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10. Sommersymposium „Lymphome & Leukämien“

Indolente B-Zell-Lymphome

Prof. Dr. Kai Hübel

21. Mai 2022

Offenlegung möglicher Interessenskonflikte

Beratungs- bzw. Gutachtertätigkeit

Roche, Celgene/BMS, Sanofi, Incyte, EUSA, AbbVie, Novartis

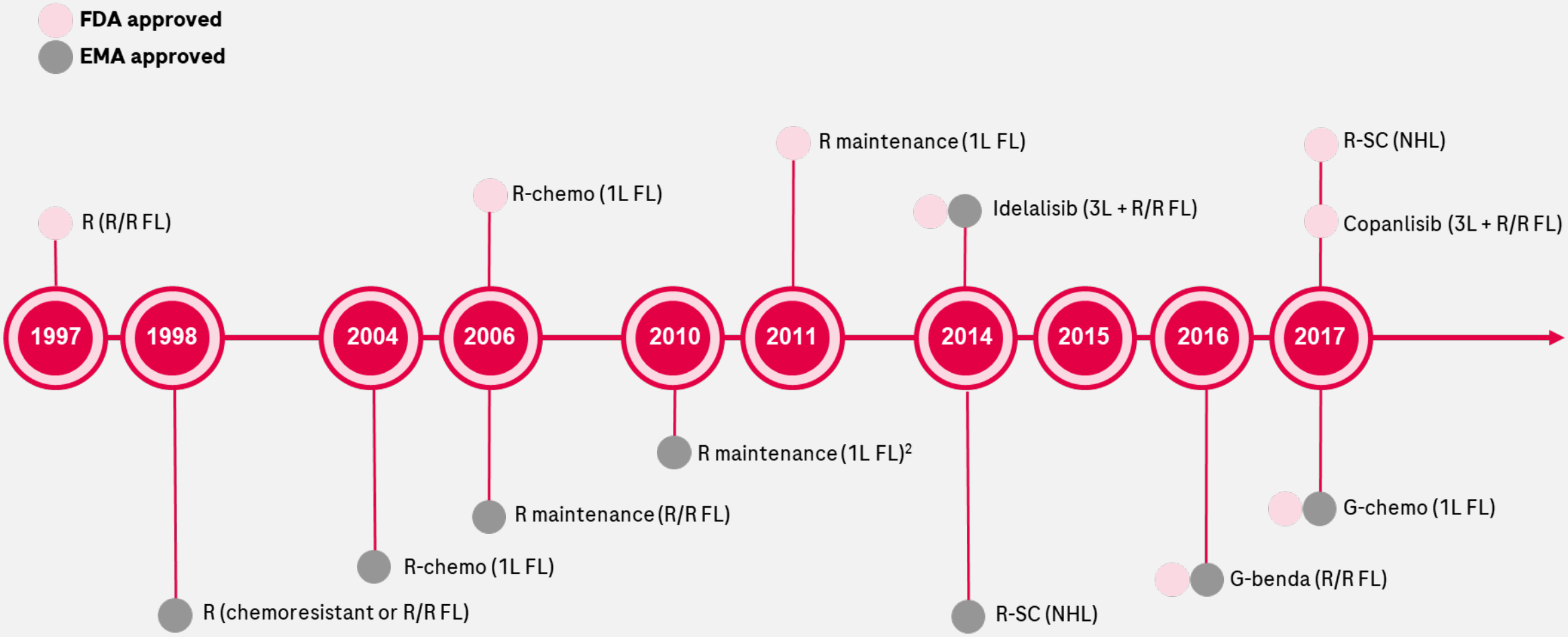
Honorare

Roche, Celgene/BMS, Incyte, Sanofi, EUSA, Novartis

Finanzierung wissenschaftlicher Untersuchungen

Roche, Celgene/BMS, Servier, Sanofi, Janssen

Therapeutische Entwicklung beim Follikulären Lymphom (1/2)



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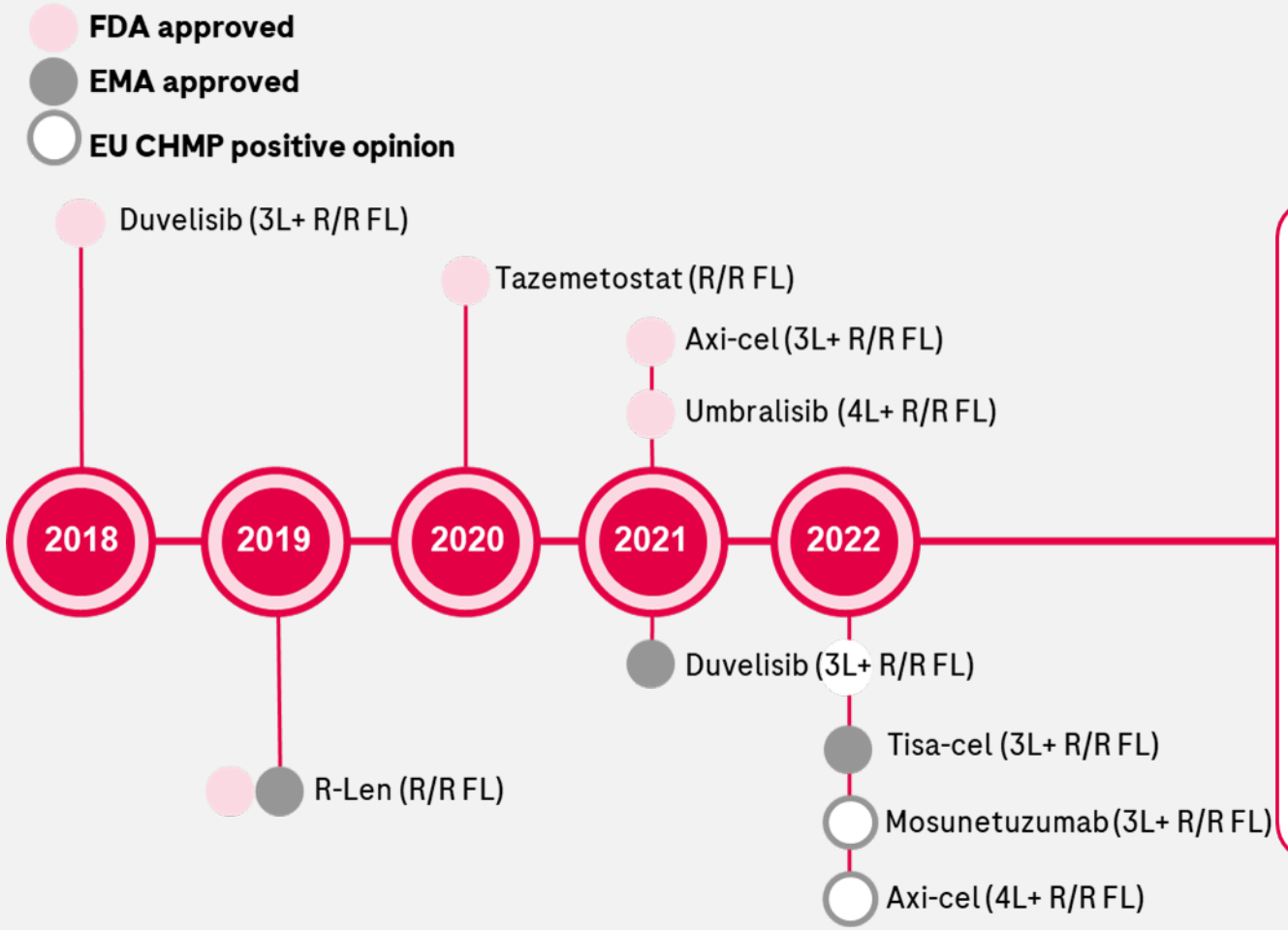
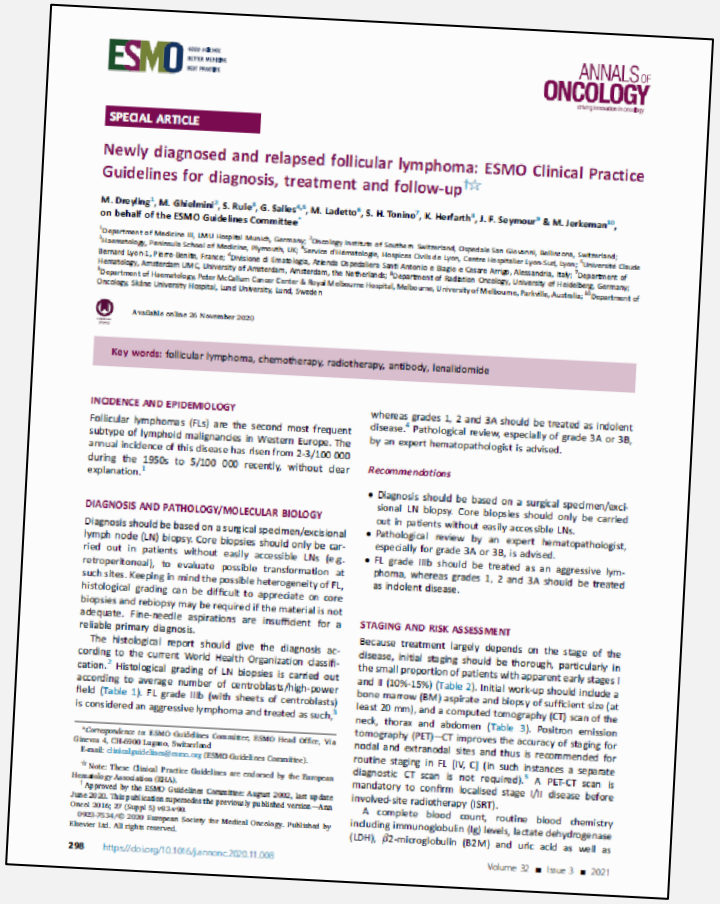
Therapeutische Entwicklung beim Follikulären Lymphom (2/2)



Investigational agents

- aCD19 antibodies: tafasitamab
- aCD19 antibody–drug conjugates: loncastuximab tesirine
- aCD47 antibodies: magrolimab, SRF231
- EZH2-inhibitors: tazemetostat
- Antibody-radionuclide conjugates: lilotomab
- Bispecific antibodies: mosunetuzumab, glofitamab, epcoritamab, odronextamab, plamotamab
- CAR-Ts: liso-cel, tisa-cel, axi-cel
- BTK inhibitors: ibrutinib, zanubrutinib
- IL-15 superagonist: N-803 (ALT-803)
- Immunomodulatory agents: Len combinations
- PI3K inhibitors: zandelisib, parsaclisib

ESMO / EHA Guidelines 2021



ESMO

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*

Available online 26 November 2020

Key words: follicular lymphoma, chemotherapy, radiotherapy, antibody, lenalidomide

INCIDENCE AND EPIDEMIOLOGY

Follicular lymphomas (FLs) are the second most frequent subtype of lymphoid malignancies in Western Europe. The annual incidence of this disease has risen from 2-3/100 000 during the 1950s to 5/100 000 recently, without clear explanation.[1]

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis should be based on a surgical specimen/excisional lymph node (LN) biopsy. Core biopsies should only be carried out in patients without easily accessible LNs (e.g. retroperitoneal), to evaluate possible transformation at such sites. Keeping in mind the possible heterogeneity of FL, histological grading can be difficult to appreciate on core biopsies and rebiopsy may be required if the material is not adequate. Fine-needle aspirations are insufficient for a reliable primary diagnosis.

The histological report should give the diagnosis according to the current World Health Organization classification.[2] Histological grading of LN biopsies is carried out according to average number of centroblasts/high-power field (Table 1). FL grade IIIb (with sheets of centroblasts) is considered an aggressive lymphoma and treated as such,[3] whereas grades 1, 2 and 3A should be treated as indolent disease.[4] Pathological review, especially of grade 3A or 3B, by an expert hematopathologist is advised.

Recommendations

- Diagnosis should be based on a surgical specimen/excisional LN biopsy. Core biopsies should only be carried out in patients without easily accessible LNs.
- Pathological review by an expert hematopathologist, especially for grade 3A or 3B, is advised.
- FL grade IIIb should be treated as an aggressive lymphoma, whereas grades 1, 2 and 3A should be treated as indolent disease.

STAGING AND RISK ASSESSMENT

Because treatment largely depends on the stage of the disease, initial staging should be thorough, particularly in the small proportion of patients with apparent early stages I and II (10%-15%) (Table 2). Initial work-up should include a bone marrow (BM) aspirate and biopsy of sufficient size (at least 20 mm), and a computed tomography (CT) scan of the neck, thorax and abdomen (Table 3). Positron emission tomography (PET)—CT improves the accuracy of staging for nodal and extranodal sites and thus is recommended for routine staging in FL [IV, C] (in such instances a separate diagnostic CT scan is not required).[5] A PET-CT scan is mandatory to confirm localised stage I/II disease before involved-site radiotherapy (ISRT).

A complete blood count, routine blood chemistry including immunoglobulin (Ig) levels, lactate dehydrogenase (LDH), β2-microglobulin (B2M) and uric acid as well as

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Giuseppe 4, CH-6900 Lugano, Switzerland.

☆ Note: These Clinical Practice Guidelines are endorsed by the European Hematology Association (EHA).

Approved by the ESMO Guidelines Committee: August 2002, last update June 2020. This publication supersedes the previously published version—Ann Oncol 2016; 27 (Suppl 5): v83–v90.

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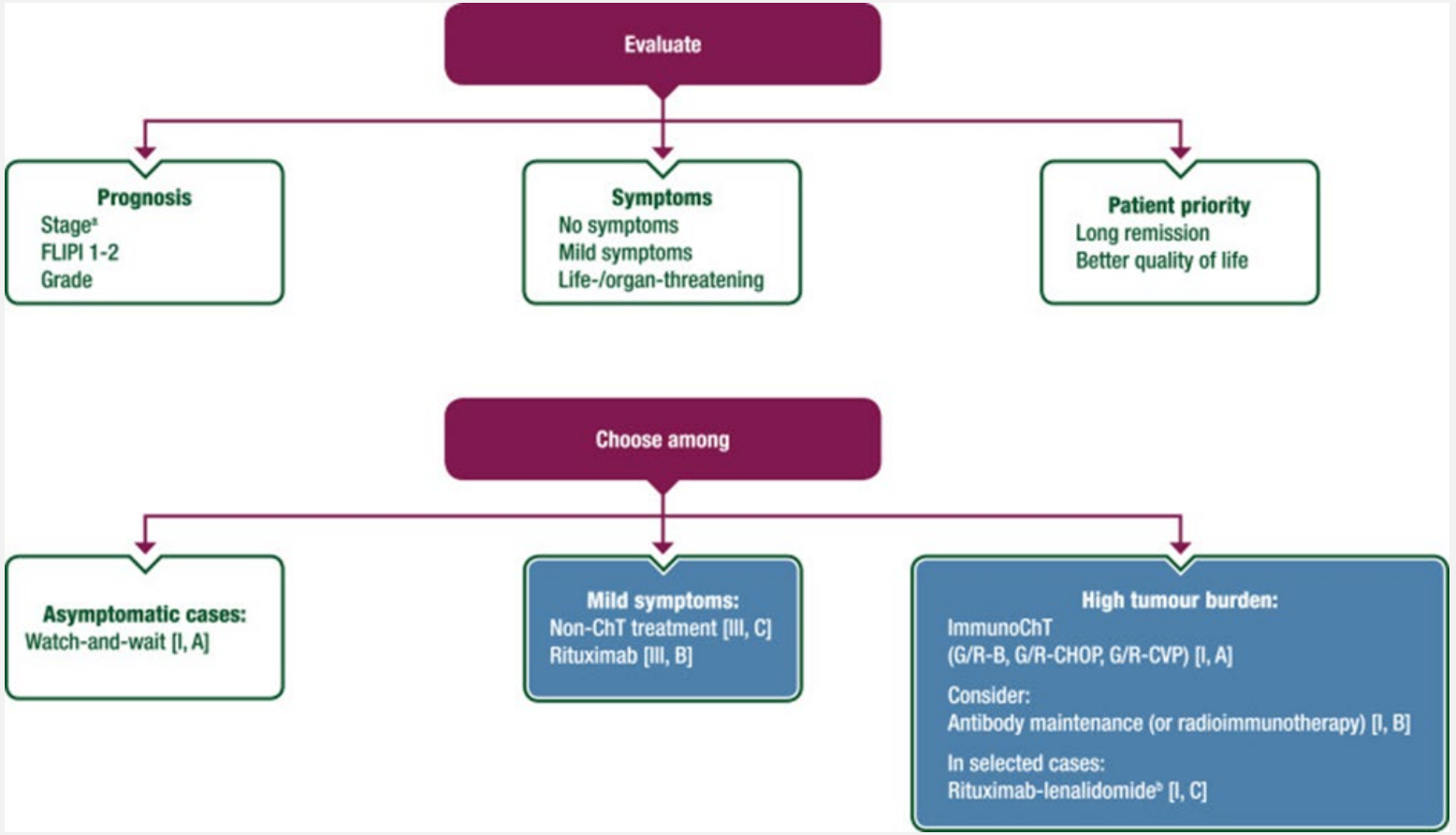
298 https://doi.org/10.1016/j.annonc.2020.11.008

Volume 32 ■ Issue 3 ■ 2021

First-line treatment of advanced FL (stage III-IV)



[a]Ann Arbor classification; [b]off-label

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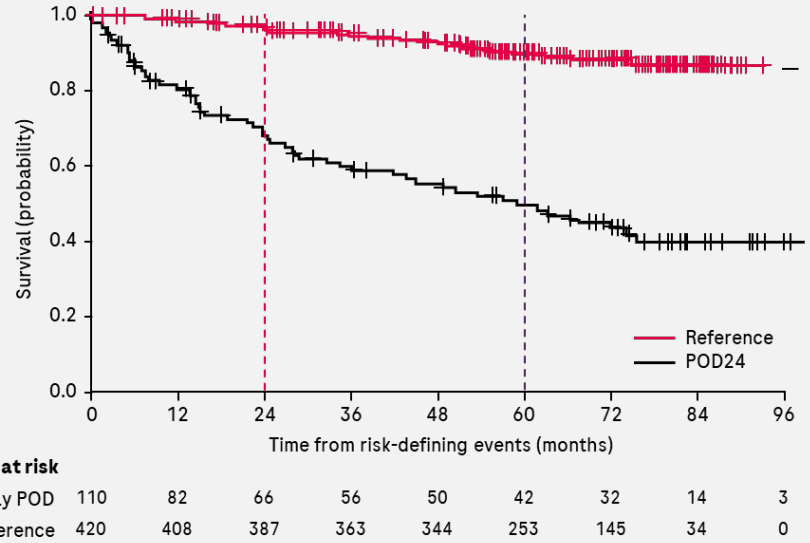
Dreyling et al. Ann Oncol 2021;32:298–308

Der Verlauf eines follikulären Lymphoms

Je höher die Therapielinie, desto kürzer das PFS

1L Therapie	2L Therapie	3L Therapie	4L Therapie	5L Therapie
PFS 6.62 Jahre	PFS 1.50 Jahre	PFS 0.83 Jahre	PFS 0.69 Jahre	PFS 0.68 Jahre

OS bei POD24 Patienten (National LymphoCare Study database)



	POD24 (n = 110)	Reference (n = 420)
2-year OS, % (95% CI)	68 (58.2–76.3)	97 (94.6–98.1)
5-year OS, % (95% CI)	50 (39.4–59.2)	90 (86.2–92.4)

Median follow-up: 7 years

Casulo C *et al. J Clin Oncol* 2015;33(23):2516–22

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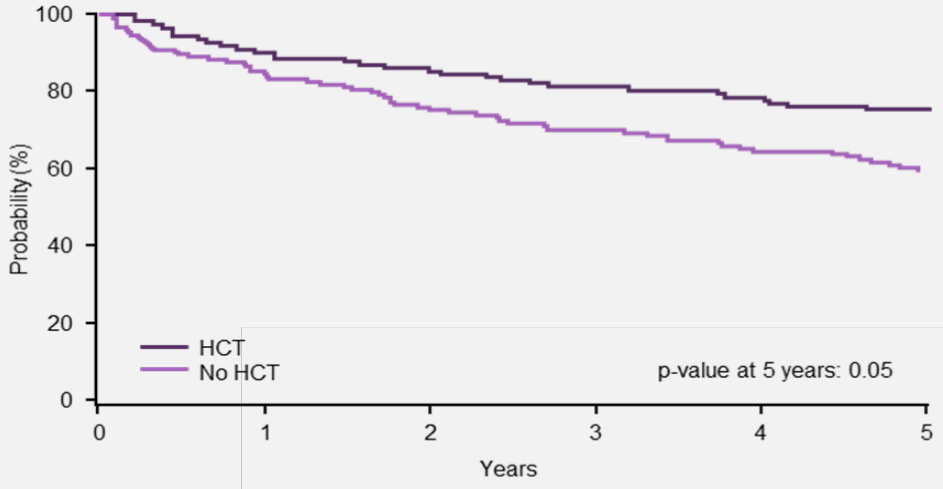
Link BK *et al. Br J Haematol* 2019;184:660–3

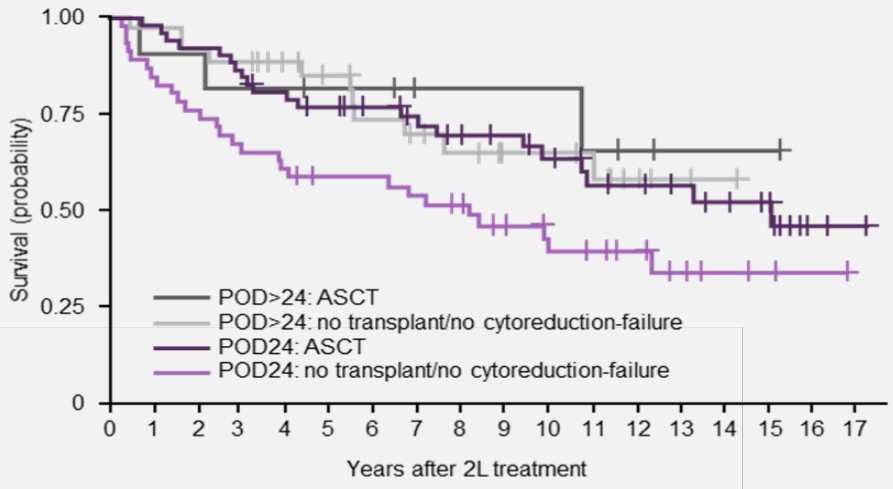
Management von POD24-Patienten

- Patienten mit POD24 haben eine schlechte Prognose
- Eine optimale Therapie für diese Patienten ist bisher nicht definiert.
- Es gibt keinen randomisierten Vergleich zwischen verschiedenen Therapieansätzen.
- Bei fitten Patienten in Remission scheint die ASCT Vorteile zu bringen.



	Early ASCT (n=123)	No ASCT (n=174)
5-year OS, % (95% CI)	73 (66–81)	60 (52–67)
p-value	0.05	

Casulo et al., Biol Blood Marrow Transplant 2018;24:1163-71



	ASCT (n=123)	No ASCT (n=174)
5-year OS, %	77	59
HR (95% CI), p-value	0.54 (0.30–0.95), p=0.031	

Jurinovic et al., Biol Blood Marrow Transplant 2018;24:1172-9

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Möglichkeiten der Risikostratifikation

Baseline PET[1]

Patienten mit niedrigem TMTV (< 510 mm^3) haben eine bessere Prognose:

- 5-year PFS: 33% vs 65% ($p < 0.001$)
- 5-year OS: 85% vs 95% ($p = 0.010$)

EOI PET[2]

Patienten mit negativem PET nach der Erstlinie haben eine bessere Prognose:

- 4-year PFS: 23% vs 63% ($p < 0.0001$)
- 4-year OS: 87% vs 97% ($p = 0.0002$)

Baseline and EOI PET[3]

Patienten mit 1 oder 2 Risikofaktoren (hohes TMTV, positives EOI PET) haben eine schlechtere Prognose:

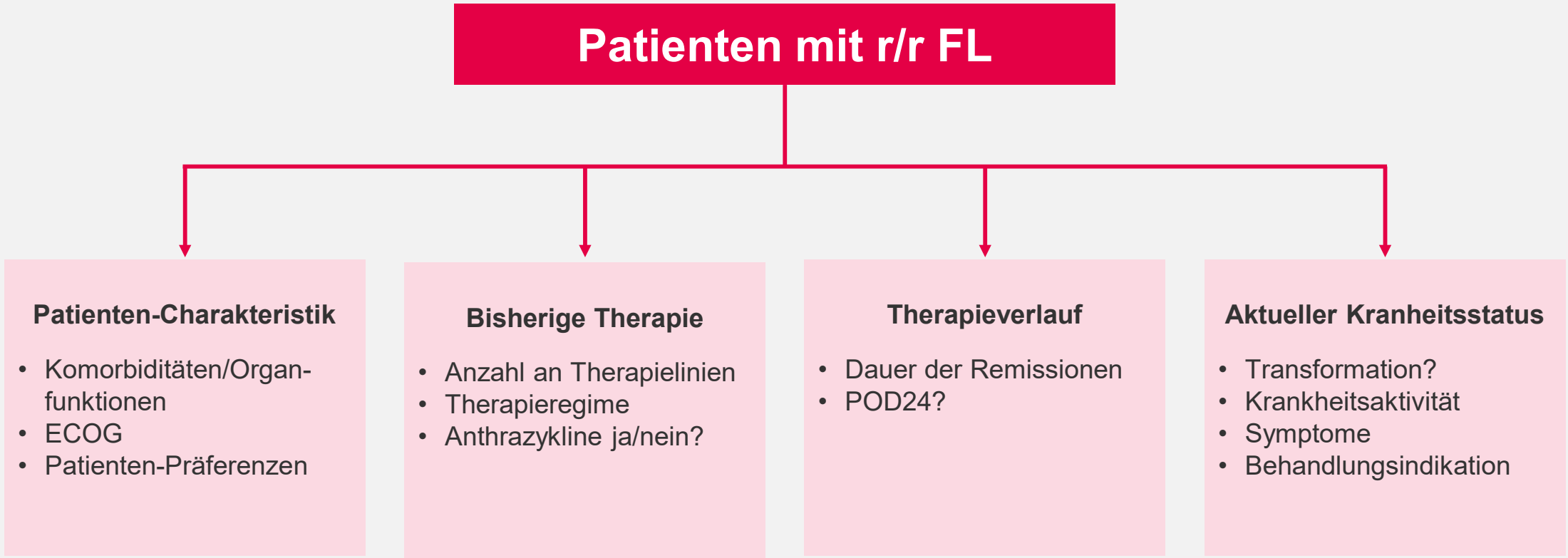
2-year PFS: 90%, 61% und 46% für Patienten mit keinem, einem oder zwei Risikofaktoren

Weitere mögliche Kriterien

- MRD
- ctDNA
- Genetische/molekulare Risikostratifikation (m7FLIPI)
- Zusammensetzung des Microenvironments

1. Meignan M *et al. J Clin Oncol* 2016;34:3618–26; 2. Trotman J *et al. Lancet Haematol* 2014;1:e17–27; 3. Cottereau AS *et al. Blood* 2018;131:2449–53

Vorgehen bei Patienten mit rezidivierten/refraktären FL

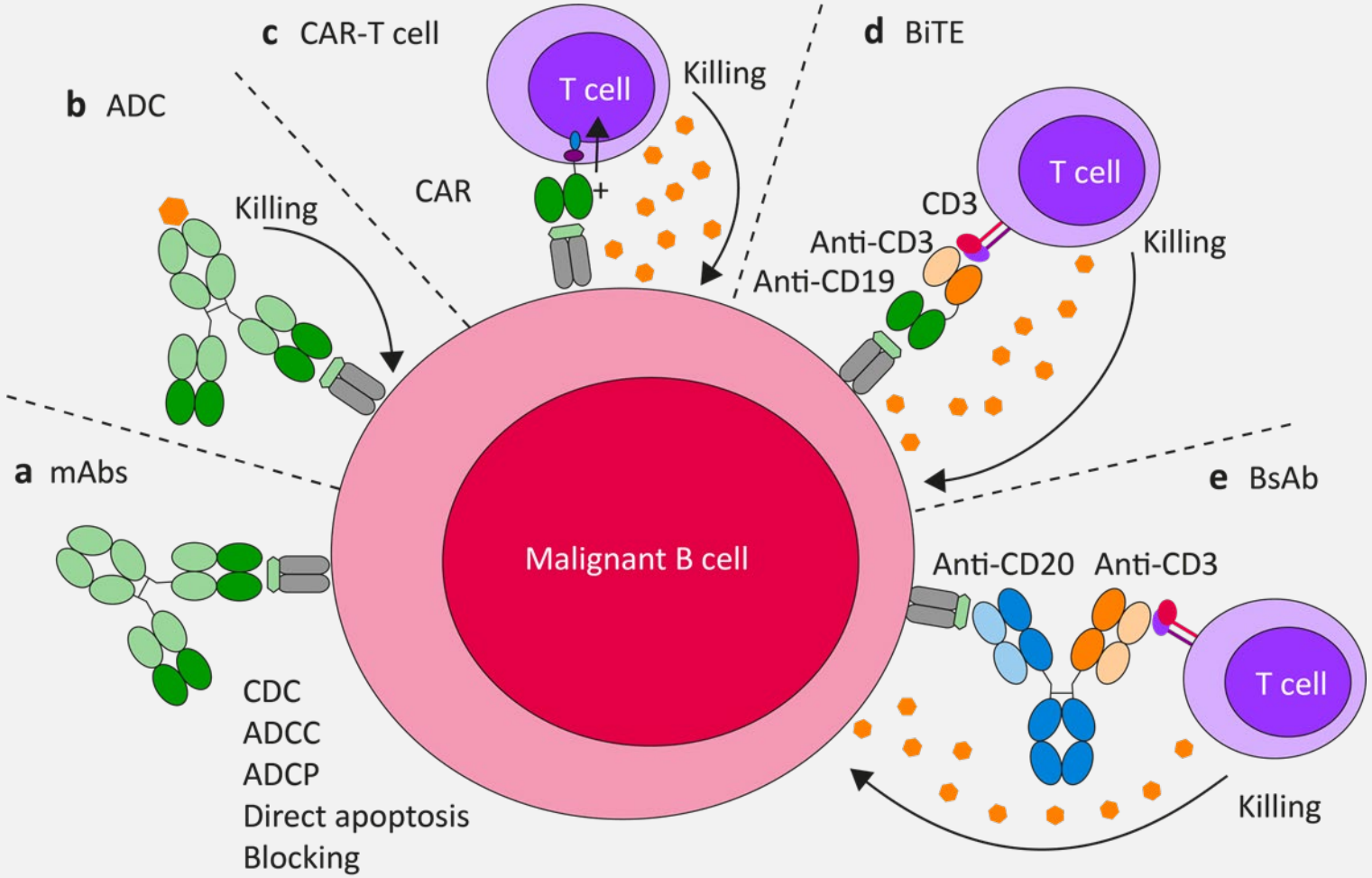


Therapeutische Überlegungen bei r/r FL

- Eine Re-Biopsie ist grundsätzlich anzustreben.
- Nach Möglichkeit sollte der Patient in eine klinische Studie eingeschlossen werden.
- Im ersten Rezidiv kann eine erneute Chemotherapie überlegt werden (Ausnahme POD24).
- Ist der Patient fit für eine autologe Transplantation und nicht Chemo-refraktär, ist die ASCT im zweiten Rezidiv zu prüfen (Ausnahme POD24).
- Ist der Patient Rituximab-refraktär: Prüfe Obinutuzumab/Bendamustin
- Ist der Patient Chemo-refraktär: Prüfe Lenalidomid/Rituximab

Insbesondere durch die Einführung der T-Zell-vermittelten Therapien wird sich die Behandlung des FL in Kürze grundlegend verändern!

Mechanism of action: T-cell engaging therapies



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BiTE, bispecific T-cell engagers; BsAb, bispecific T cell-engaging tandem scFv antibody; CAR, chimeric antigen receptor; CDC, complement-dependent cytoxicity; mAbs, monoclonal antibodies

Høydahl LS *et al. Antibodies* 2019;8:32

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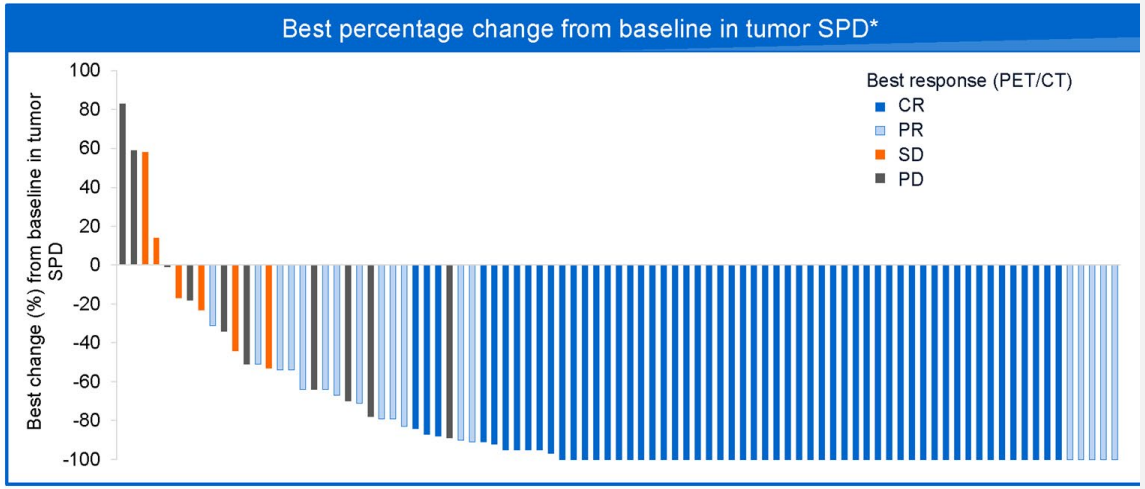
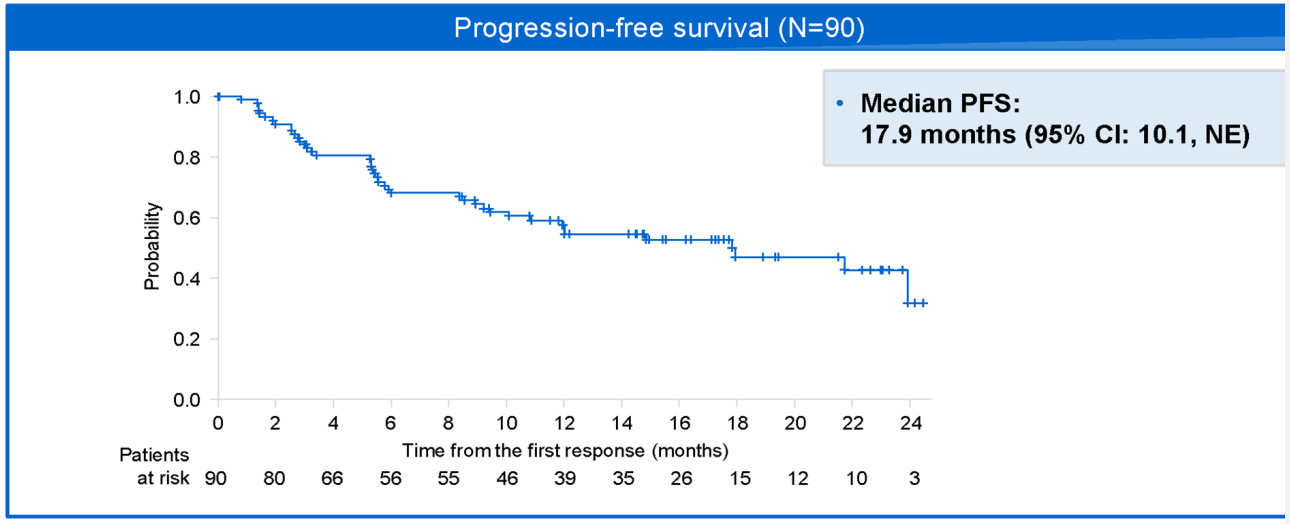
Mosunetuzumab (n=90, Phase I/II, ab 3. Linie)

Anti-tumor efficacy



*in all patients with a baseline and ≥1 post-baseline SPD available; PD, progressive disease; SPD, sum of product diameters

Progression-free survival



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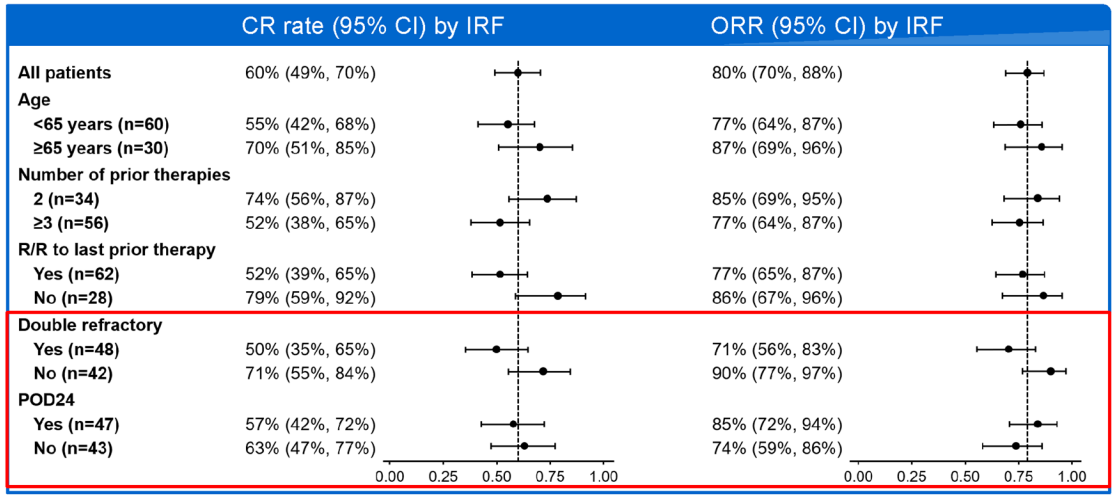
Budde et al. ASH 2021, Abstract 127

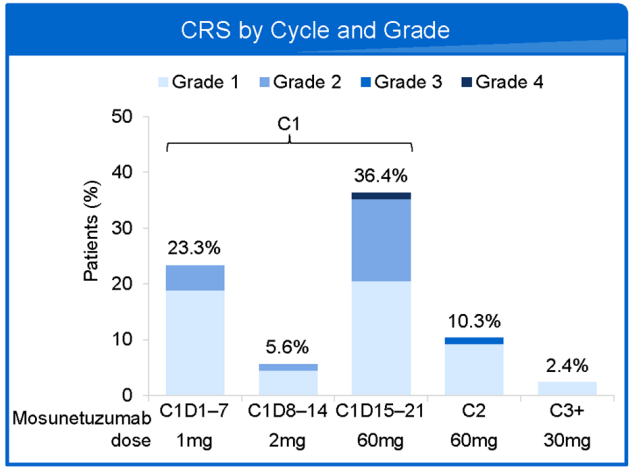
Mosunetuzumab (n=90, Phase I/II, ab 3. Linie)

Comparable response rates in high-risk subgroups



Cytokine release syndrome

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)



- **CRS was predominately low Grade and in Cycle 1. All events resolved.**

*assessed using ASTCT criteria[1]; †patient with leukemic phase FL

1. Lee et al. Biol Blood Marrow Transplant 20192019;25:625–38

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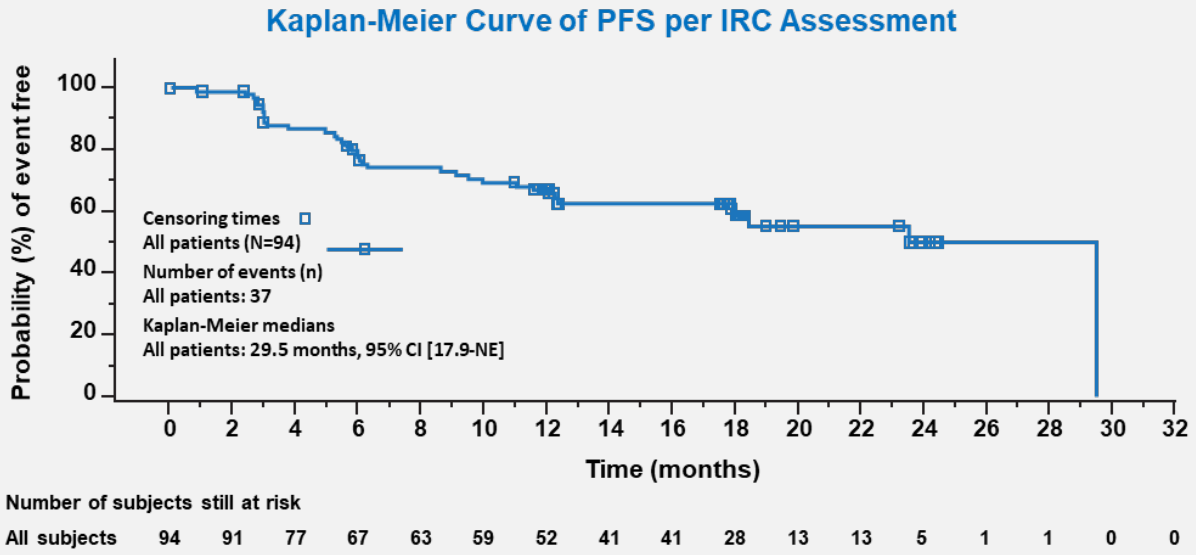
Budde et al. ASH 2021, Abstract 127

ELARA: Tisa-Cel beim rezidivierten/refraktären FL

Phase-II-Studie mit 94 Patienten ab der 3. Therapielinie (refraktär / Rezidiv < 6 Monate)



Medianes PFS: 29,5 Monate

Events innerhalb der ersten 8 Wochen	All Patienten (N=97) (%)
Patienten mit CRS	48.5
CRS Grad	
Grade 1	27.8
Grade 2	20.6
Grade 3/4	0
Medianer Beginn des CRS (Tag)	4.0
Min-Max	1-14
Mediane Dauer des CRS (Tage)	4.0
Min-Max	1-24

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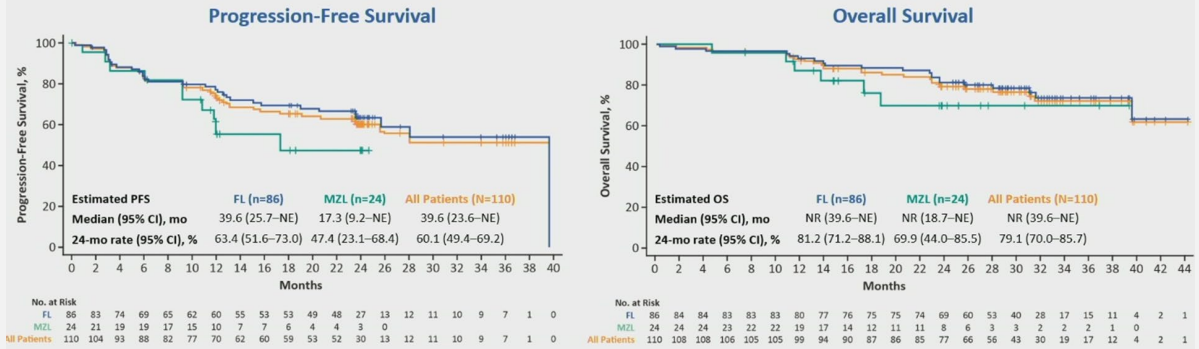
Thieblemont et al. ASH-Abstract 2021: 131

ZUMA-5: Axi-Cel beim rezidivierten/refraktären FL

Phase-II-Studie mit 124 Patienten ab der 3. Therapielinie

PFS and OS



- Median OS was not yet reached in efficacy-eligible patients with FL or MZL
- Among patients with FL, 3 deaths occurred after Month 24[a]; no disease progression events occurred after Month 24

[a] Of the 3 deaths, 2 were from COVID-19 and 1 was from sepsis.
FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Efficacy Outcomes in Patients With FL by POD24 Status

Parameter (95% CI)	Follicular Lymphoma (n=78)[a] With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

- Patients with FL who had POD24 benefitted from axi-cel, with estimated medians and 24-month rates of DOR and PFS consistent with all efficacy-eligible patients
  - Medians of DOR and PFS among patients without POD24 were not yet reached at data cutoff

[a] Axi-cel–treated patients with FL and available efficacy data on progression after an anti-CD20 mAb + alkylating agent were included in the POD24 analysis.
Axi-cel, axicabtagene ciloleucel; DOR, duration of response; FL, follicular lymphoma; mAb, monoclonal antibody; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; POD24, progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy.

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Neelapu et al. ASH-Abstract 2021: 93

Die Definition eines sinnvollen Therapiealgorithmus, möglichst basierend auf Patienten-individuellen Faktoren, ist eine der Herausforderungen der kommenden Zeit.

Morbus Waldenström

Waldenström's Macroglobulinemia – first described by Jan Gosta Waldenström in 1944

Acta Medica Scandinavica. Vol. CXVII, fasc. III—IV, 1944.

Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia — a new syndrome?

By

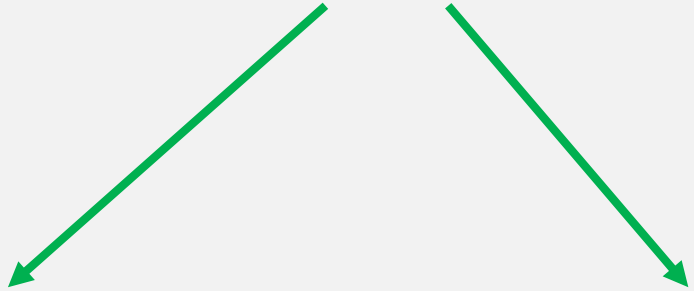
JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.

The real nature of myelomatosis.

The title of this paper may at first seem somewhat surprising. The myeloma has of old had a reputation as a well defined clinical entity. With the aid of the typical changes on the X-ray film and guided by the examination of the cells from a sternal puncture the diagnosis should therefore be easy and there ought not to be found any serious diagnostical troubles. In the following I am going to give a description of two cases, who have several symptoms suggesting myelomatosis but also show decided differences. They are very much alike even as regards details in the chemistry of the blood proteins and it seems probable according to my opinion, that they suffer from the same malady. A third case very much resembles these two patients but also shows other signs, that do not fit in so well with the picture.

Der M. Waldenström ist eine klinisch und molekular heterogene Erkrankung



Klinisch

- B-Symptome
- IgM-Neuropathie
- Anämie
- Hyperviskositäts-Syndrom
- Lymphadenopathie
- Splenomegalie

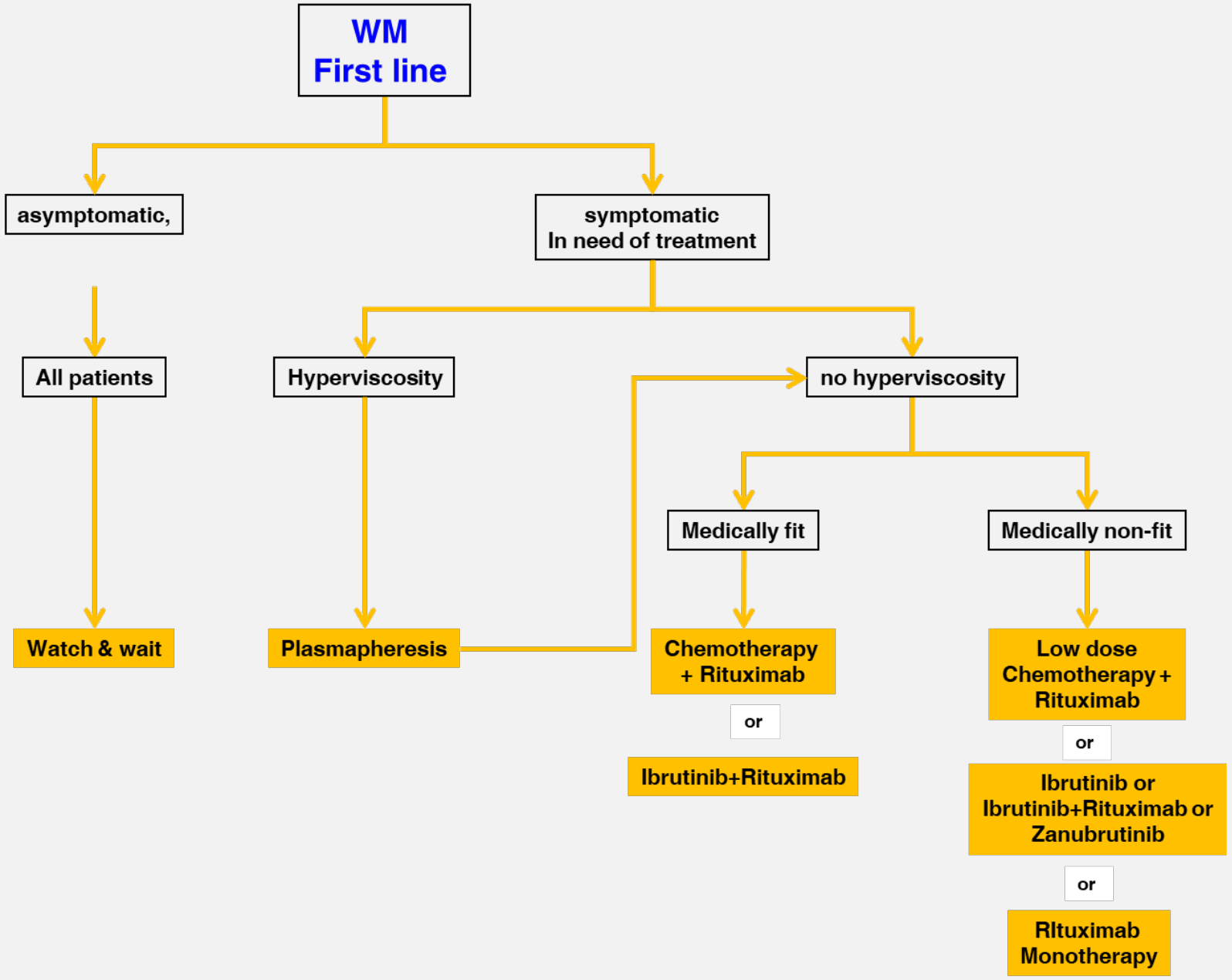
Molekular

- MYD88-Mutation (ca. 95%)
- CXCR4-Mutation (ca. 40%)

Die molekularen Veränderungen bestimmen das Therapieansprechen auf BTK-Inhibitoren!

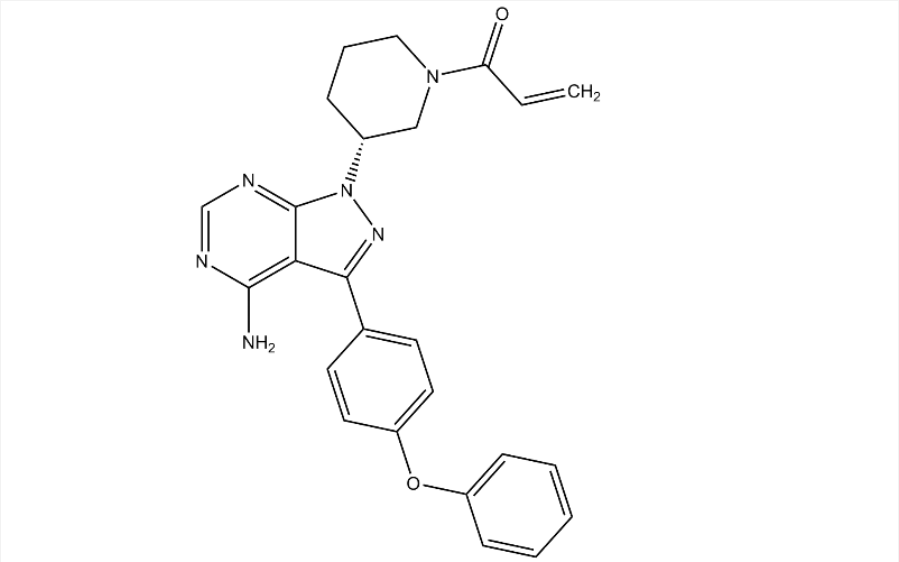
MYD88/ CXCR4	Ibrutinib OR	Ibrutinib VGPR/PR
+/WT		
+/+		
WT/WT		

Onkopedia-Leitlinie zur Erstlinientherapie (01/22)

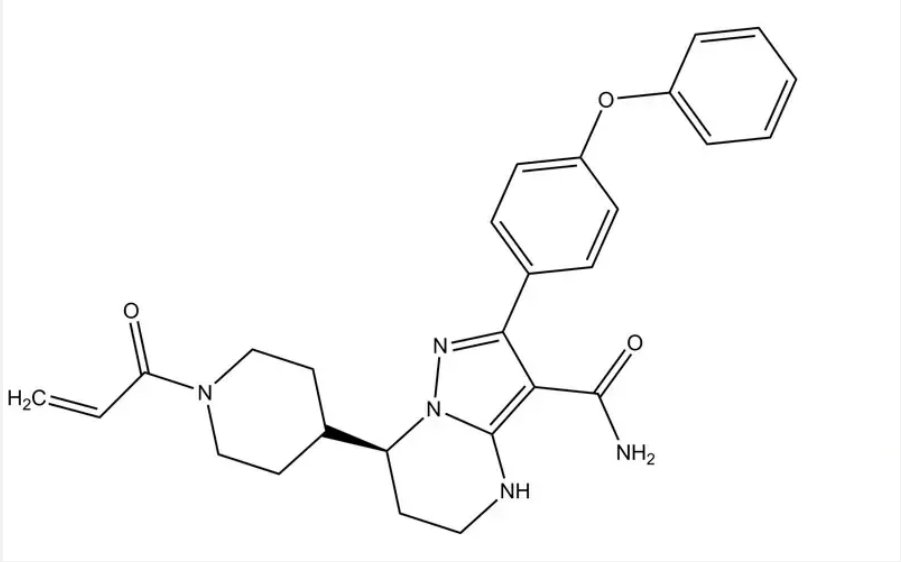


BTK-Inhibitoren beim M. Waldenström

Ibrutinib



Zanubrutinib



Ibrutinib beim r/r M. Waldenström: Effektivität

	(N= 63)	(%)
VGPR	10	15.9
PR	36	57
MR	11	17.5

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)

ORR: 90.5% Major RR (≥ PR): 73%

	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{WHIM}	MYD88^{WT} CXCR4^{WT}	p-value
N=	36	21	5	
Overall RR	100%	85.7%	60%	<0.01
Major RR	91.7%	61.9%	0%	<0.01

Treon et al, NEJM 2015; 372(15):1430-40

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

M.A. Dimopoulos, A. Tedeschi, J. Trotman, R. García-Sanz, D. Macdonald, V. Leblond, B. Mahe, C. Herbaux, C. Tam, L. Orsucci, M.L. Palomba, J.V. Matous, C. Shustik, E. Kastritis, S.P. Treon, J. Li, Z. Salman, T. Graef, and C. Buske, for the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia*

Dimopoulos et al., N Engl J Med 2018;378(25):2399-2410.

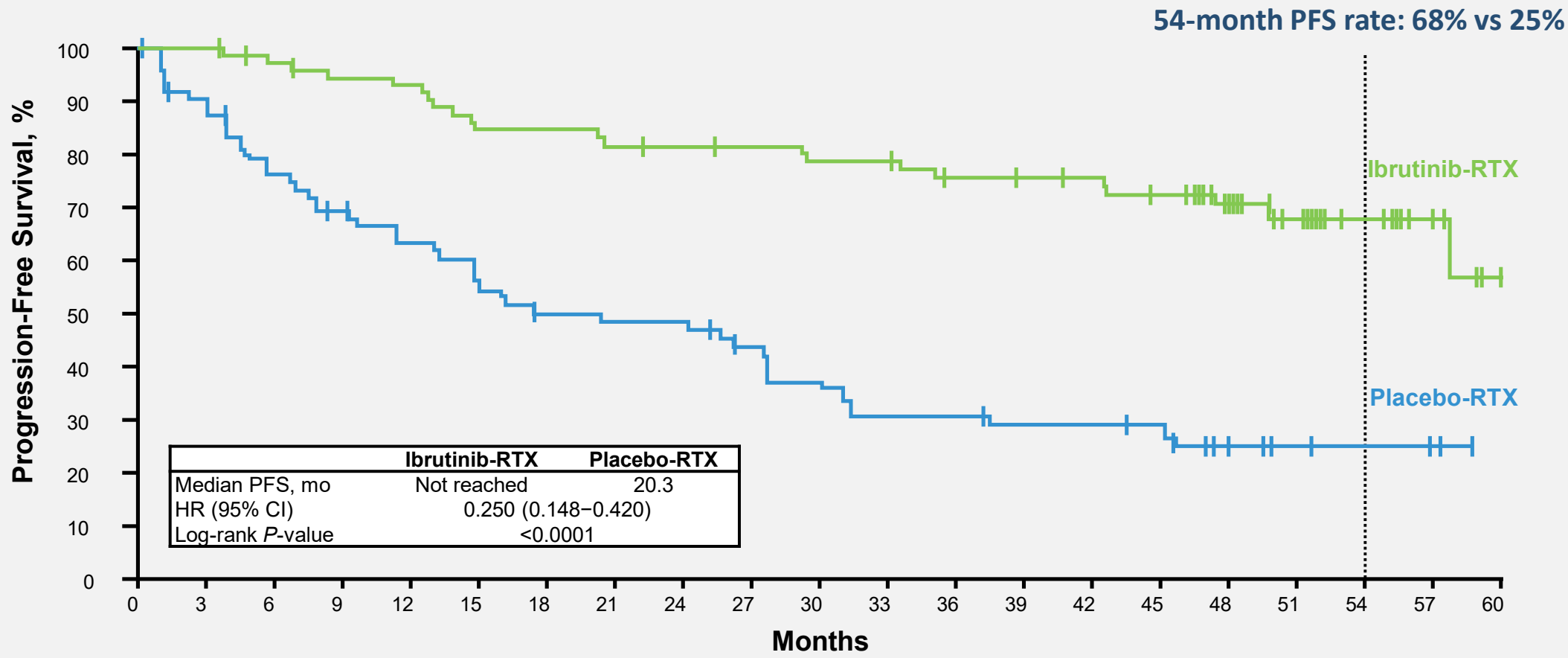
Buske et al., J Clin Oncol 2022;40(1):2399-2410

original reports

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

Christian Buske, MD[1]; Alessandra Tedeschi, MD[2]; Judith Trotman, MBChB[3]; Ramón García-Sanz, MD, PhD[4]; David MacDonald, MD[5]; Veronique Leblond, MD, PhD[6]; Beatrice Mahe, MD[7]; Charles Herbaux, MD[8]; Jeffrey V. Matous, MD[9]; Constantine S. Tam, MBBS, MD[10]; Leonard T. Heffner, MD[11]; Marzia Varettoni, MD[12]; M. Lia Palomba, MD[13]; Chaim Shustik, MD[14]; Efstathios Kastritis, MD[15]; Steven P. Treon, MD, PhD[16]; Jerry Ping, PhD[17]; Bernhard Hauns, MD, PhD[17]; Israel Arango-Hisijara, MD[17]; and Meletios A. Dimopoulos, MD[15]

Progressions-freies Überleben

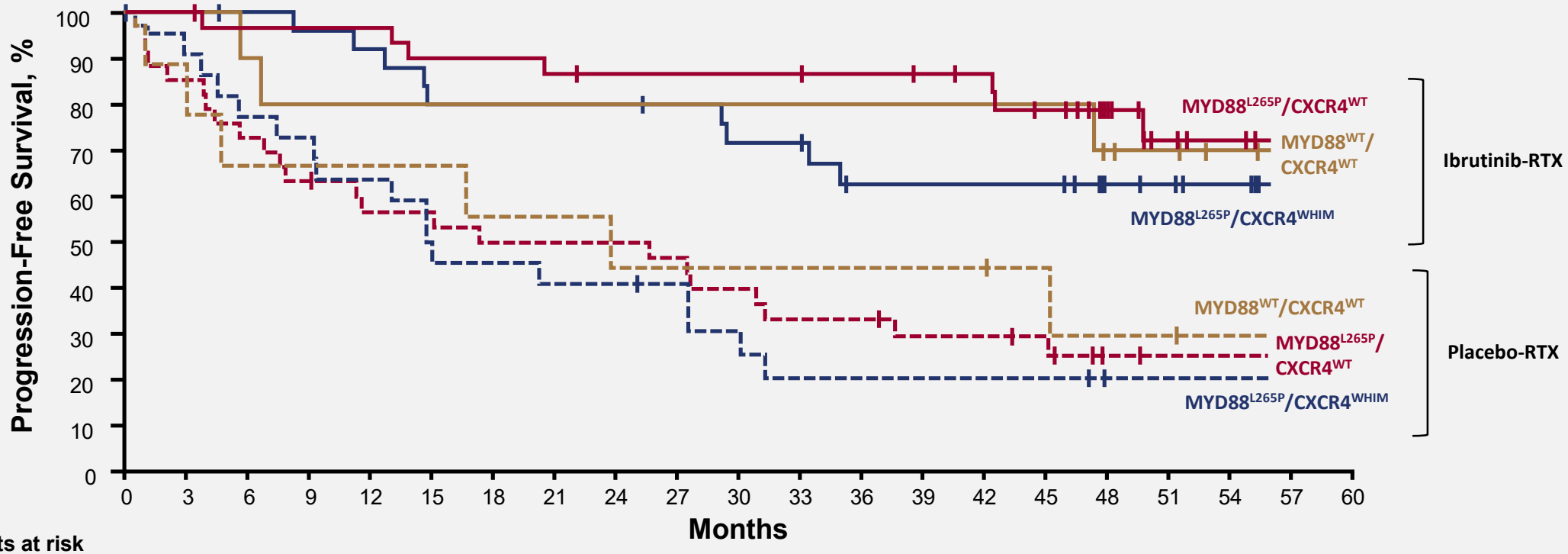


Patients at risk

Ibrutinib-RTX	75	73	69	67	66	60	60	58	57	56	54	54	46	48	47	44	32	22	15	7
Placebo-RTX	75	64	54	48	43	39	33	32	31	27	23	19	19	17	17	15	7	4	3	2

Buske et al., JCO 2022

Progressions-freies Überleben nach Genotyp



Patients at risk

Ibrutinib-RTX MYD88^{L265P}/CXCR4^{WHIM}	26	26	25	24	23	20	20	20	20	19	17	17	13	13	13	13	8	7	5
Ibrutinib-RTX MYD88^{L265P}/CXCR4^{WT}	32	31	29	29	29	27	27	26	25	25	25	25	24	23	22	19	15	8	5
Ibrutinib-RTX MYD88^{WT}/CXCR4^{WT}	11	10	9	8	8	8	8	8	8	8	8	8	8	8	8	8	6	5	3
Placebo-RTX MYD88^{L265P}/CXCR4^{WHIM}	23	20	17	16	14	11	10	9	9	8	6	4	4	4	4	4	2	1	1
Placebo-RTX MYD88^{L265P}/CXCR4^{WT}	35	28	23	20	17	17	15	15	15	14	12	10	10	8	8	7	3	1	1
Placebo-RTX MYD88^{WT}/CXCR4^{WT}	9	8	6	6	6	6	5	5	4	4	4	4	4	4	4	3	2	2	1

Kaplan-Meier curves are shown for timepoints with ≥10 patients at risk.

Buske et al., JCO 2022

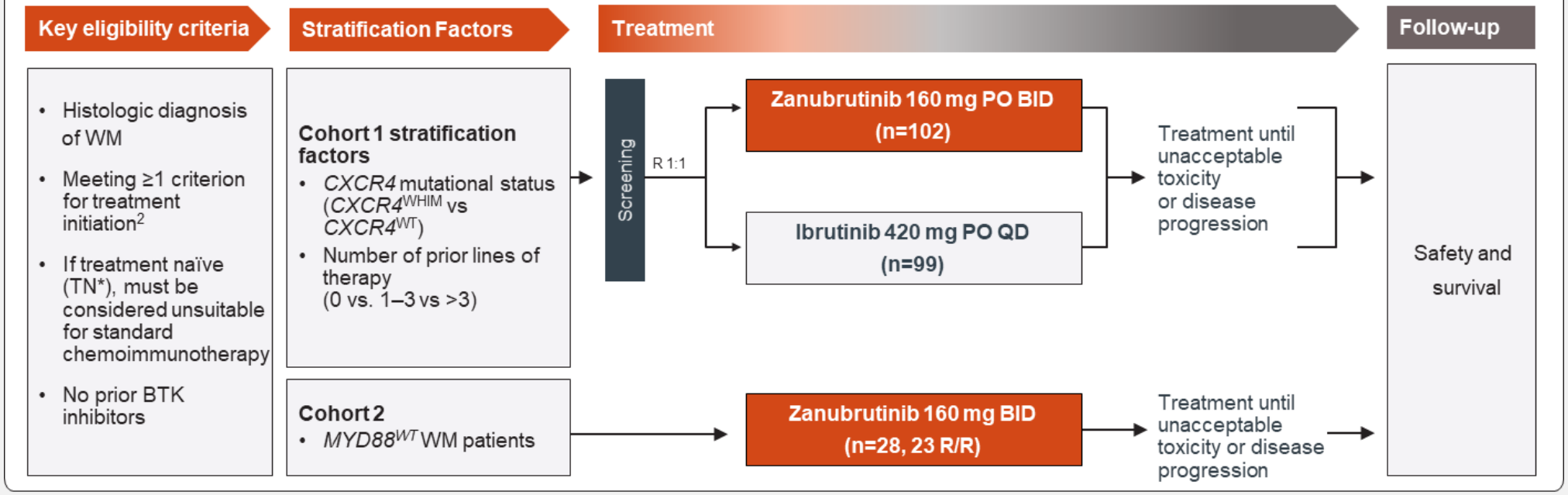
Ibrutinib vs Zanubrutinib: ASPEN-Studie

ASPEN
Phase 3 Waldenström Macroglobulinemia

Phase 3

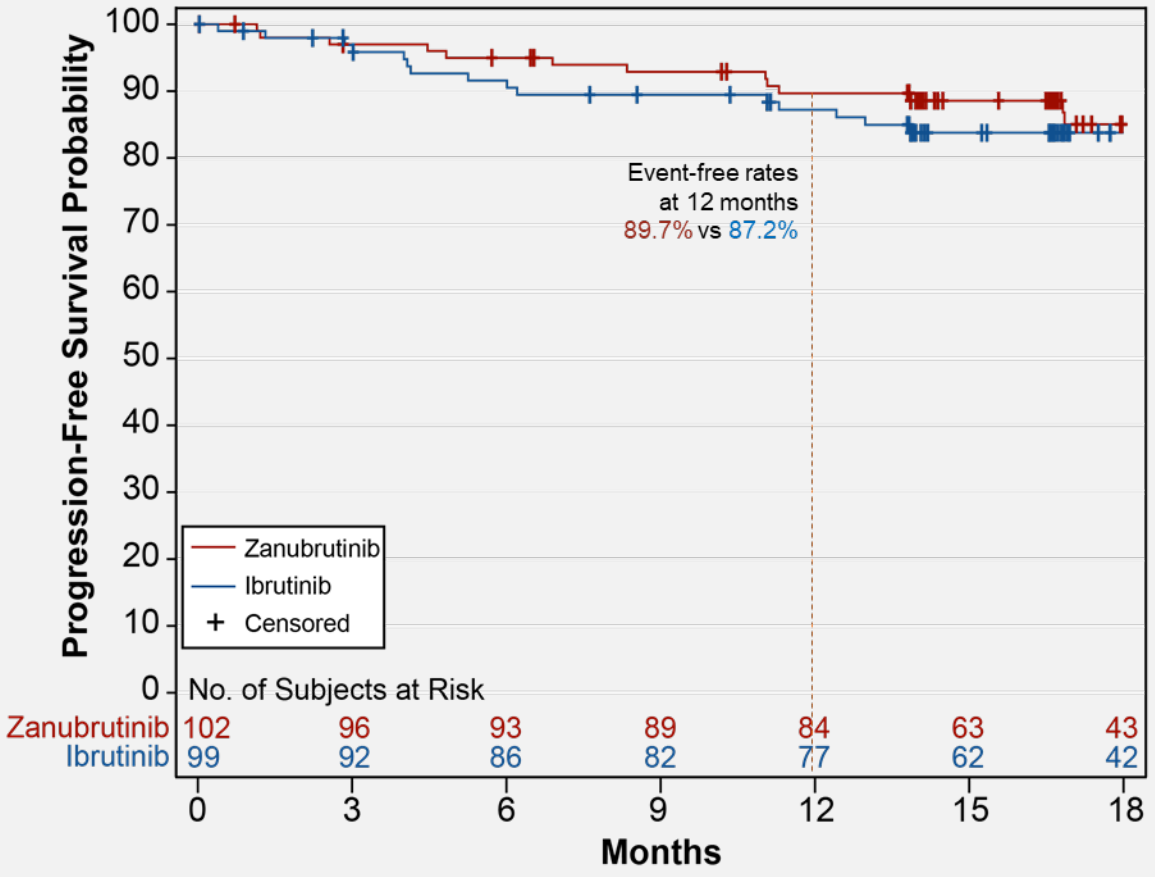
Study Identifier: BGB-3111-302, NCT03053440

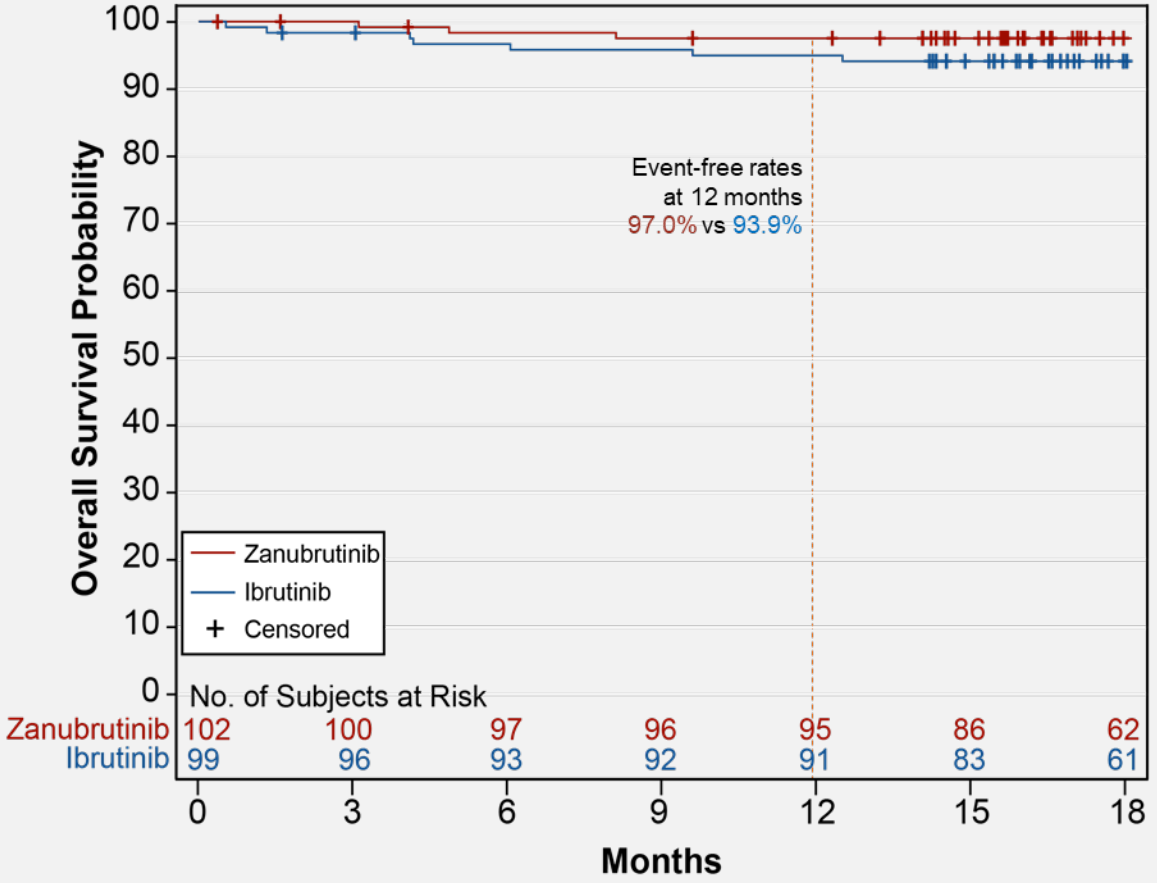
Primary Endpoint: CR/VGPR rate
Key Secondary Endpoints: MRR (≥PR), PFS, OS, DOR, symptom resolution, safety
Exploratory Endpoints: PK, QoL



Tam CS et al. ASCO 2020. Abstract 8007

Progressions-freies Überleben und Gesamtüberleben in der ITT-Population





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BTK-typische Nebenwirkungen

AE *Categories*, n (%) *(pooled terms)*	All Grades		Grade ≥ 3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	**18 (18.4%)**	3 (3.0%)	**7 (7.1%)**	0
Diarrhea (PT)	**32 (32.7%)**	22 (21.8%)	2 (2.0%)	3 (3.0%)
Hemorrhage	**59 (60.2%)**	51 (50.5%)	9 (9.2%)	6 (5.9%)
Major hemorrhage†	10 (10.2%)	6 (5.9%)	9 (9.2%)	6 (5.9%)
Hypertension	20 (20.4%)	13 (12.9%)	**15 (15.3%)**	8 (7.9%)
Neutropenia*‡	15 (15.3%)	**32 (31.7%)**	8 (8.2%)	**23 (22.8%)**
Infection	70 (71.4%)	70 (69.3%)	23 (23.5%)	19 (18.8%)
Second malignancy	12 (12.2%)	13 (12.9%)	1 (1.0%)	3 (3.0%)

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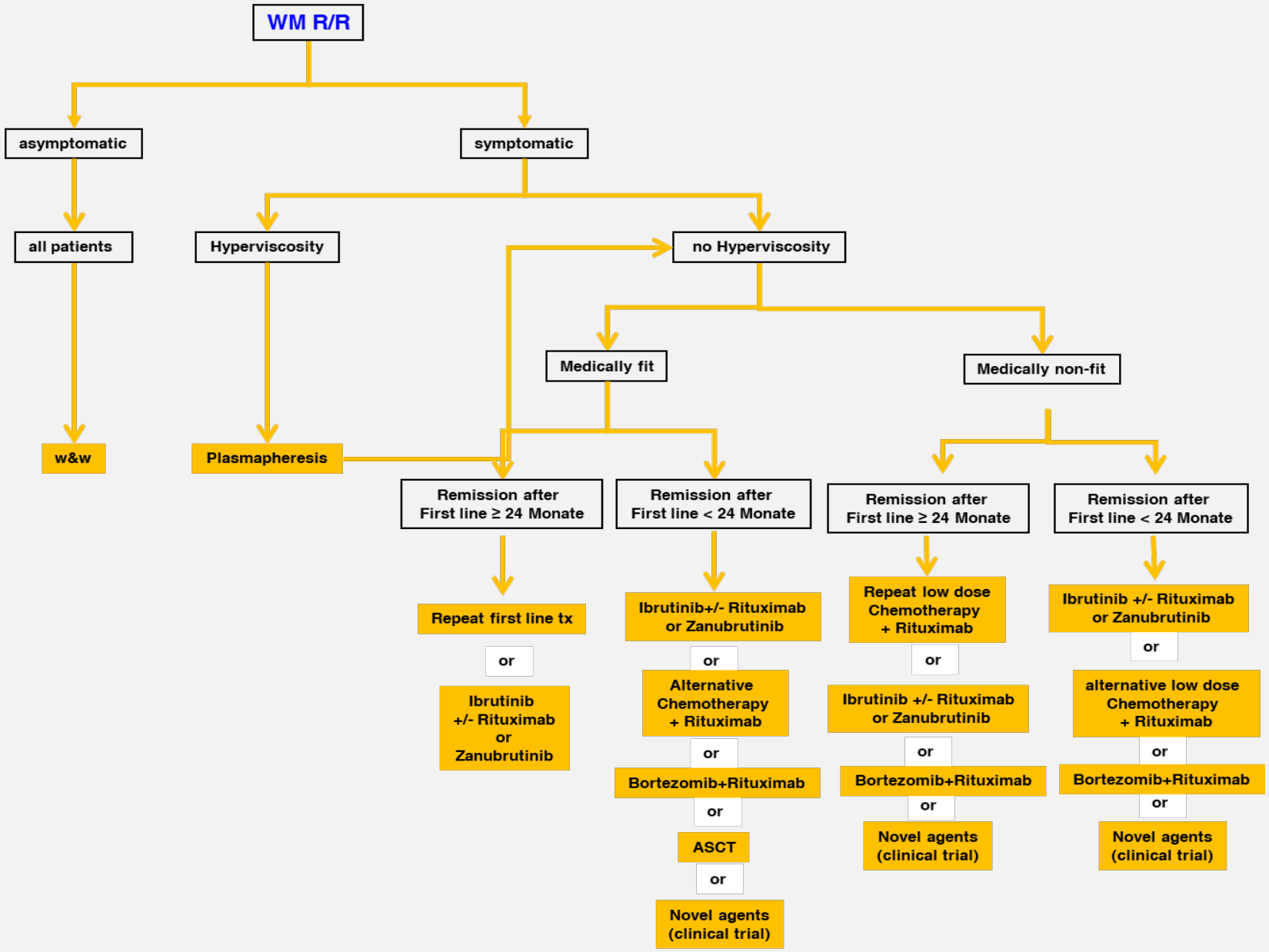
Onkopedia-Leitlinie zur Rezidivtherapie (01/22)



Vielen Dank!