTs 146000/mmc

Ecografia addome: milza 19 cm

BOM: infiltrato del 20-25% di piccoli linfociti aventi immunofenotipo
CD20+ CD79a+ CD5- CD10- CD23- ciclinaD1- ki67 5-6%

Come procediamo?

- 57 aa
- Recidiva dopo 13 mesi da terapia frontline
- Terapia anticoagulante con Acenocumarolo e LAC positivo



- Chemioimmunoterapia
- Rituximab in monoterapia
- Ibrutinib
- Zanubrutinib

05/06/2023 Inizia Zanubrutinib a 160 mg x 2 vv/die

Figure 1. OS by POD24 vs nonPOD24

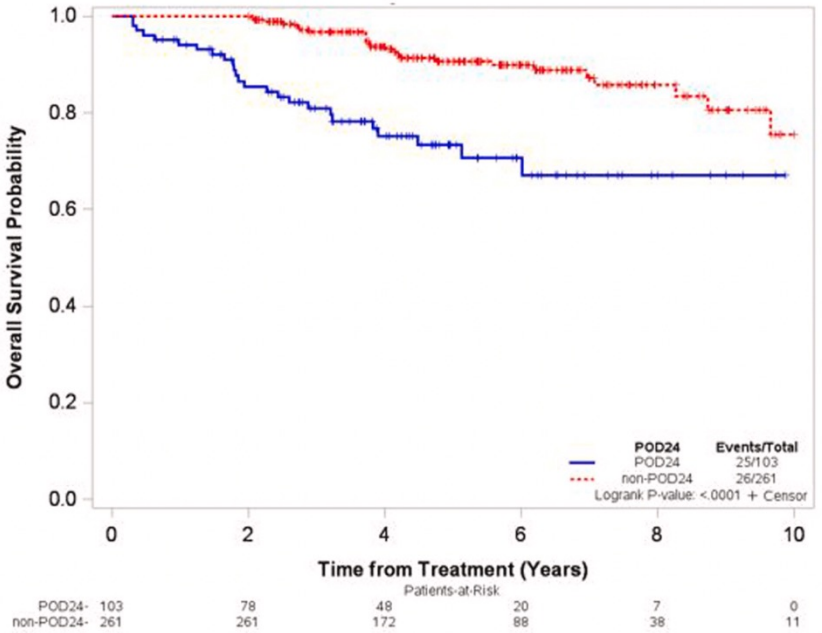
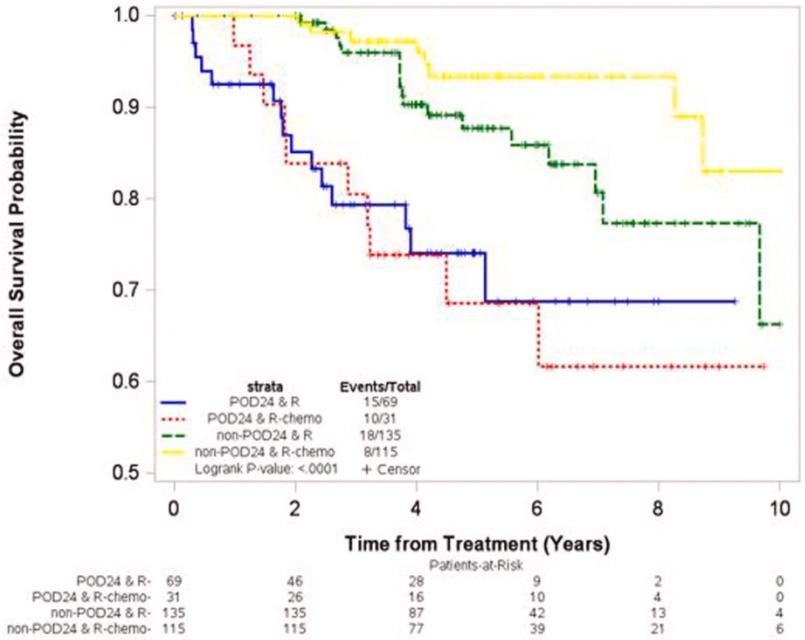


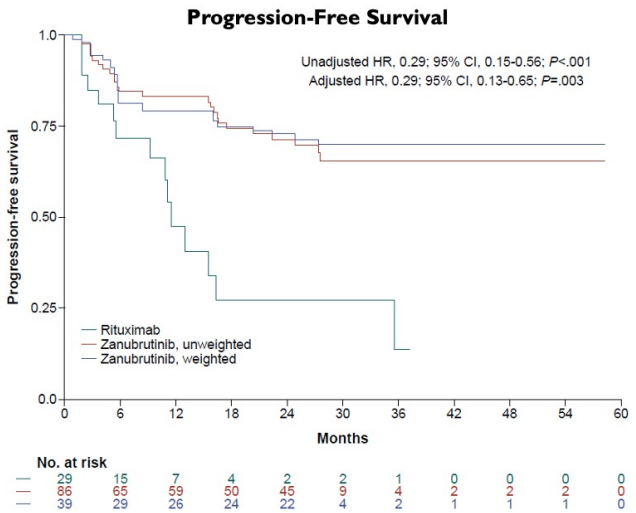
Figure 2. OS by POD24 vs nonPOD24 and treatment modality

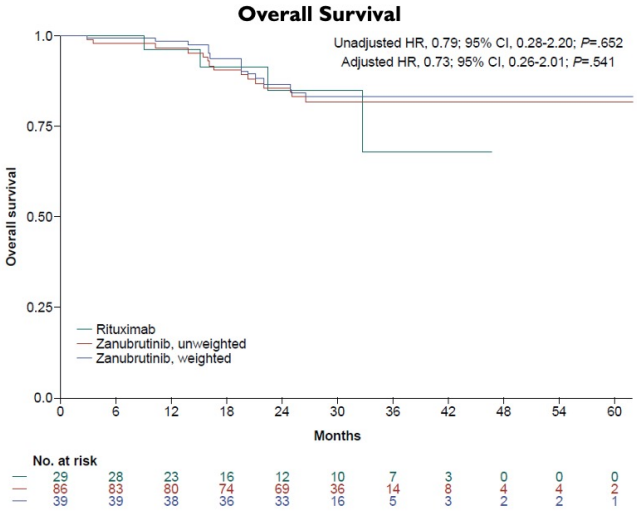


Narendranath Epperla, Rui Li, Pallawi Torka, Lauren Shea, Reem Karmali, Andrea Anampa-Guzman, Timothy Seijung Oh, Kathryn Lindsey, Irl Brian Greenwell, Sayan Mullick Chowdhury, Kaitlin Annunzio, Beth Christian, Geoffrey Shouse, Alex F. Herrera, Nancy L. Bartlett, Natalie S. Grover, Adam J. Olszewski; Early Relapse within 24 Months after Frontline Systemic Therapy (POD24) Is Associated with Worse Survival in Patients with Marginal Zone Lymphoma: A US Multisite Study. *Blood* 2022; 140 (Supplement 1): 1926–1928. doi: https://doi.org/10.1182/blood-2022-166785

MAIC of Zanubrutinib and Rituximab in Base-Case PFS and OS Analysis

MAIC – Zanubrutinib vs Rituximab in R/R MZL



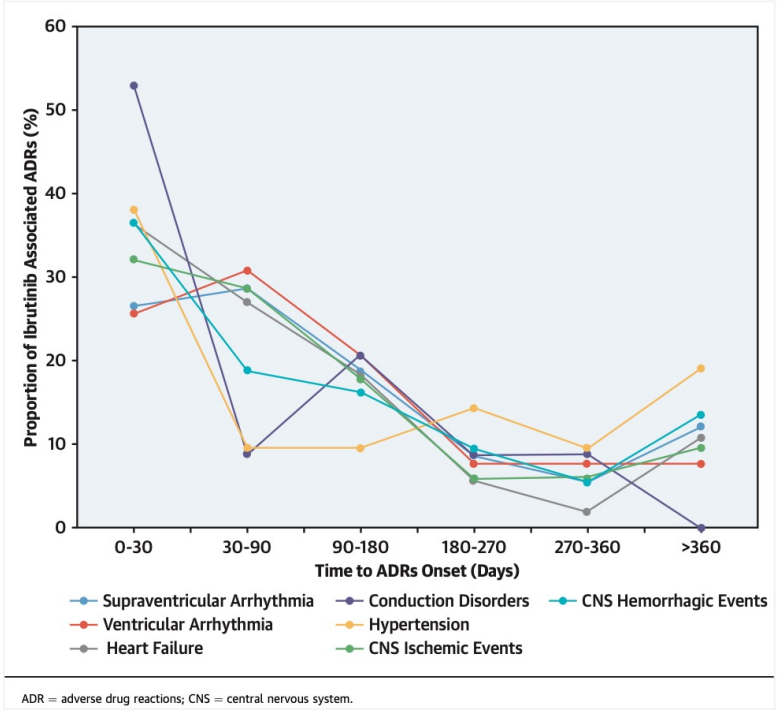


- Zanubrutinib significantly reduced the risk of progression and had a significantly higher probability of response compared with rituximab
- OS was comparable for zanubrutinib and rituximab, which is consistent with survival expectancy for indolent lymphomas, although point estimates were in favor of zanubrutinib
- The leave-one-out analysis showed that removing any of the characteristics from the propensity score model yielded comparable results

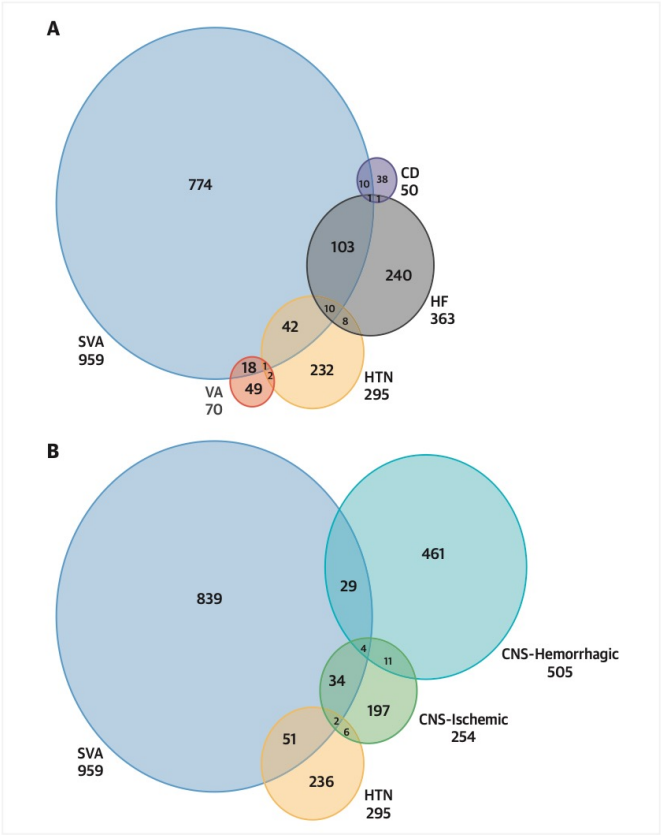
CI=confidence interval, HR=hazard ratio, MAIC=matching-adjusted indirect comparison, MZL=marginal zone lymphoma, OS=overall survival, PFS=progression-free survival

Thieblemont C et al. Poster presented at EHA 2023; abstract number: P1113

Cardiovascular Toxicities Associated With Ibrutinib

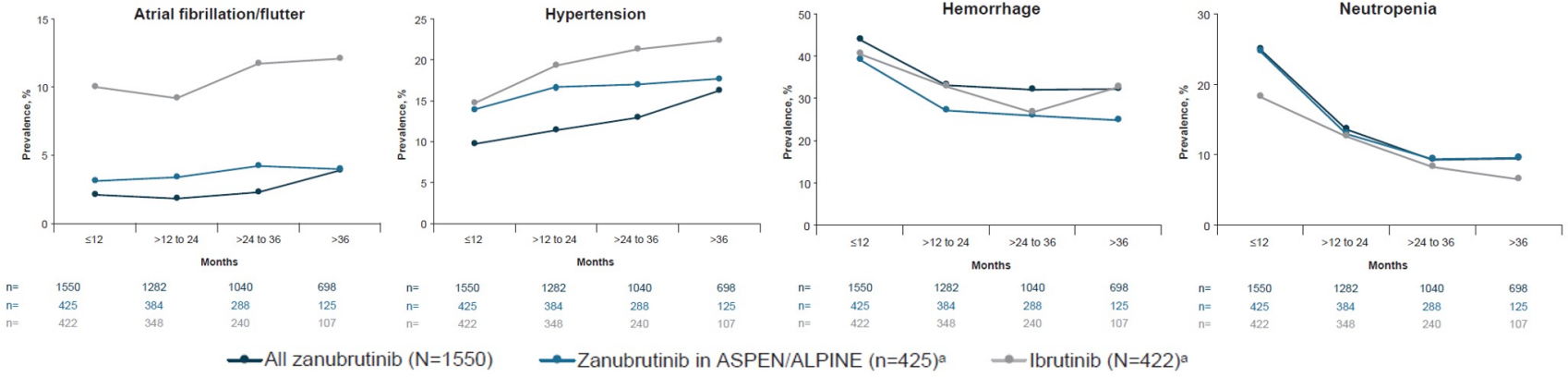


ADR = adverse drug reactions; CNS = central nervous system.



Salem JE et alii. J Am College of Cardiol 2019, 74(13): 1667-1678

Pooled Safety – Zanubrutinib and Ibrutinib Safety Profile Comparisons

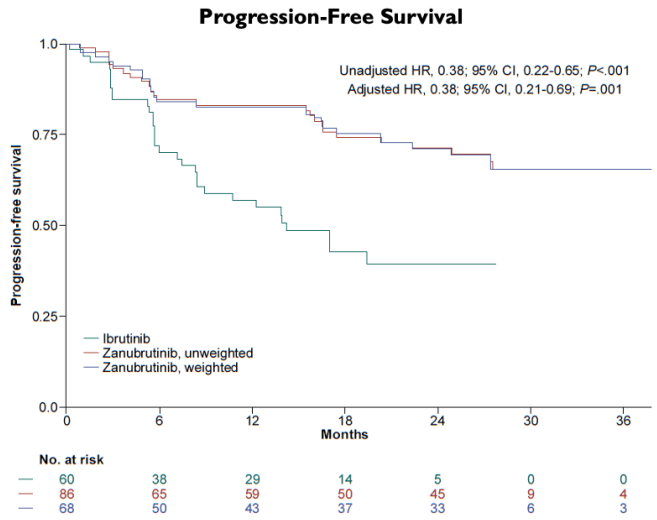


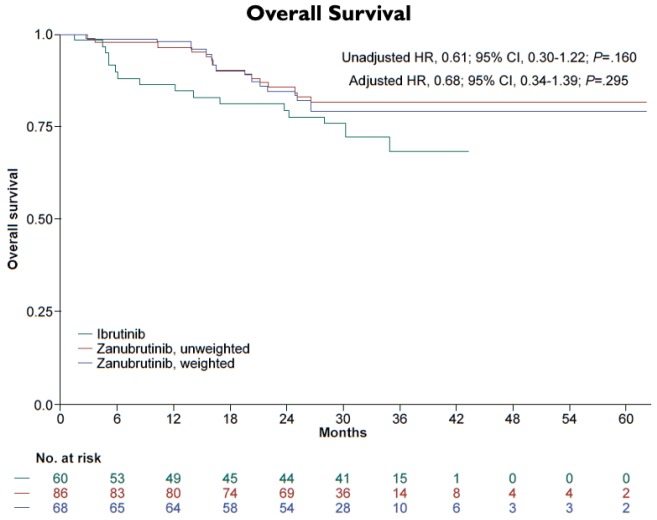
- The prevalence of AESIs tended to remain constant or decrease over time with zanubrutinib
  - In head-to-head comparisons of the ASPEN/ALPINE study populations, hypertension tended to increase over time with ibrutinib, whereas it remained relatively stable with zanubrutinib
  - The prevalence of atrial fibrillation with zanubrutinib remained lower than with ibrutinib over time

[a]Zanubrutinib was compared head-to-head with ibrutinib in the phase 3 ASPEN (cohort 1) and ALPINE trials.
AESI=adverse event of special interest,
Brown J et al. Poster presented at EHA 2023; abstract number: P631

MAIC of Zanubrutinib and Ibrutinib in Base-Case PFS and OS Analysis

MAIC – Zanubrutinib vs Ibrutinib in R/R MZL





- Compared with ibrutinib, zanubrutinib significantly reduced the risk of progression and was associated with a significantly higher ORR
- OS was comparable for zanubrutinib and ibrutinib, which is consistent with expectations for indolent lymphomas, although point estimates were in favor of zanubrutinib
- The sensitivity analysis accounting for additional prognostic factors suggested that the 2 treatments were comparable across all outcomes, owing in part to the low ESS for zanubrutinib in the expanded models, although point estimates were in favor of zanubrutinib
- A leave-one-out analysis showed significantly improved PFS for zanubrutinib when excluding B symptoms, time since last therapy, or bulky disease from the expanded model

Cox Proportional Hazards Models

CI=confidence interval, ESS=effective sample size, HR=hazard ratio, MAIC=matching-adjusted indirect comparison, MZL=marginal zone lymphoma, OS=overall survival, PFS=progression-free survival

Thieblemont C et al. Poster presented at EHA 2023; abstract number: P1093

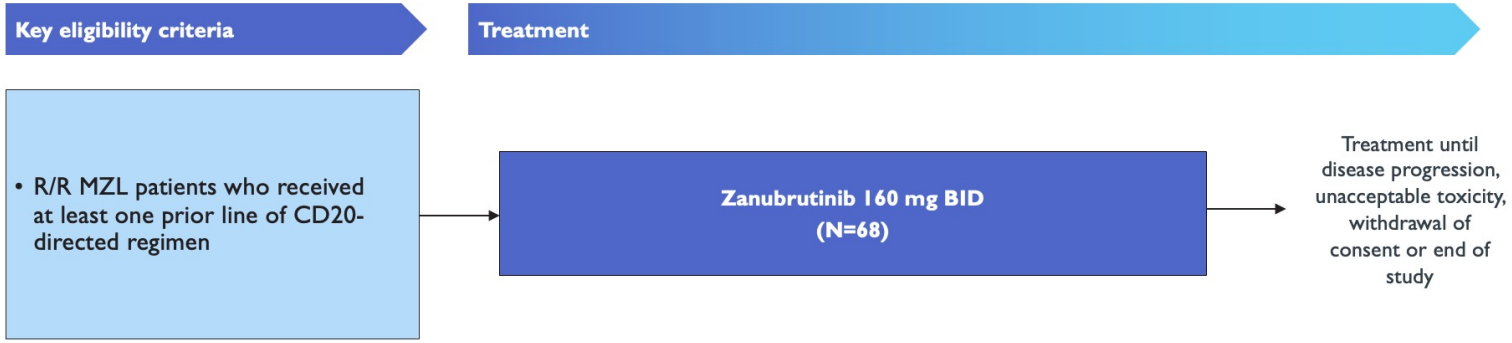
Study Design[1,2]

MAGNOLIA – Longer-Term Follow-Up

Phase 2

Study identifier: BGB-3111-214, NCT03846427

Primary endpoint: ORR assessed by IRC according to Lugano classification 2014[3]
Key secondary endpoints: ORR by PI, PFS, OS, DOR, safety



- Response based on the Lugano classification for NHL[3]
  - PET-based criteria for patients with IRC-confirmed FDG-avid disease
  - CT-based criteria for non-FDG-avid patients
  - Additional sensitivity analysis for all evaluable patients using CT-based criteria
- Biomarker correlative sub-study by the Australasian Leukaemia and Lymphoma Group

BID=twice a day, CD=cluster of differentiation, CT=computed tomography, DOR=duration of response, FDG=fluorodeoxyglucose, IRC=independent review committee, MZL=marginal zone lymphoma, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, PI=principal investigator, R/R=relapsed/refractory.

1. Opat S et al. Poster presented at EHA 2023; abstract number: P1084 2. Opat S et al. ASH 2020. Abstract 339. 3. Cheson BD et al. J Clin Oncol. 2014;32:3059–3067. This study is registered at ClinicalTrials.gov (NCT03846427).

Best Overall Response by IRC and Investigator Assessment

MAGNOLIA – Longer-Term Follow-Up

	IRC (N=66)[a]		INV (N=66)[a]
Efficacy	**PET and/or CT** (primary endpoint)[b]	**CT only** (sensitivity analysis)[f]	**PET and/or CT**
ORR, n (%) [95% CI] P-value	45 (68) [55.6, 79.1] <0.0001[c]	44 (67) [54.0, 77.8]	50 (76) [63.6 85.5]
Best response, n (%)			
CR	17 (26)	16 (24)	19 (29)
PR	28 (42)	28 (42)	31 (47)
SD	14 (21)[d,e]	16 (24)	10 (15)
PD	6 (9)	5 (8)	5 (8)
Discontinued study prior to 1st assessment, n (%)	1 (1)	1 (1)	1 (1)
Median time to response (range), months	2.8 (1.7-11.1)	3.0 (1.8-22.2)	2.8 (1.7-16.6)

Data cutoff date: 04 May 2022.

aTwo patients were excluded from the efficacy population owing to lack of central confirmation of MZL. bPatients with IRC-confirmed FDG-avid disease were assessed by PET-based criteria; non–FDG-avid patients were assessed by CT-based Lugano criteria. cP-value for the primary endpoint was computed with the binomial exact test against the null hypothesis of ORR = 30% with alternative of ORR > 30%. dFive (7.6%) patients with stable disease are remaining on study treatment (after 12-18 cycles). eIncludes one patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD; CT showed stable disease at cycle 3. fAdditional sensitivity analysis using CT-based Lugano criteria for all 66-evaluable patients regardless of PET status at baseline.

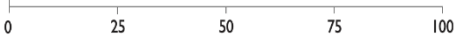
CI=confidence interval, CR=complete response, CT=computed tomography, INV=investigator, IRC=independent review committee, ORR=overall response rate, PD=progressive disease, PET=positron emission tomography, PR=partial response, SD=stable disease,

Opat S et al. Poster presented at EHA 2023; abstract number: P1084

Subgroup Analysis of ORR by IRC

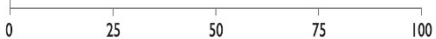
MAGNOLIA – Longer-Term Follow-Up

Subgroup	Patients/response	ORR, % (95% CI)[a]
All patients	45/66	68.2 (55.6, 79.1)
Age group		
<65	15/26	57.7 (36.9, 76.7)
≥65	30/40	75.0 (58.8, 87.3)
<75	28/48	58.3 (43.2, 72.4)
≥75	17/18	94.4 (72.7, 99.9)
MZL subtype		
MALT	16/25	64.0 (42.5, 82.0)
NMZL	19/25	76.0 (54.9, 90.6)
SMZL	8/12	66.7 (34.9, 90.1)
Unknown	2/4	50.0 (6.8, 93.2)
Disease stage		
I	2/4	50.0 (6.8, 93.2)
II	3/5	60.0 (14.7, 94.7)
III	5/7	71.4 (29.0, 96.3)
IV	35/50	70.0 (55.4, 82.1)



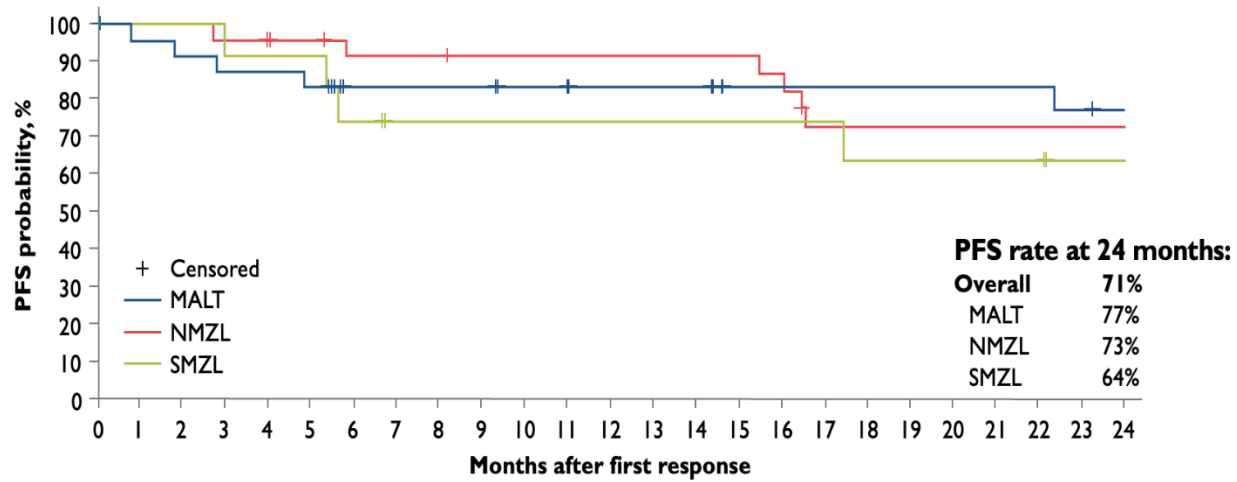
MAGNOLIA – Longer-Term Follow-Up

Subgroup	Patients/response	ORR, % (95% CI)[a]
Bone marrow involvement		
Yes	19/29	65.5 (45.7, 82.1)
No	26/37	70.3 (53.0, 84.1)
Disease status		
Relapsed	31/43	72.1 (56.3, 84.7)
Refractory	14/21	66.7 (43.0, 85.4)
Prior lines of systemic therapy		
<3	36/48	75.0 (60.4, 86.4)
≥3	9/18	50.0 (26.0, 74.0)
Prior treatment		
RCVP	20/25	80.0 (59.3, 93.2)
RCHOP	9/17	52.9 (27.8, 77.0)
BR	16/22	72.7 (49.8, 89.3)
R-lenalidomide	1/2	50.0 (1.3, 98.7)
Rituximab monotherapy	7/7	100.0 (59.0, 100.0)
CHOP	2/3	66.7 (9.4, 99.2)
R-chlorambucil	2/5	40.0 (5.3, 85.3)



PFS by MZL Subtypes by IRC Assessment

MAGNOLIA – Longer-Term Follow-Up



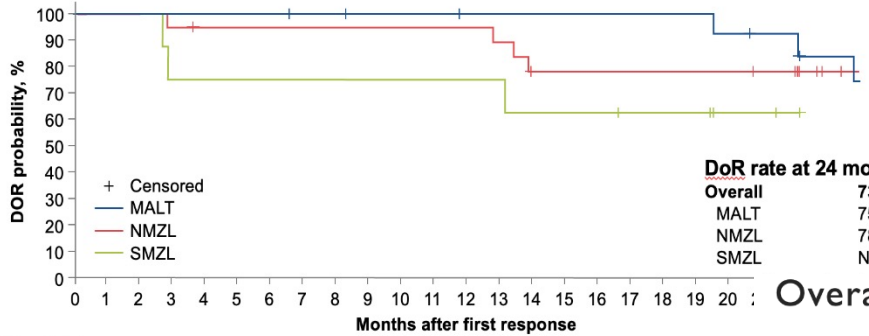
No. at risk

MALT	25	23	22	21	21	20	18	18	18	18	17	17	16	16	16	14	14	14	14	14	14	14	14	13	12
NMZL	25	25	25	24	24	23	21	21	21	20	20	20	20	20	20	20	19	15	15	15	15	15	15	15	15
SMZL	12	12	12	11	11	11	8	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	4	4

Data cutoff date: 04 May 2022.
IRC=independent review committee, MALT=mucosa-associated lymphoid tissue, MZL=marginal zone lymphoma, NMZL=nodal marginal zone lymphoma, PFS=progression-free survival, SMZL=splenic marginal zone lymphoma,
Opat S et al. Poster presented at EHA 2023; abstract number: P1084

DOR by MZL Subtypes by IRC Assessment

MAGNOLIA – Longer-Term Follow-Up



No. at risk

MALT	16	16	16	16	16	16	16	15	15	14	14	14	13	13	13	13	13	13	13	13	12
NMZL	19	19	19	18	17	17	17	17	17	17	17	17	17	17	17	16	13	13	13	13	13
SMZL	8	8	8	6	6	6	6	6	6	6	6	6	6	6	5	5	5	4	4	4	2

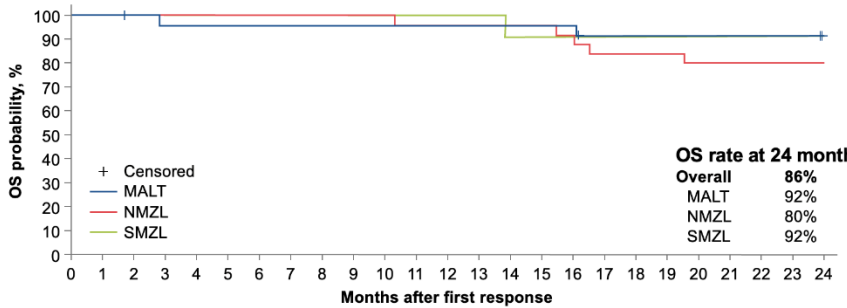
DoR rate at 24 months:

Overall	**73%**
MALT	75%
NMZL	78%
SMZL	NE

Data cutoff date: 04 May 2022.
DoR=duration of response, IRC=independent review committee, MALT=mucosa-associated lymphoid tissue, MZL=marginal zone lymphoma, NMZL=nodal marginal zone lymphoma, SMZL=splenic marginal zone lymphoma.
Opat S et al. Poster presented at EHA 2023; abstract number: P1084

Overall Survival by MZL Subtypes

MAGNOLIA – Longer-Term Follow-Up

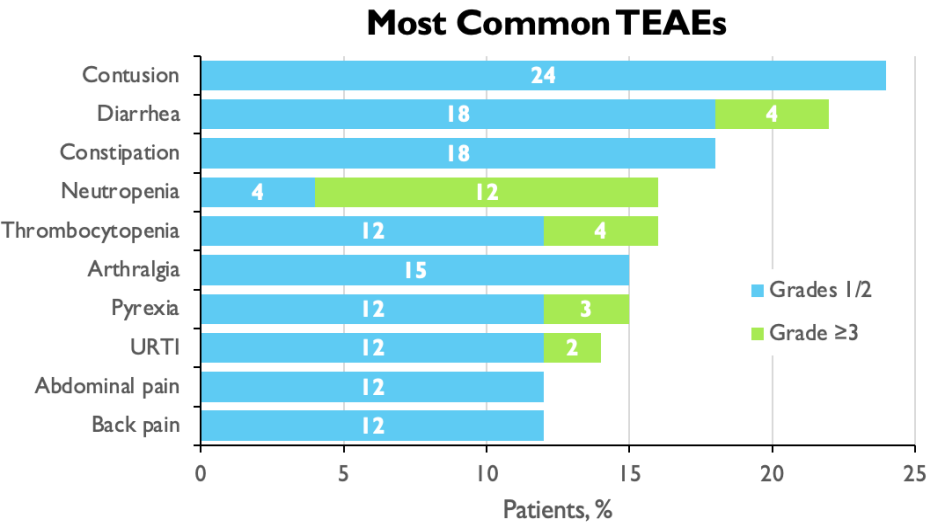


No. at risk

MALT	25	25	24	23	23	23	23	23	23	23	23	23	23	23	23	23	21	21	21	21	21	21	21
NMZL	25	25	25	25	25	25	25	25	25	25	25	24	24	24	24	24	23	21	21	21	20	20	20	20	20
SMZL	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	10

OS rate at 24 months:

Overall	**86%**
MALT	92%
NMZL	80%
SMZL	92%



TEAEs of interest, n (%)	N=68 All grade	Grade ≥3
Infections	38 (56)	15 (22)[a]
Hemorrhage	28 (41)	1 (1.5)[b]
Cardiac		
Hypertension	3 (4)[c]	2 (3)
Atrial fibrillation/flutter	2 (3)[d]	1 (1.5)
Ventricular extrasystole	1 (1.5)[e]	0
Second primary malignancy	5 (7)[f]	3 (4)

Luglio 2023: +1 mese circa da inizio Zanubrutinib

Non più sudorazioni notturne

Emocromo: Hb 11.4 g/dl WBC 3960/mmc N 2510/mmc PLTs 142000/mmc

Splenomegalia in riduzione

Non registrati eventi avversi

Take home messages

- POD24 nei MZL costituisce un gruppo di pazienti ad alto rischio che necessitano di terapie innovative;
- Zanubrutinib ha mostrato elevate percentuali di risposta e buon controllo della malattia in pazienti con MZL R/R; è ben tollerato e l'incidenza di eventi cardiovascolari è inferiore rispetto ad Ibrutinib;
- MAIC tra Zanubrutinib e Ibrutinib ha mostrato benefici in termini di ORR e PFS a favore di Zanubrutinib;
- Terapia anticoagulante: elemento essenziale nella nostra scelta terapeutica.

Grazie per l’attenzione