Marginalzonenlymphom:

Was gibt es Neues?

Markus Raderer
Internal Medicine I, Oncology
Medical University Vienna

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition

Keine

2. Beratungs- bzw. Gutachtertätigkeit

Keine

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

Keine

4. Patent, Urheberrecht, Verkaufslizenz

Keine

5. Honorare

Beigene, Celgene, Ipsen, Novartis, Eisai, Gilead, BMS, Roche, Eli Lilly

6. Finanzierung wissenschaftlicher Untersuchungen

Keine

7. Andere finanzielle Beziehungen

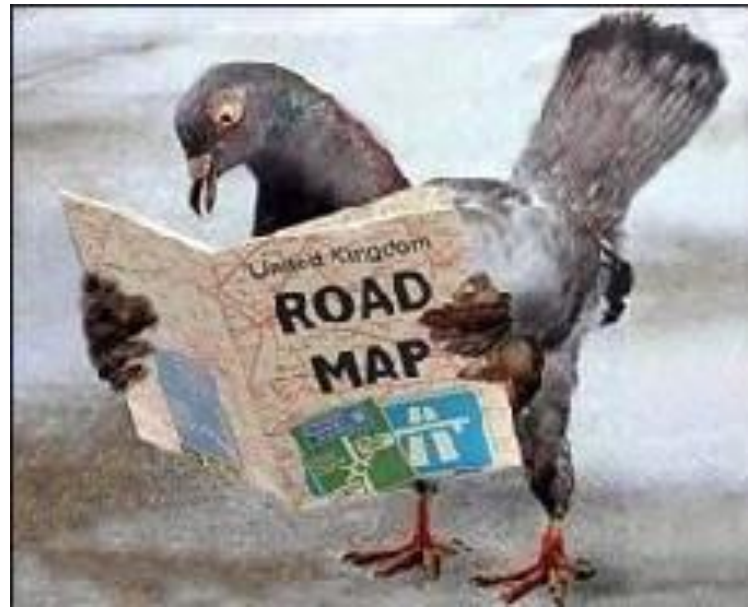
keine

8. Immaterielle Interessenkonflikte

Keine

Was gibt es Neues….?

- Pathologie
- Diagnostik
- Therapie



WHO Klassifikation 2022

REVIEW ARTICLE OPEN

Check for updates

LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], nitoba-Johnson[21], Harris[26], e Karube[31], Werner Kempf[32], [37], Alexander J. Lazar[38], legan S. Lim[21], Michal[45], Valentina Nardi[22], [52], Marie Parrens[52], enwald[3], Jonathan Said[56], Reiner Siebert[62], e Vergier[65],

Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	(Same)
(Entity deleted)	B-cell prolymphocytic leukaemia
Splenic B-cell lymphomas and leukaemias	
Hairy cell leukaemia	(Same)
Splenic marginal zone lymphoma	(Same)
Splenic diffuse red pulp small B-cell lymphoma	(Same)
Splenic B-cell lymphoma/leukaemia with prominent nucleoli	*Not previously included* (encompassing hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma	
Lymphoplasmacytic lymphoma	(Same)
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	(Same)
Primary cutaneous marginal zone lymphoma	*Not previously included (*originally included under "extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue")
Nodal marginal zone lymphoma	(Same)
Paediatric marginal zone lymphoma	(Same)

Leukemia 2022

ICC Klassifikation 2022

Table 1 International Consensus Classification of follicular lymphomas, marginal zone lymphomas, and related entities

Follicular lymphoma
In situ follicular neoplasia
Duodenal-type follicular lymphoma
*BCL2-R-negative, CD23-positive follicle center lymphoma**
Pediatric-type follicular lymphoma
Primary cutaneous follicle center lymphoma
Testicular follicular lymphoma*
Large B-cell lymphoma with *IRF4* rearrangement*
Splenic marginal zone lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Primary cutaneous marginal zone lymphoproliferative disorder*
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma

Items in italics represent provisional entities

*Changes from the 2017 WHO classification

Virchows Archiv (2023) 482:149–162
https://doi.org/10.1007/s00428-022-03432-2

REVIEW

Follicular lymphoma and marginal zone lymphoma: how many diseases?

Camille Laurent[1] · James R. Cook[2] · Tadashi Yoshino[3] · Leticia Quintanilla-Martinez[4] · Elaine S. Jaffe[5]

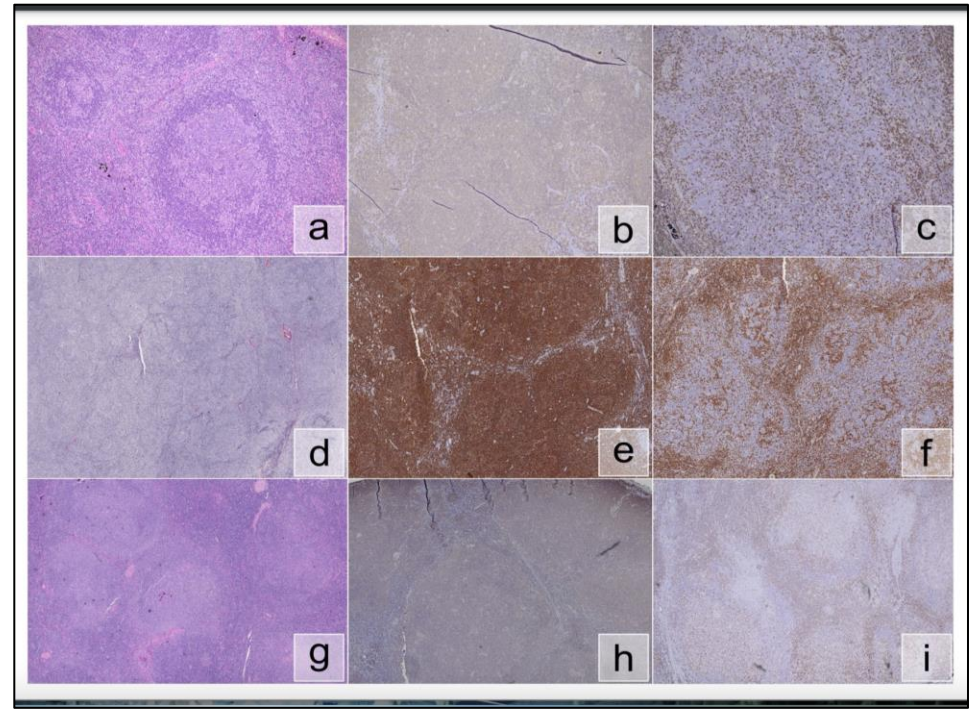
Received: 2 August 2022 / Revised: 4 October 2022 / Accepted: 15 October 2022 / Published online: 17 November 2022

Marginalzone Lymphoma:

„A royal family?“

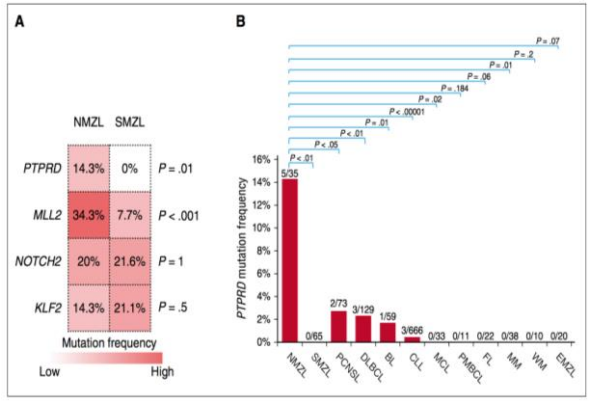
Pediatric nodal MZL

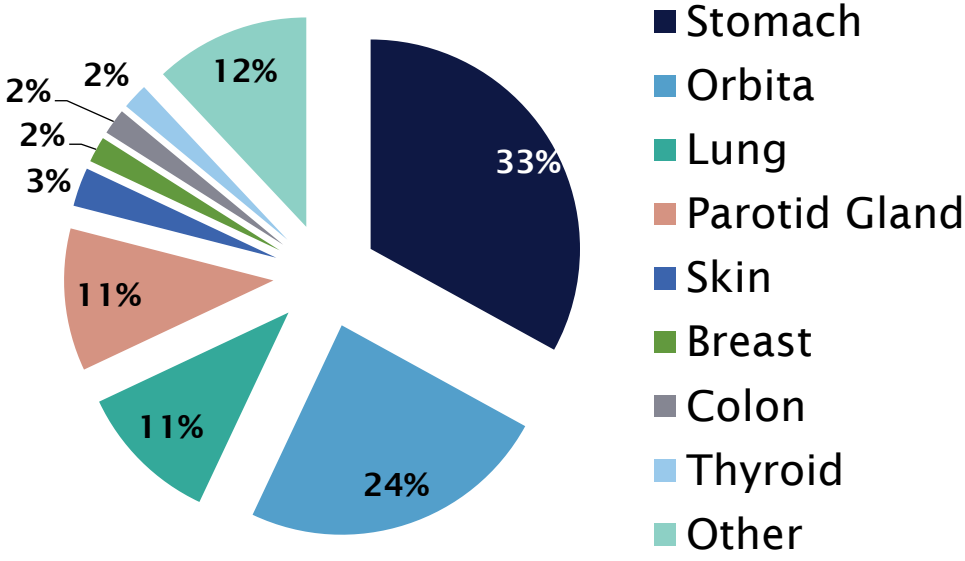
- Männliche Prädominanz (6 - 10:1)
- Auch bei jungen Erwachsenen
- Lokalisation: bevorzugt HNO
- Extrem indolent!
- DD: nMZL
  ptFL
  Marginalzonen-Hyperplasie

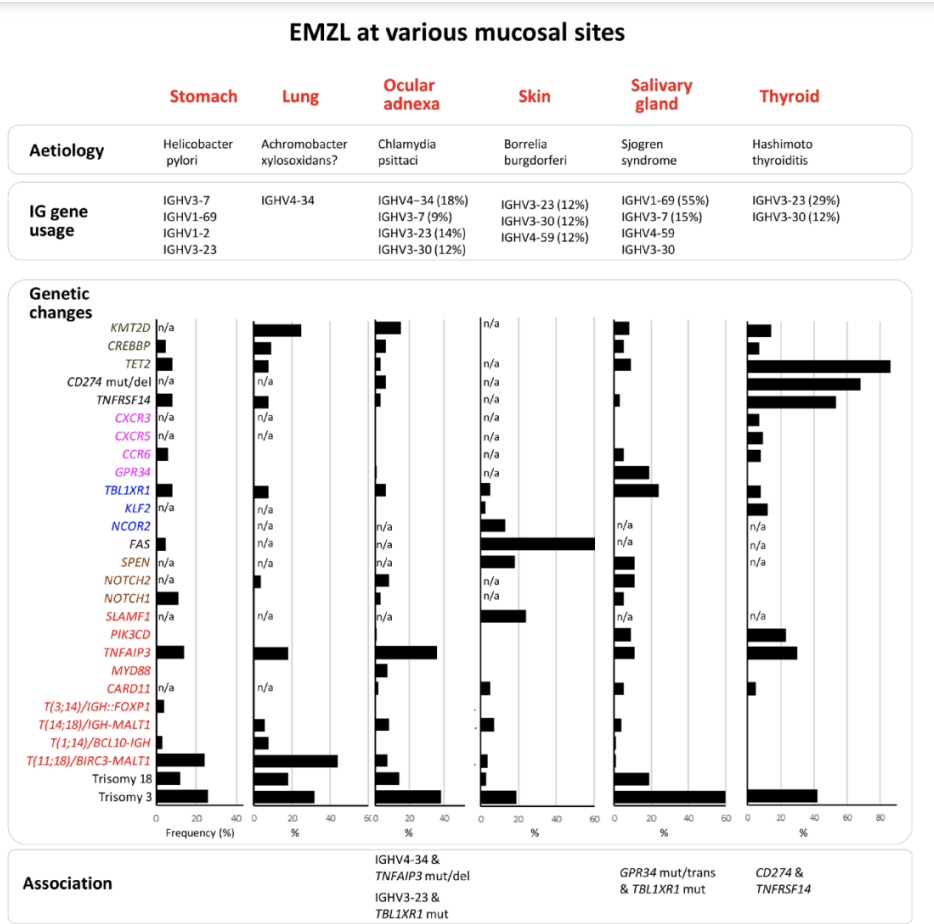


Zamo et al, Virchows Archiv 2023

“GUT – Grand Unified Theory”?







WHO Classification 2022,
Raderer et al, Ther Adv Oncol 2023

TABLE 1. ^{18}F-FDG Avidity of Lymphoma According to World Health Organization Histopathologic Classification

Histology	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Hodgkin disease	233	233	0	100
Burkitt lymphoma	18	18	0	100
Mantle cell lymphoma	14	14	0	100
Anaplastic large T-cell lymphoma	14	14	0	100
Marginal zone lymphoma, nodal	8	8	0	100
Lymphoblastic lymphoma	6	6	0	100
Angioimmunoblastic T-cell lymphoma	4	4	0	100
Plasmacytoma	3	3	0	100
Natural killer/T-cell lymphoma	2	2	0	100
Diffuse large B-cell lymphoma	222	216	6	97
Follicular lymphoma	140	133	7	95
Peripheral T-cell lymphoma	10	9	1	90
Small lymphocytic lymphoma	29	24	5	83
Enteropathy-type T-cell lymphoma	3	2	1	67
Marginal zone lymphoma, splenic	3	2	1	67
MALT marginal zone lymphoma	50	27	23	54
Lymphomatoid papulosis	2	1	1	50
Primary cutaneous anaplastic large T-cell lymphoma	5	2	3	40
All	766	718	48	94

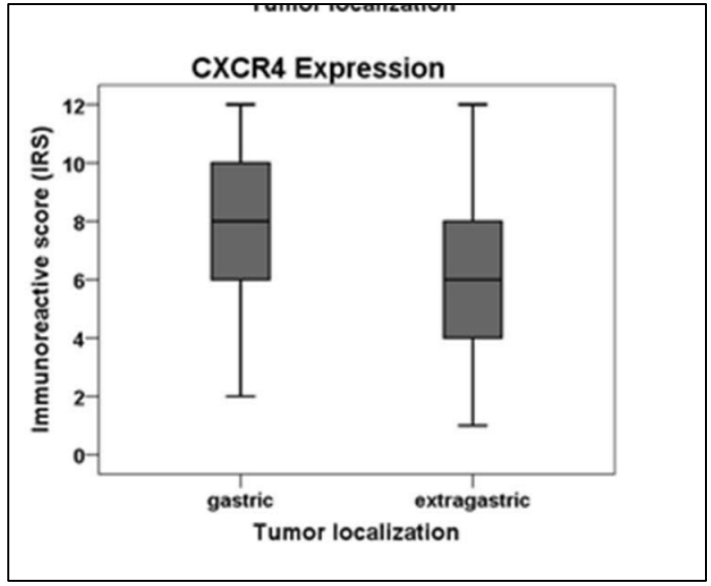
Weiler-Sagie et al, J Nucl Med 2010

J Cancer Res Clin Oncol (2016) 142:2239–2247
DOI 10.1007/s00432-016-2220-6

ORIGINAL ARTICLE – CANCER RESEARCH

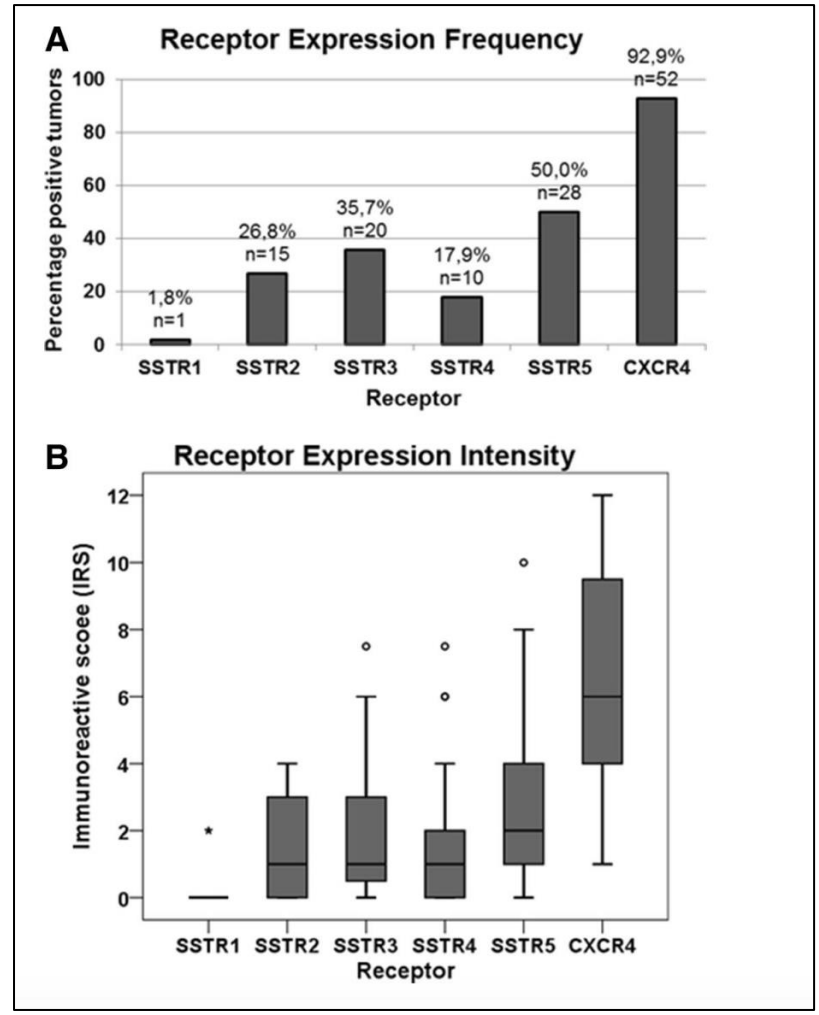
Differential somatostatin and CXCR4 chemokine receptor expression in MALT-type lymphoma of gastric and extragastric origin

Susann Stollberg[1] · Daniel Kämmerer[2] · Elisa Neubauer[1] · Stefan Schulz[1] · Ingrid Simonitsch-Klupp[3] · Barbara Kiesewetter[4] · Markus Raderer[4] · Amelie Lupp[1]

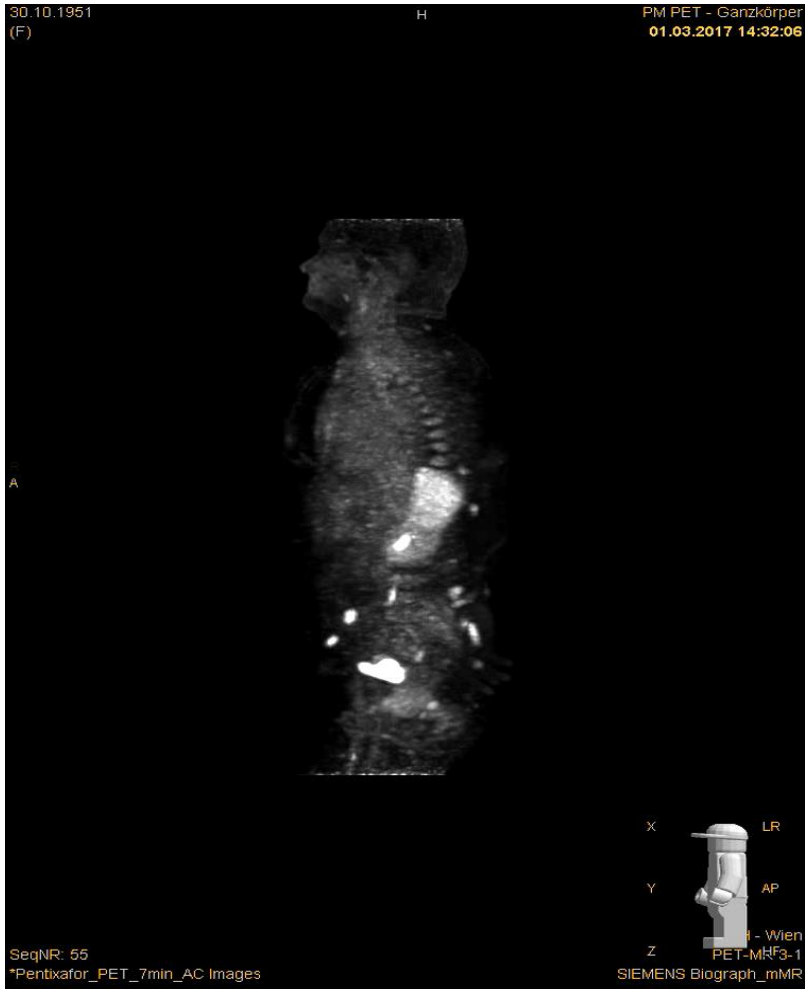


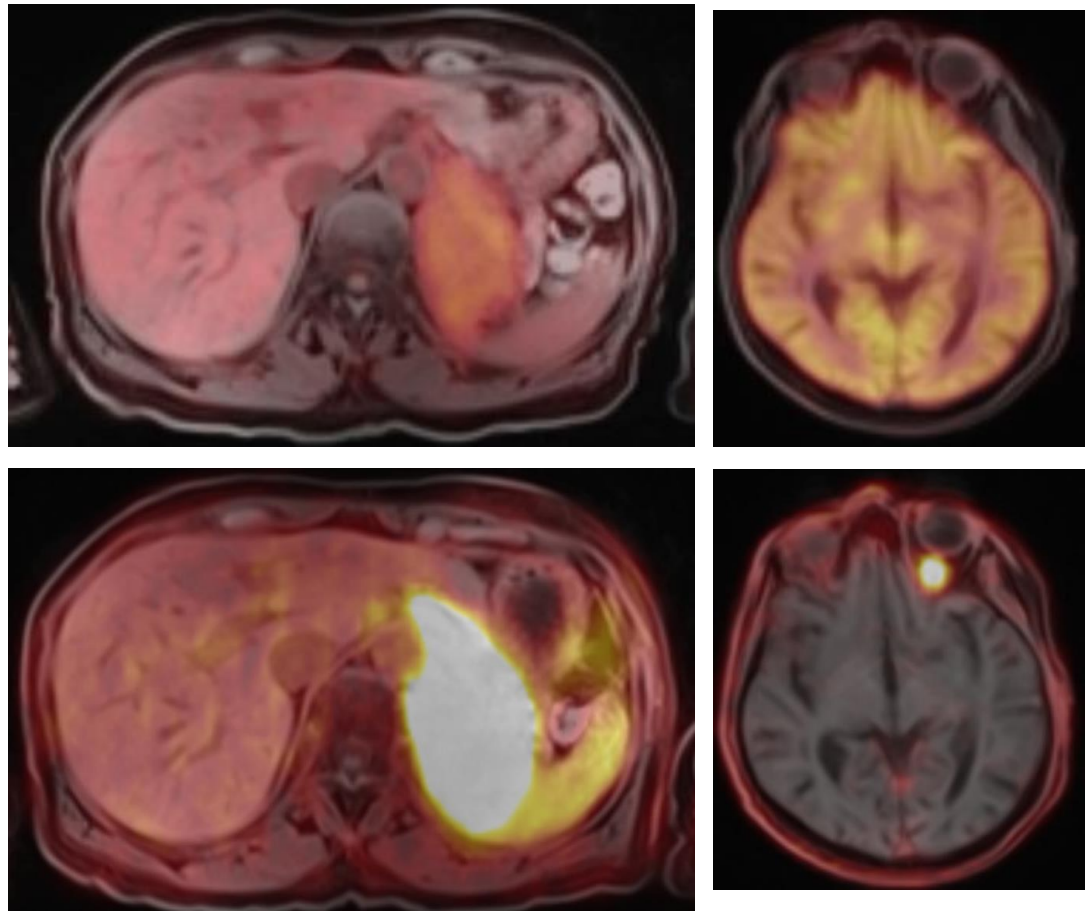
N = 55

Gastric:	11
Extragastric:	44

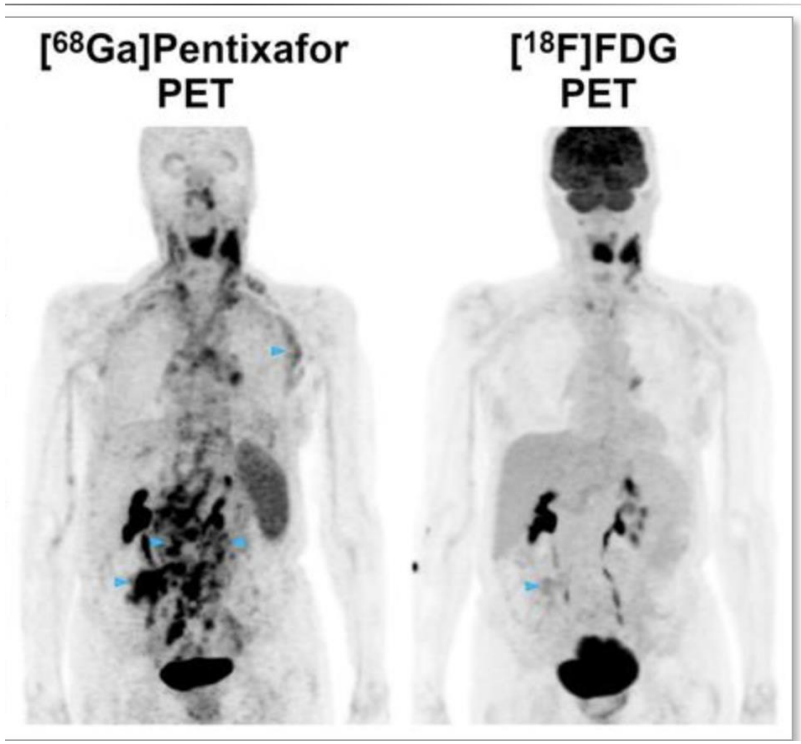


Pentixafor-PET/MR

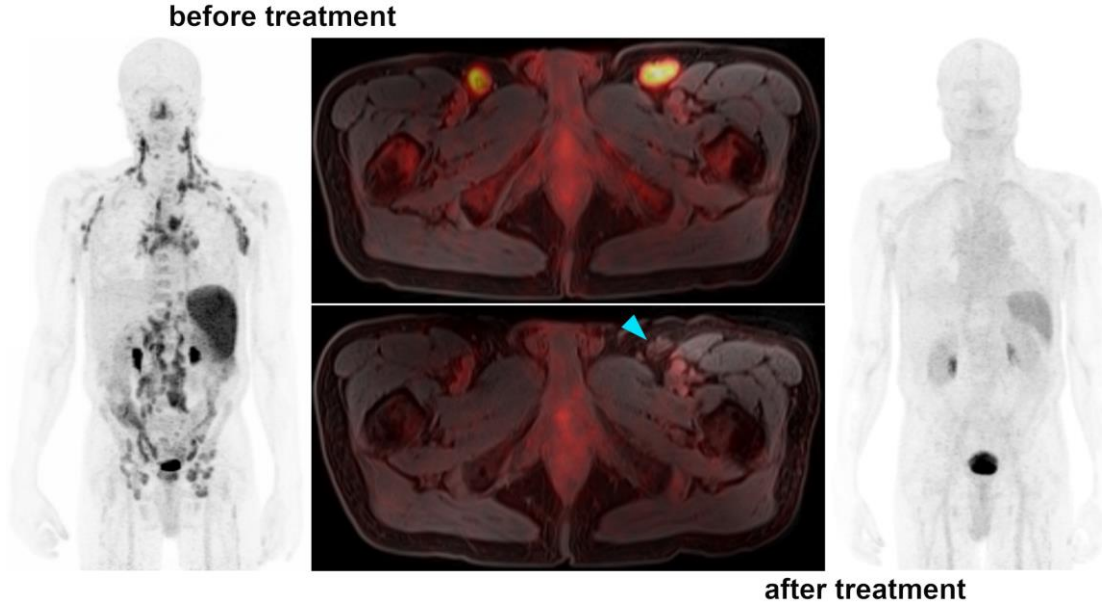




Sidestep: Mantle Cell Lymphoma



Mayerhoefer et al, Theranostics 2021



Mayerhoefer et al, Clin Nuclear Med 2023

18F-FDG-PET/CT versus 68Ga-Pentixafor-PET/CT

- N = 21, untreated
- PET/CTs within 14 days

	Pentixafor	**18-F-FDG**
• MALT:	14 / 15	6 / 15
• nMZL:	5 / 5	3 / 5
• sMZL:	1 / 1	0 / 1
	95%	42%

Viering et al, J Nucl Med 2019

Journal of Nuclear Medicine, published on October 5, 2023 as doi:10.2967/jnumed.123.266074

Chemokine Receptor PET/CT Provides Relevant Staging and Management Changes in Marginal Zone Lymphoma

Johannes Duell[1], Andreas K. Buck[2], Philipp E. Hartrampf[2], Wiebke Schlötelburg[2], Simone Schneid[2], Alexander Weich[1], Niklas Dreher[2], Constantin Lapa[3], Malte Kircher[3], Takahiro Higuchi[2], Samuel Samnick[2], Sebastian E. Serfling[2], Markus Raderer[4], Leo Rasche[1,5], Hermann Einsele[1,5], Max S. Topp[1,5], Aleksander Kosmala*[2], and Rudolf A. Werner*[2,6]

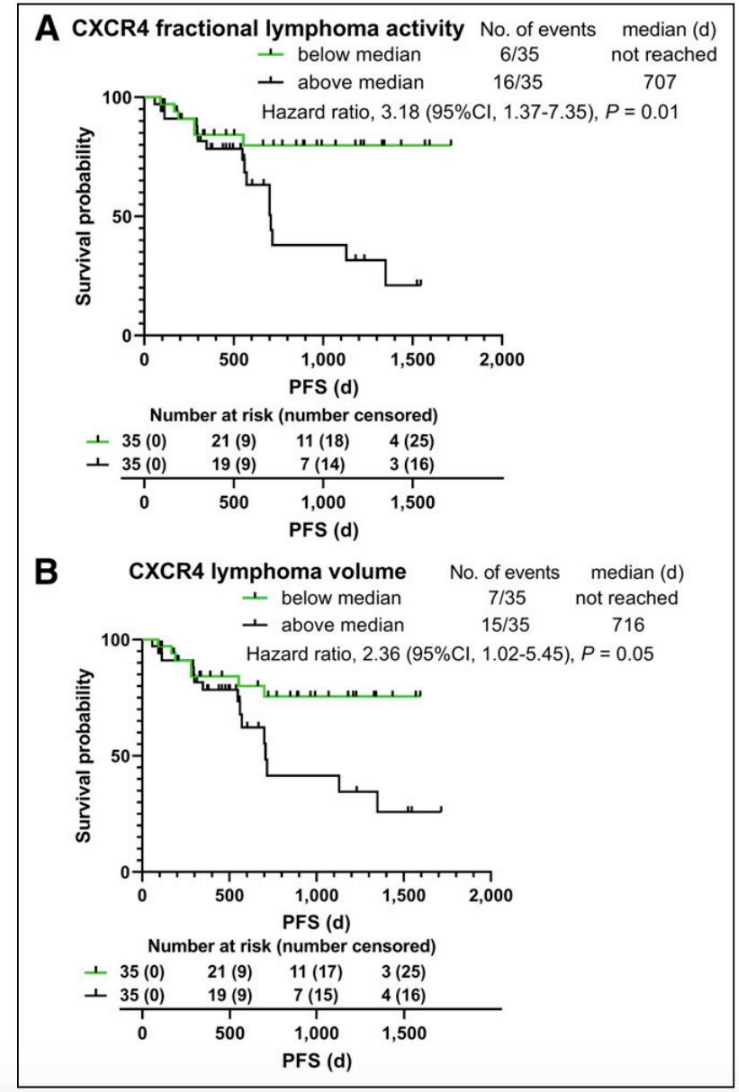
[1]*Medical Department II, University Hospital Würzburg, Würzburg, Germany;* [2]*Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany;* [3]*Nuclear Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany;* [4]*Department of Internal Medicine I, Medical University Vienna, Vienna, Austria;* [5]*Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Würzburg, Germany; and* [6]*Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland*

TABLE 1
Numbers of Organ Systems Affected as Detected by [^{68}Ga]Ga-Pentixafor PET/CT and Diagnostic CT Alone

Organ	Concordant	Pentixafor+ /CT−	Sum
Lymph nodes	41	10	51
Bone and bone marrow	0	20	20
Orbit	12	7	19
Gastrointestinal tract	2	16	18
Salivary glands	7	7	14
Spleen	9	3	12
Lung	7	0	7
Kidneys	5	0	5
Other soft tissue	14	5	19

Diagnostic accuracy GI-tract: 94%

N = 100



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

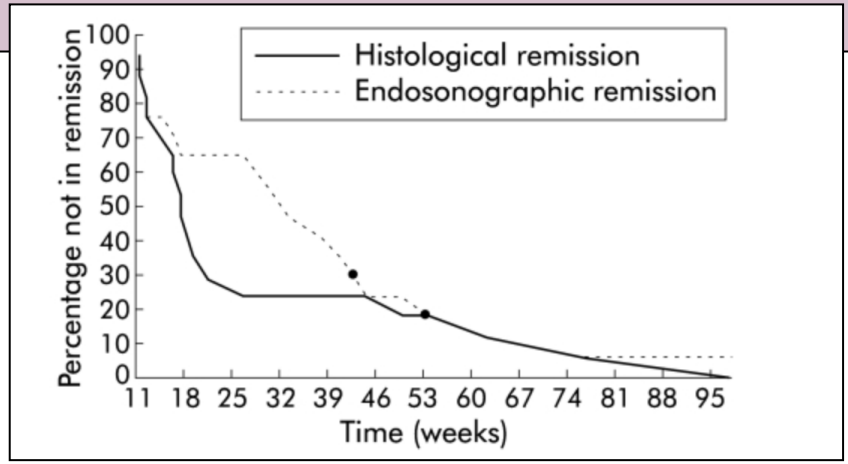
SPECIAL ARTICLE

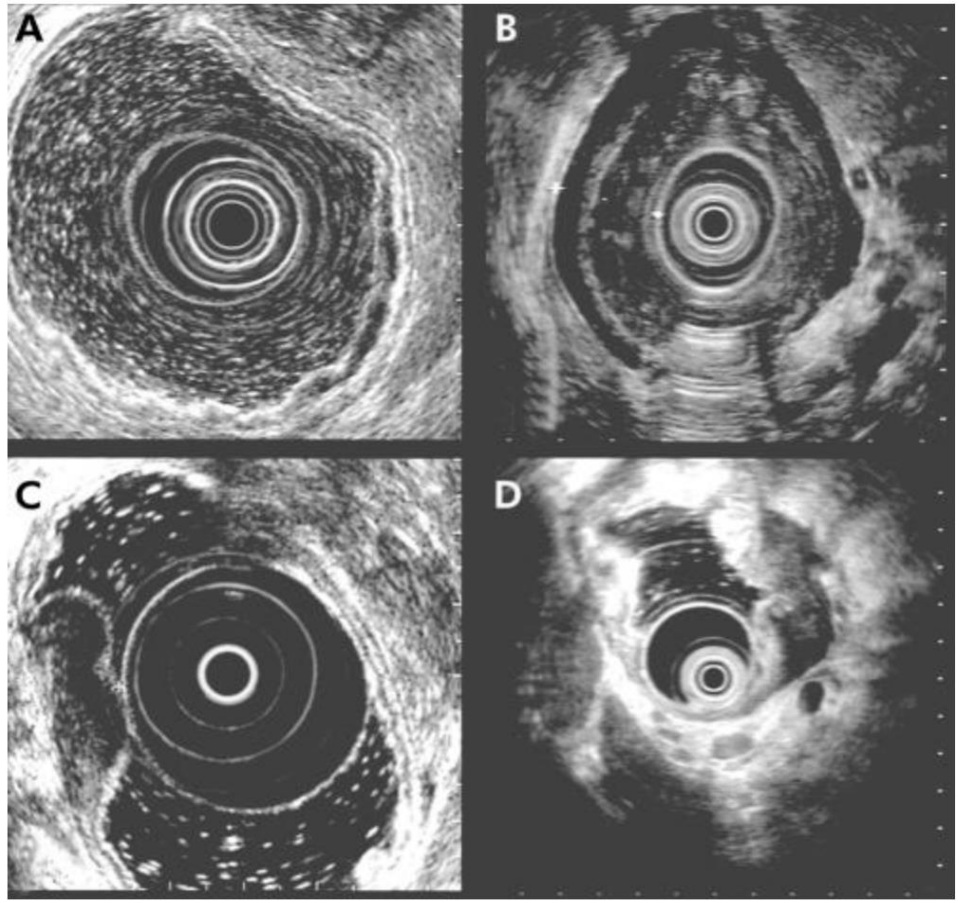
Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

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*

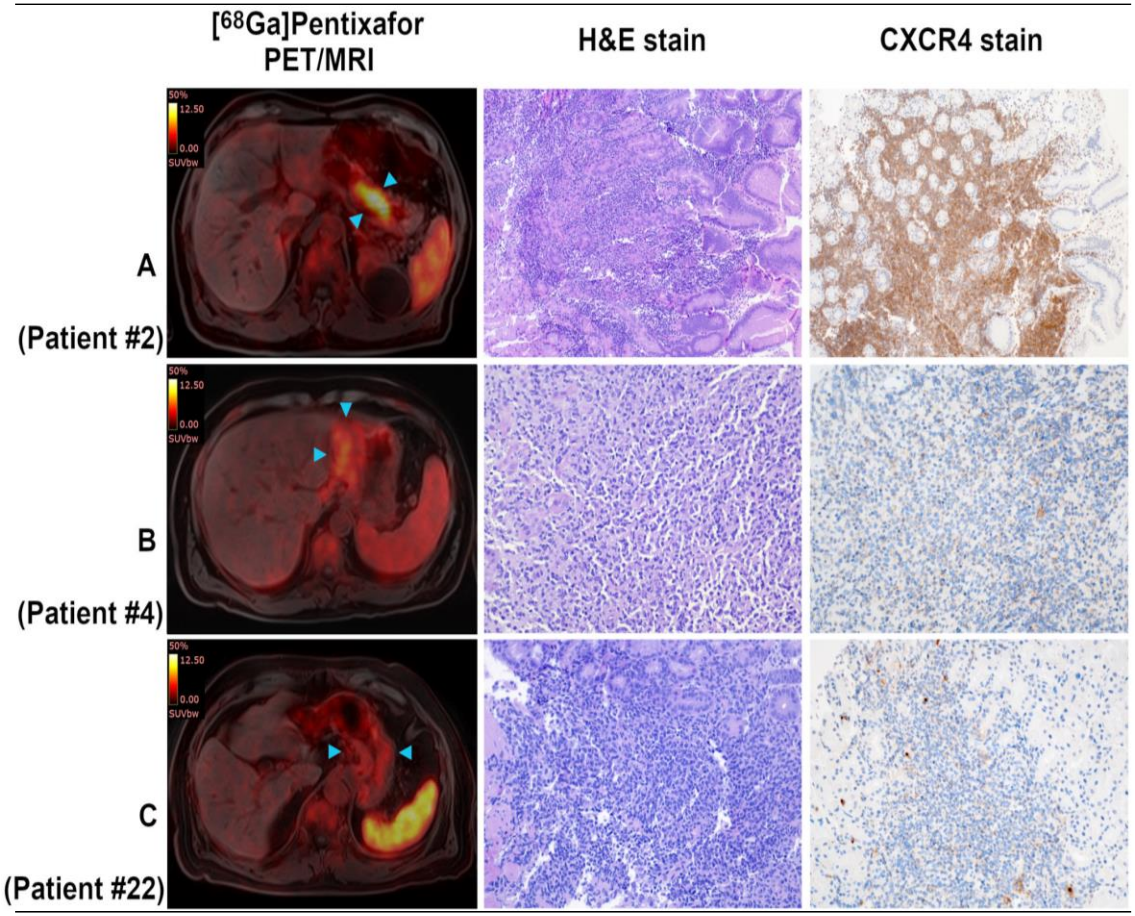
Table 3. Specific staging and work-up procedures for EMZL at different prin

Site	Exam
Stomach	EGD Endoscopic US IHC





68Ga-Pentixafor PET/MR follow-up



<u>26 patients, HP-eradication</u>
(46 post-eradication PET/MRs)

Comparison to matched biopsies (GELA)

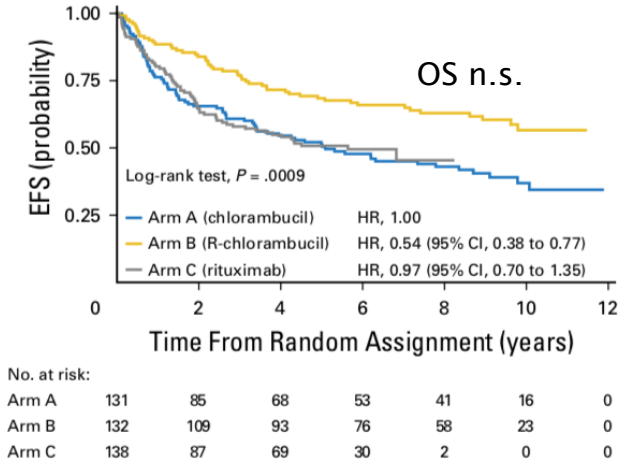
<u>Sensitivity:</u> 95%
<u>Specifitiy:</u> 100%

Mayerhöfer et al, Blood 2021

Neuigkeiten in der Therapie?

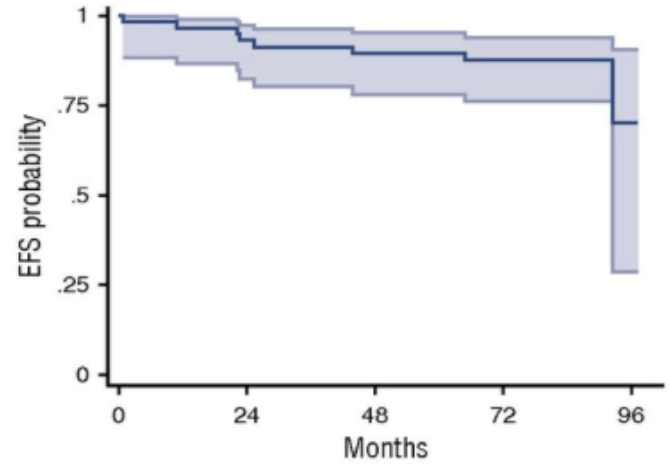
IELSG 19 Chlorambucil +/-R

-JCO 2013 & 2017
-Randomized Phase III, 454 patients
-Chlorambucil 5-year EFS 51%
-Rituximab 5-year EFS 50%
-R-Chlorambucil 5yr EFS 68%



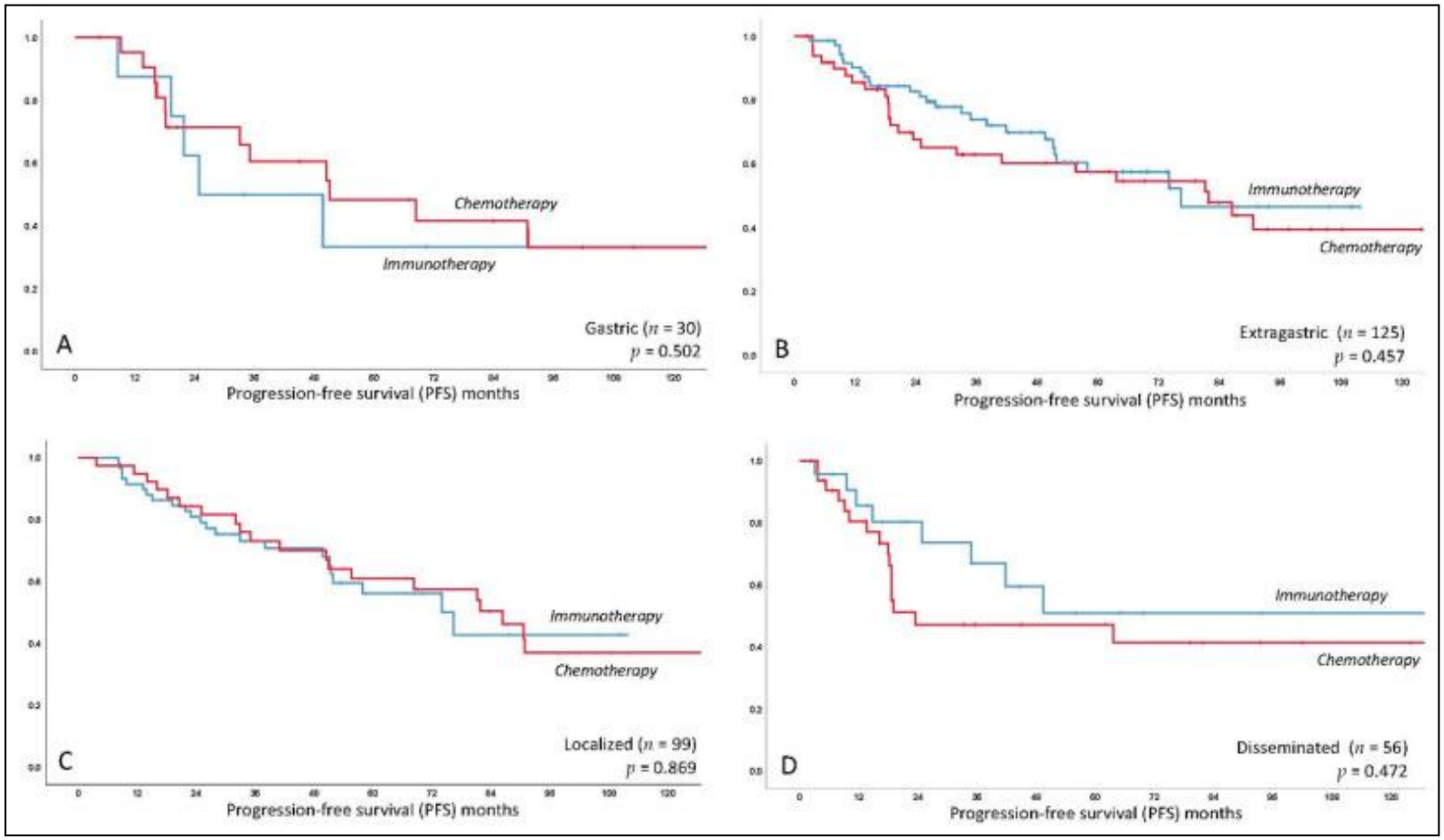
MALT 2008-01 R-Bendamustine

-Lancet Haematol 2014, Blood 2017
-Phase II, 60 patients
-ORR 100%, CRu 98%
-EFS 7yr 88%
-Option for treatment stop - CR4 (75%)



Zucca E et al, J Clin Oncol 2013 & 2017
Salar A et al, Lancet Haematol 2014, Blood 2017

Chemo vs “targeted therapies“



ORR:

90% vs 68%

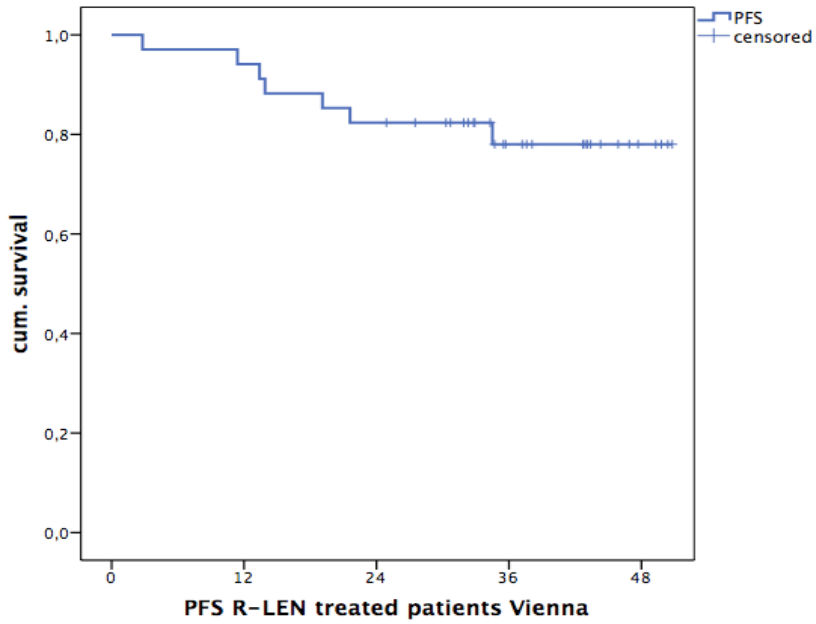
CR:

75% vs 73 %

Kiesewetter et al, Cancers 2020

Chemo-free approaches: Rituximab/Revlimid (R2)

OVERALL RESPONSE RATE	80.4% (37/46)
Complete remission	54.3% (25/46)
Partial remission	26.1% (12/46)
Stable disease	17.4% (8/46)
Progressive disease	2.3% (1/46)

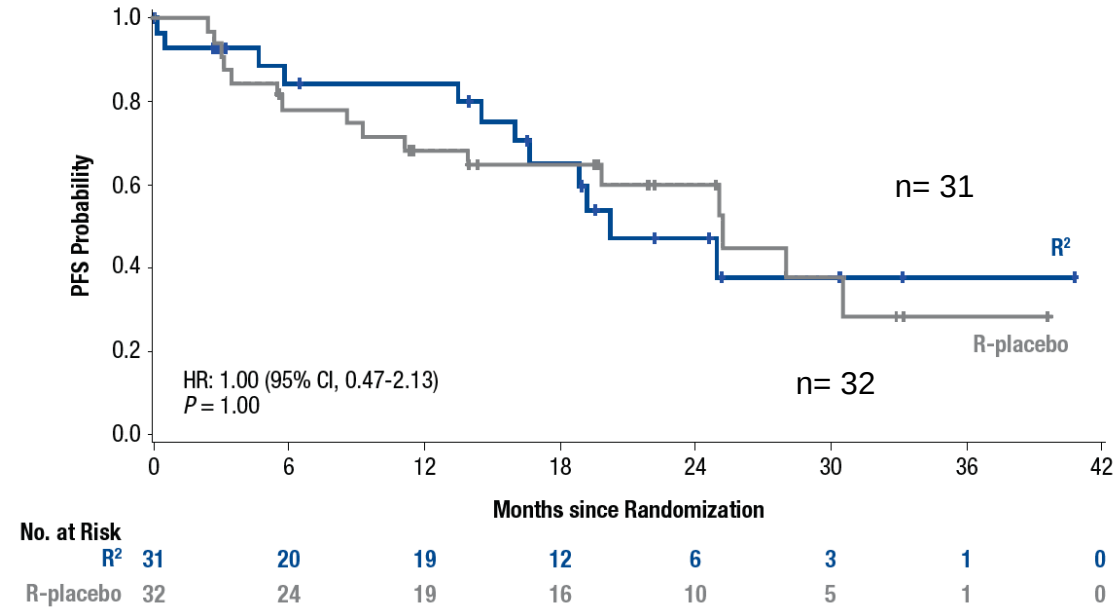


Number of patients	46
Median FUP:	38.6 months
Median PFS	**Not reached**
Number of relapses	7 (11-34m)
Alive at last FUP:	94% (32/34)
Disease related deaths	1 (transformed)

Kiesewetter et al, BLOOD 2017

AUGMENT subgroup - R² in r/r MZL patients

EHA 2019



After a median follow-up of 27.9 months (range, 0.5-51.3), median PFS was 20.2 months in the R² arm vs 25.2 months in the R-placebo arm (*P* = 1.0)

Thieblemont C, EHA 2019 PS1262

haematologica
Open access journal of the Ferrata-Storti Foundation, a non-profit organization

LETTERS TO THE EDITOR

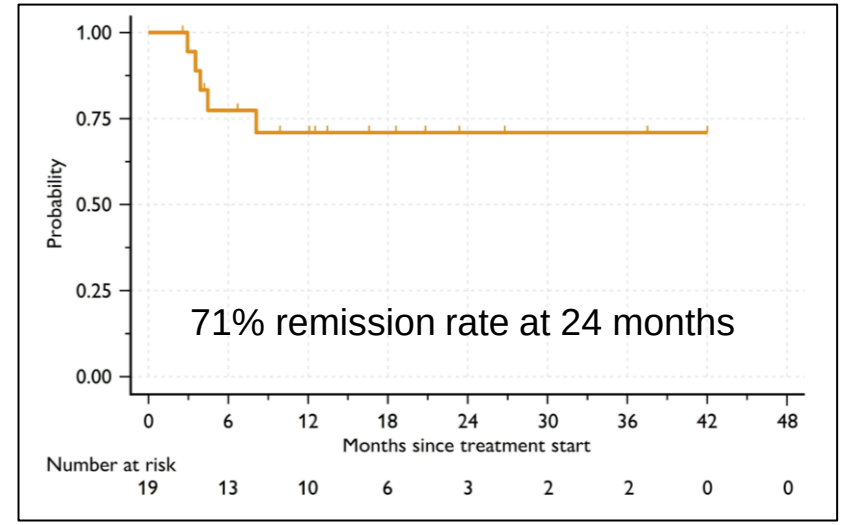
IELSG40/CLEO phase II trial of clarithromycin and lenalidomide in relapsed/refractory extranodal marginal zone lymphoma

Footnotes
References

Maria Cristina Pirosa, Marianna Sassone, Barbara Kiesewetter, Armando Lopez Guillermo, Liliana Devizzi, Eva Domingo Domènech, Alessandra Tucci, Donato Mannina, Michele Merli, Antonio Salar, Carlo Visco, Fabiana Esposito, Luisella Bonomini, Emanuele Zucca, Andrés J. M. Ferreri, Markus Raderer

Vol. 108 No. 6 (2023): June, 2023 https://doi.org/10.3324/haematol.2022.281963

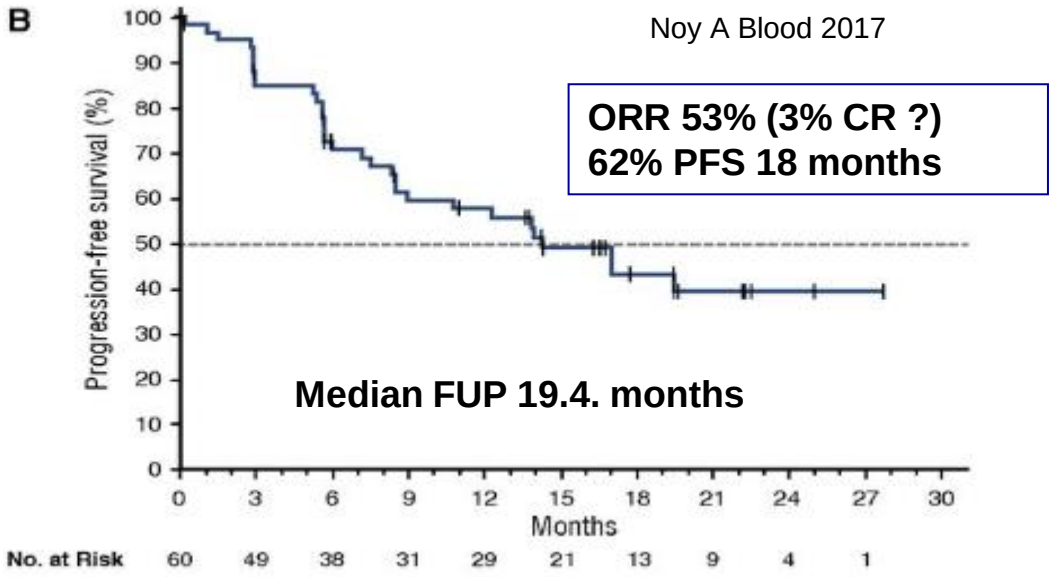
Median PFS 40 mos (ITT)



Response	ITT patient population (total 43 patients) N (%; 95% CI)	Evaluable patients (total 38 patients) N (%; 95% CI)	Treatment entirely completed (total 21 patients) N (%; 95% CI)
Overall response rate	19 (44; 29-60)	19 (50; 33-67)	14 (67; 43-85)
Complete response	6 (14; 5-28)	6 (16; 6-31)	6 (29; 11-52)
Partial response	13 (30; 17-46)	13 (34; 20-51)	8 (38; 18-62)
Stable disease	14 (33; 19-49)	14 (37; 22-54)	7 (33; 15-57)
Progressive disease	5 (12; 4-25)	5 (13, 4-28)	0
Not evaluable	5 (12; 4-25)	na	na

ITT: intent-to-treat; 95% CI: 95% confidence interval; na: not applicable.

Ibrutinib



Noy A Blood 2017

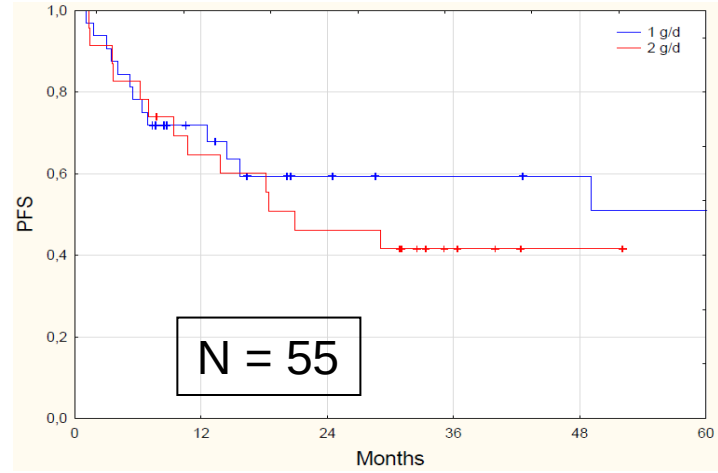
ORR 53% (3% CR ?)
62% PFS 18 months

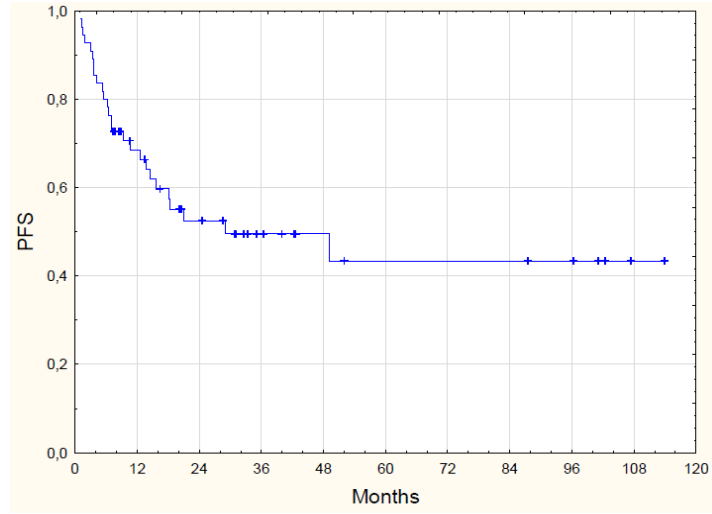
Median FUP 19.4. months

- **N = 63 (MALT 32,** nodal 17, splenic 14**)**
- Events: 13 PD, 7 relapse after initial response and 6 PDs after SD
- No cases of HGT
- Failures involved the primary site of disease in all cases but two.

Clarithromycin

ORR 54%, 24% CR
52% PFS 36 months

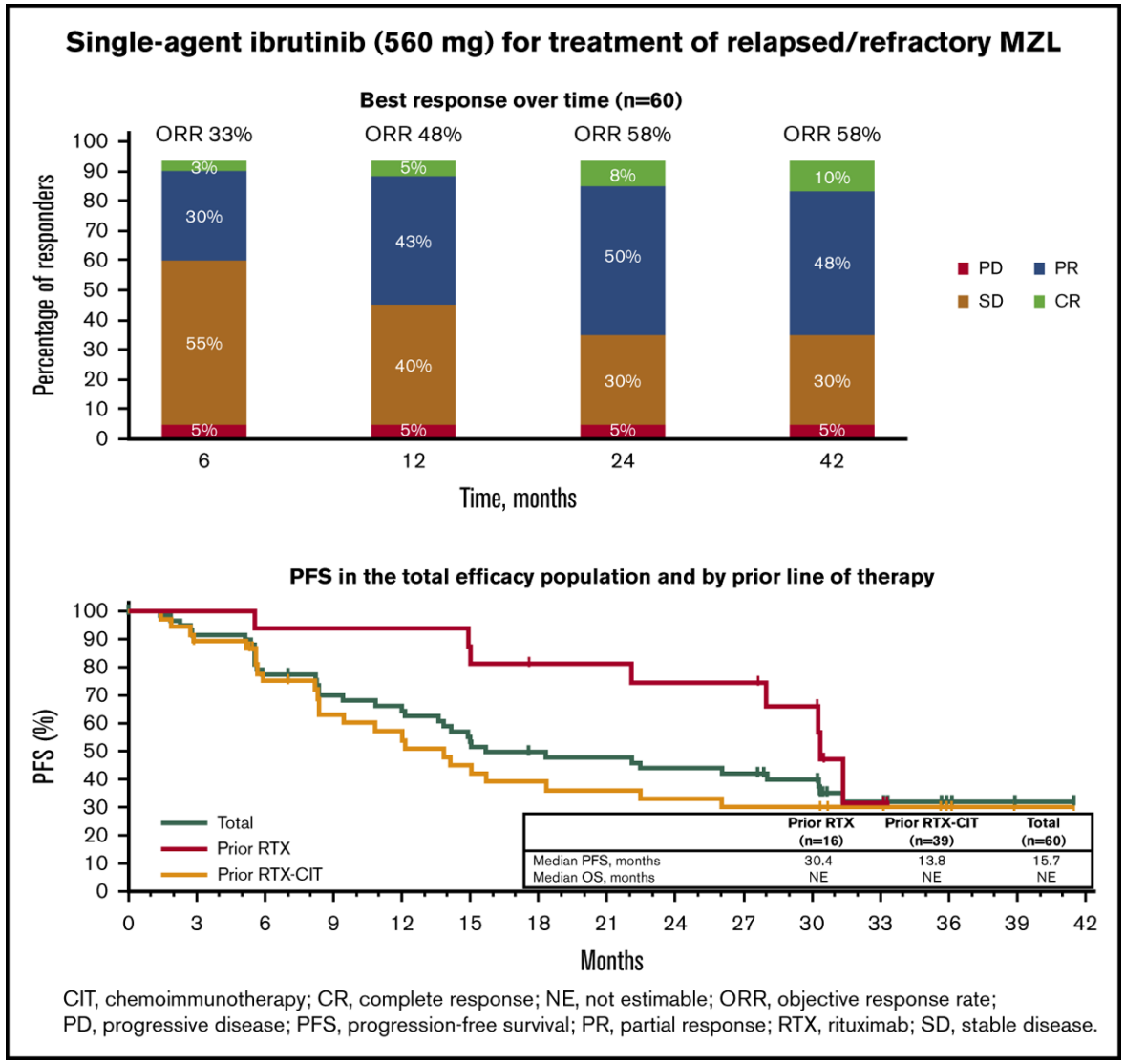




Clarithromycin median FUP 33 months

Ferreri et al, ICML 2017

Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis



ORR:

EMZL	63%
nMZL	47%
sMZL	62%

Noy et al, Blood Adv 2022

Patients
R/R MZL
(N=43)

Median age, y	Median # prior therapies
69	1

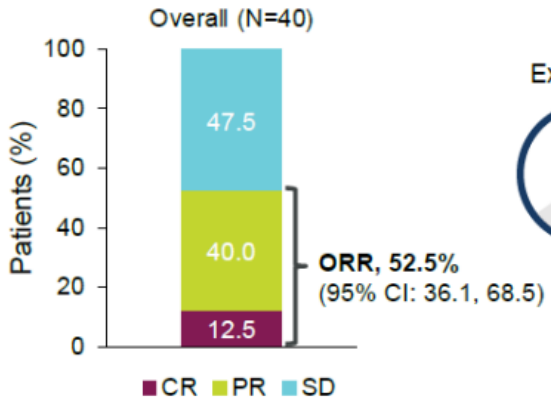
Subtype

Extranodal	Nodal	Splenic
44%	30%	26%

Acalabrutinib monotherapy
PO 100 mg BID

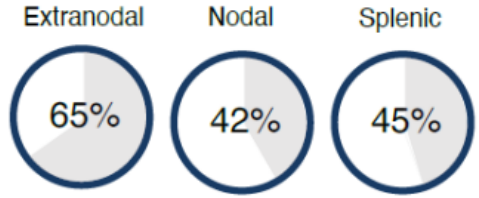
Median follow-up 13.3 mo Data cutoff January 4, 2022

Investigator-Assessed ORR in Evaluable Patients

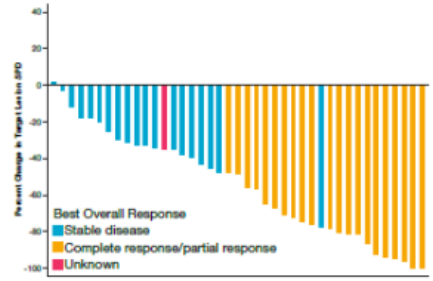


- Median duration of response was not estimable
- 12-month duration of response rate: 75.8%

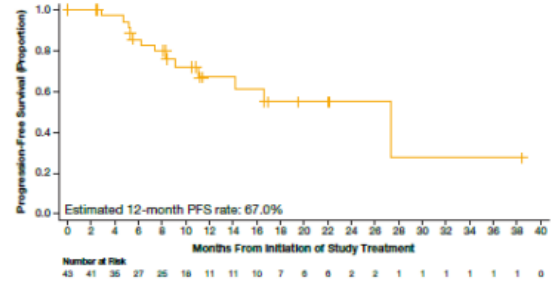
ORR by Subtype



Best Percent Change in Sum of Product Diameters



Progression-free Survival



Safety

- Most adverse events were **grade 1 or 2 in severity**
- **5% discontinued acalabrutinib** due to adverse events
- **No atrial fibrillation/flutter,** ventricular arrhythmias, or major hemorrhage
- **One death** due to adverse event (septic shock)

Conclusions

- **With an ORR of 53%, these results support acalabrutinib as an alternative therapy for patients with R/R MZL**
- **Adverse events reported were consistent with the known safety profile of acalabrutinib**

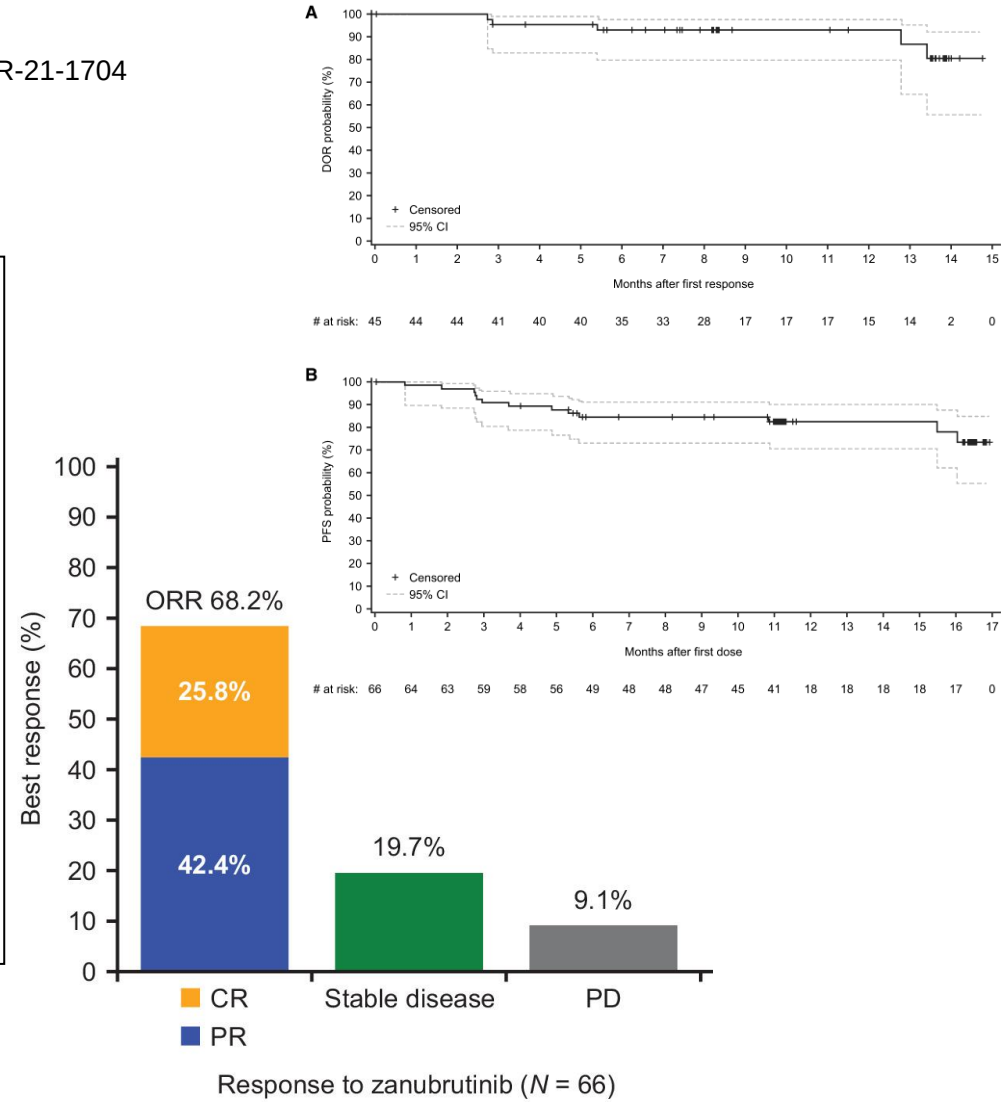
BID, twice daily; CI, confidence interval; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SPD, sum of product diameters.

From: **The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma**

Clin Cancer Res. 2021;27(23):6323-6332. doi:10.1158/1078-0432.CCR-21-1704

N = 68

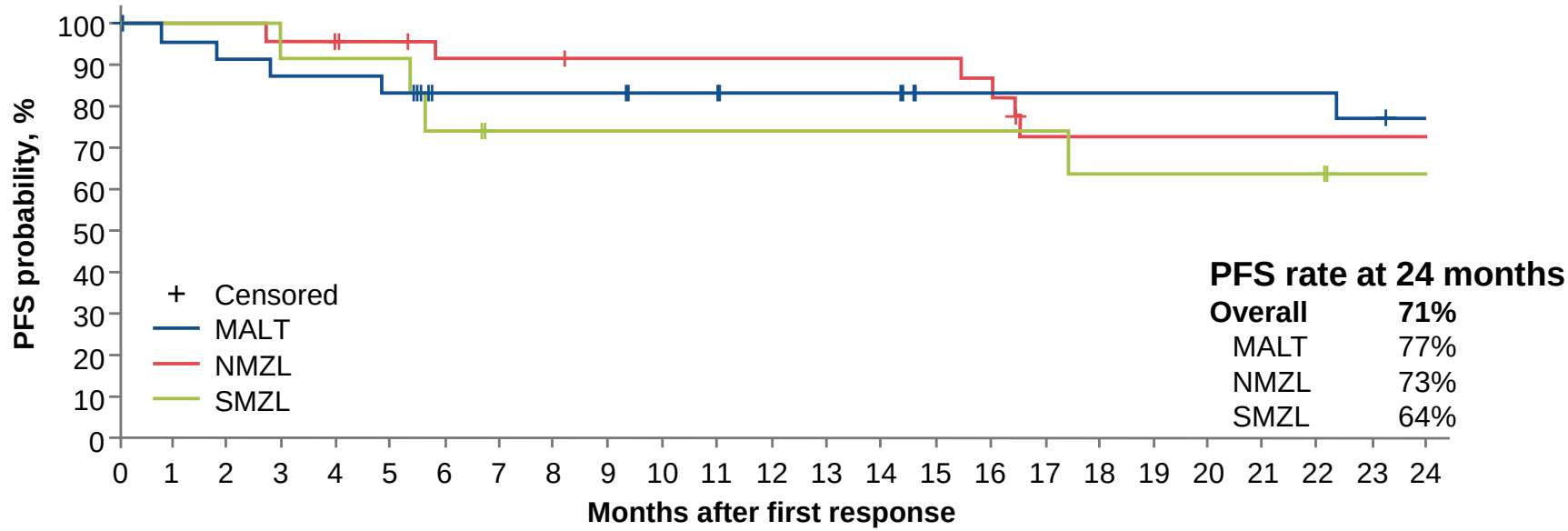
Refractory disease[c]	22 (32.4)
Evidence of FDG-avid disease by IRC, *n* (%)	
FDG-avid	61 (89.7)
Non–FDG-avid	7 (10.3)
MZL subtype, *n* (%)	
Extranodal (MALT)	26 (38.2)
Nodal	26 (38.2)
Splenic	12 (17.6)
Unknown[d]	4 (5.9)
Site of disease for MALT subtype, *n* (%)	
Gastric	2 (7.7)
Cutaneous	4 (15.4)
Nongastric/noncutaneous	19 (73.1)
Unknown	1 (3.8)



Zugelassen nach CD20-Therapie!

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.

Opat S et al. Oral presentation presented at ASH 2022. Abstract 234

Take Home Message:

Extranodales Marginalzonen-Lymphom (MALT LYMPHOM)

Sprache:	German
Bereich:	Onkopedia
DokumentTyp:	Guideline
Klassifizierung:	ONKOPEDIA::Hematological Malignancies
Fachgesellschaften:	DGHO OeGHO SGHSSH SGMO
Stand:	10/2023
ICD10:	
LLThema:	Extranodales Marginalzonen-Lymphom (MZoL)

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