

Mannheimer Onkologie Praxis

Dr. Phil nat. Jürgen Brust
Prof. Dr. Manfred Hensel
Dr. Nicolai Härtel
Dr. med. Christoph Plöger
PD. Dr. med. Roger Vogelmann

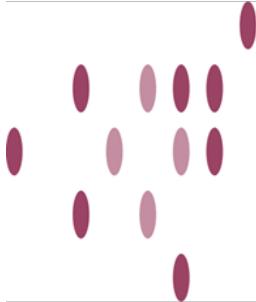


Onkologische Tagesklinik
am Diakonissenkrankenhaus
OTD

Makroglobulinämie Waldenström

Was gibt es Neues?

Prof. Dr. Manfred Hensel



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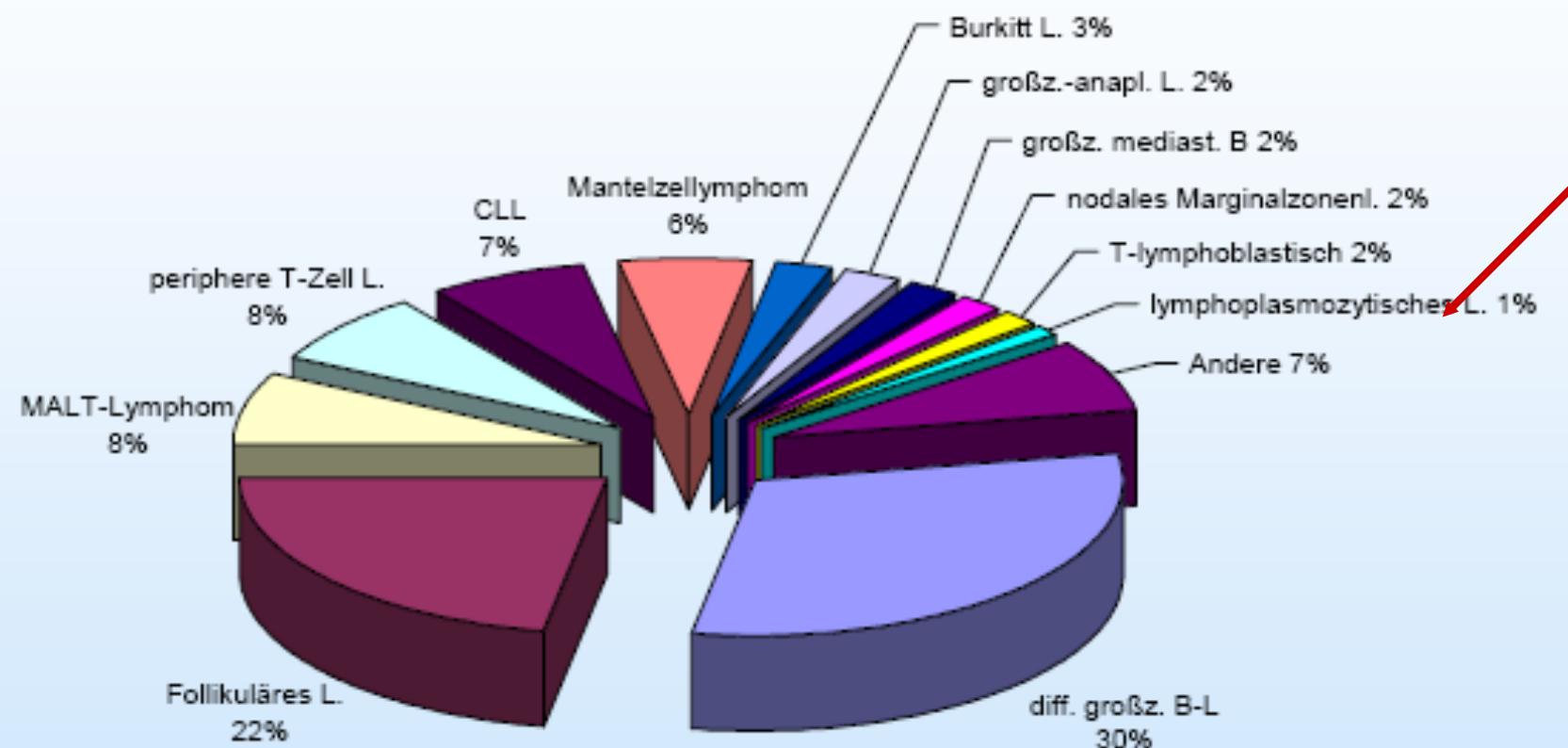
11th International Workshop on Waldenstrom's Macroglobulinemia

Thursday, October 27 through Sunday, October 30, 2022

Agenda

- Ein paar Grundlagen
 - Therapieprinzipien
 - wann?
 - wie
 - warum?
- Kongress
 - Programm
 - Daten zu bekannten Therapien
 - Blick in die Zukunft: neue Substanzen und Verfahren

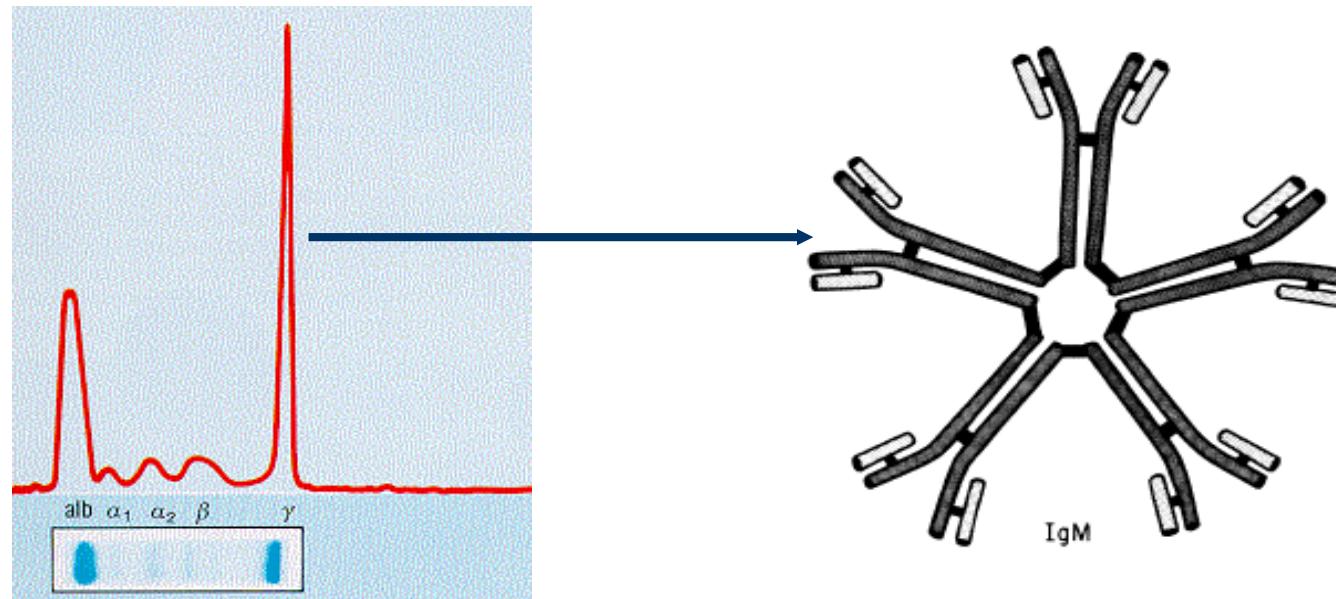
WHO-Klassifikation maligner Lymphome: häufige Entitäten (ohne Hodgkin-Lymphom und Myelom)





M. Waldenström: *Definition*

Knochenmarkinfiltration durch
lymphoplasmozytisches Lymphom
+
Monoklonales IgM



Hensel et al., 2007, Deutsches Ärzteblatt

Wann Therapiebeginn?

- Kein Vorteil für frühzeitige Therapie
- Asymptomatische Patienten sollten nur beobachtet werden
- IgM alleine ist nicht entscheidend
- einen definierten Grenzwert gibt es nicht (6000 mg/dl ?)

- Beginn erst bei:
 - Auftreten von Symptomen, z.B. Nachschweiß
 - Abfall Hb-Wert < 10 g/dl, Thrombo < 100/nl
 - Schwere Neuropathie
 - symptomatische Milzvergrößerung
 - große Lymphome
 - starker Gewichtsverlust
 - symptomatische Hyperviskosität
 - Amyloidose
 - Kryoglobulinämie
 - Kälteagglutininkrankheit

Ziel der Behandlung?

- Besserung der Symptome
- Normalisierung der Blutwerte
- Normalisierung von LK und Milz
- Verbesserung der Lebensqualität
- Verlängerung der Lebenserwartung

Welche Therapieform?



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- Chemoimmuntherapie:
 - Rituximab-Bendamustin (R-B)
 - Rituximab-Cyclophosphamid-Dexamethason (RCD)
- Kinaseinhibitoren
 - Ibrutinib (Imbruvica[®])
 - Zanubrutinib (Brukinsa[®])
 - Acalabrutinib, Venetoclax
- Neue Substanzen
 - bispezifische Antikörper
 - CAR-T-Zellen

Deutsche Leitlinien



Mannheimer Onkologie Praxis



onkopedia leitlinien



COVID-19
bei Krebspatienten



Inhaltsverzeichnis

Zusammenfassung

Grundlagen

Definition und Basisinfor-
mation

Epidemiologie

Pathogenese

Risikofaktoren

Morbus Waldenström (Lymphoplasmozytisches Lymphom)

Hinweise zu COVID-19 finden Sie in der [COVID-19-Leitlinie](#)

ICD-10: C88.0

Stand: Januar 2022

Dies ist die aktuell gültige Version des Dokuments

Erstellung der Leitlinie: [Regelwerk](#) [Interessenkonflikte](#)

Autoren: Christian Buske, Dominik Heim, Michael Herold, Philipp Bernhard Staber, Martin Dreyling

Vorherige Autoren: Mathias J. Rummel

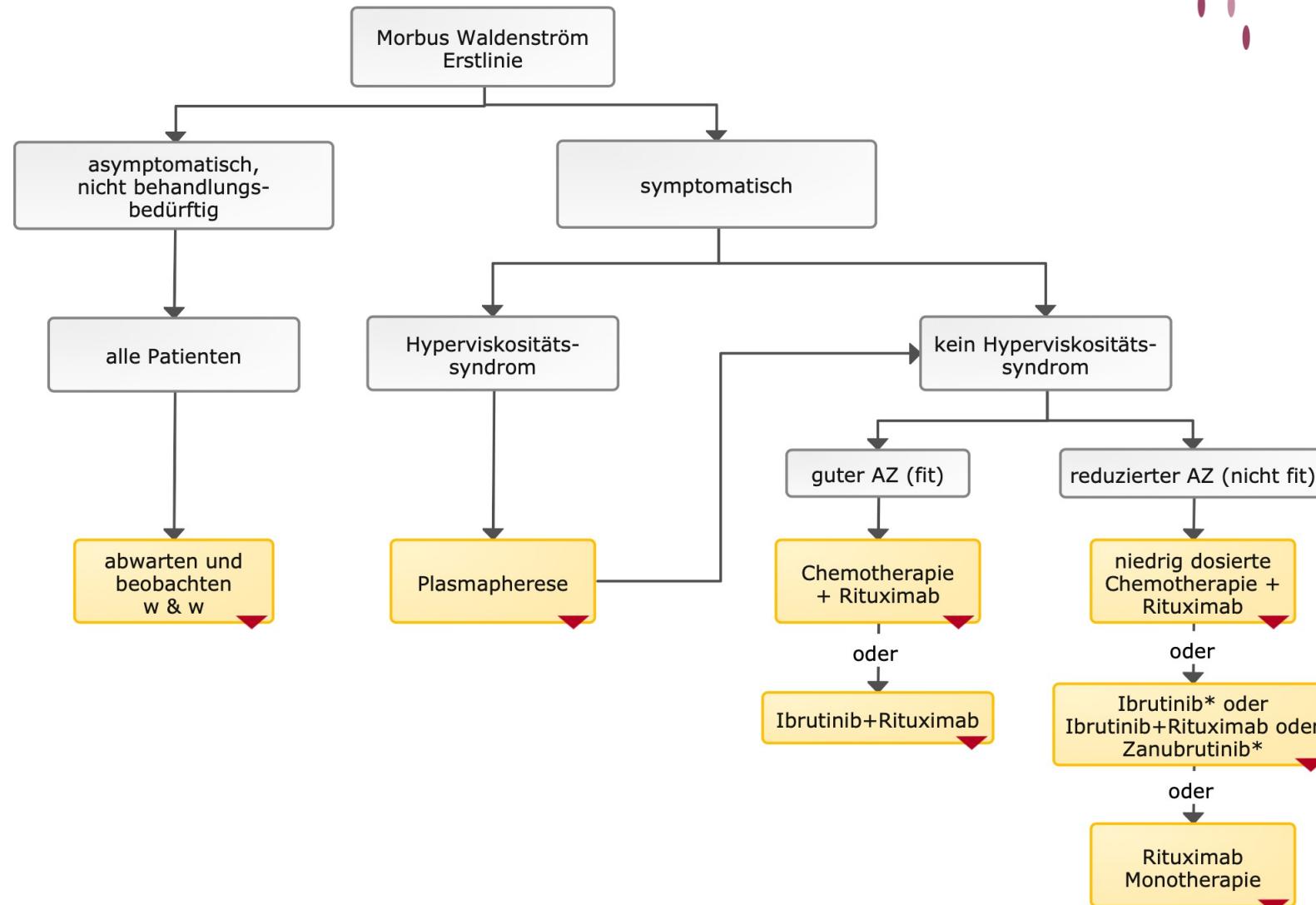
Beteiligte
Fachgesellschaften:



Primärtherapie



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Legende: — kurative Intention; — palliative Intention;

AZ – Allgemeinzustand, * nicht geeignet für Immunchemotherapie

Agenda

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 - wann?
 - wie
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 - Blick in die Zukunft: neue Substanzen und Verfahren



Donnerstag, [17:45-18:00] Keynote Lecture

What the genomics of WM tells us about its curability

Keynote Speaker: Steve Treon, Dana Farber, USA

Conclusions

- Activating MYD88 mutations drive multiple growth and survival pathways, many of which are on path with MYD88's function for innate immune response.
- While BTK and IRAK1/IRAK4 are key components of canonical NFkB signaling and pharmacologically important targets, alternate survival signaling likely accounts for the lack of CRs clinically.
- ERK is a critical mediator of tumor survival, and tumor-tumor communication leading to pro-survival signaling and drug resistance cues to ibrutinib.
- Aberrant HCK expression mediated by mutated MYD88 and drives broad pro-survival signaling including BTK, ERK, and SYK.
- HCK inhibitors may represent more optimal agents to extinguishing more broadly pro-survival circuitry mediated by MYD88.

Friday, 28.10.22

[9:15-10:45] Session VIII

Chemoimmunotherapy

Veronique Leblond, Jorge Castillo [Chairs]

B-RCD vs. RCD Randomized Trial in WM

Pierre Morel, Centre Hospitalier Universitaire Amiens Picardie, France

RCD vs BCD Randomized Trial

Lugui Qiu, National Clinical Research Center for Blood Diseases, China

Bendamustine/Rituximab: Dose Intensity and Patient Outcomes

Suzanne Arulogun, UC London Hospitals NHS, UK

FILO Bendamustine Rituximab Study

Véronique Leblond, Hôpital Pitié Salpêtrière, France

STIL Maintenance Rituximab

Mathias Rummel, University of Giessen, Germany

BRB: Bendamustine, Rituximab, Bortezomib Study: Fondazione Italiana Linfomi Study

Giulia Benevolo, University of Torino, Italy

Friday, 28.10.22



Bendamustine/Rituximab: Dose Intensity and Patient Outcomes

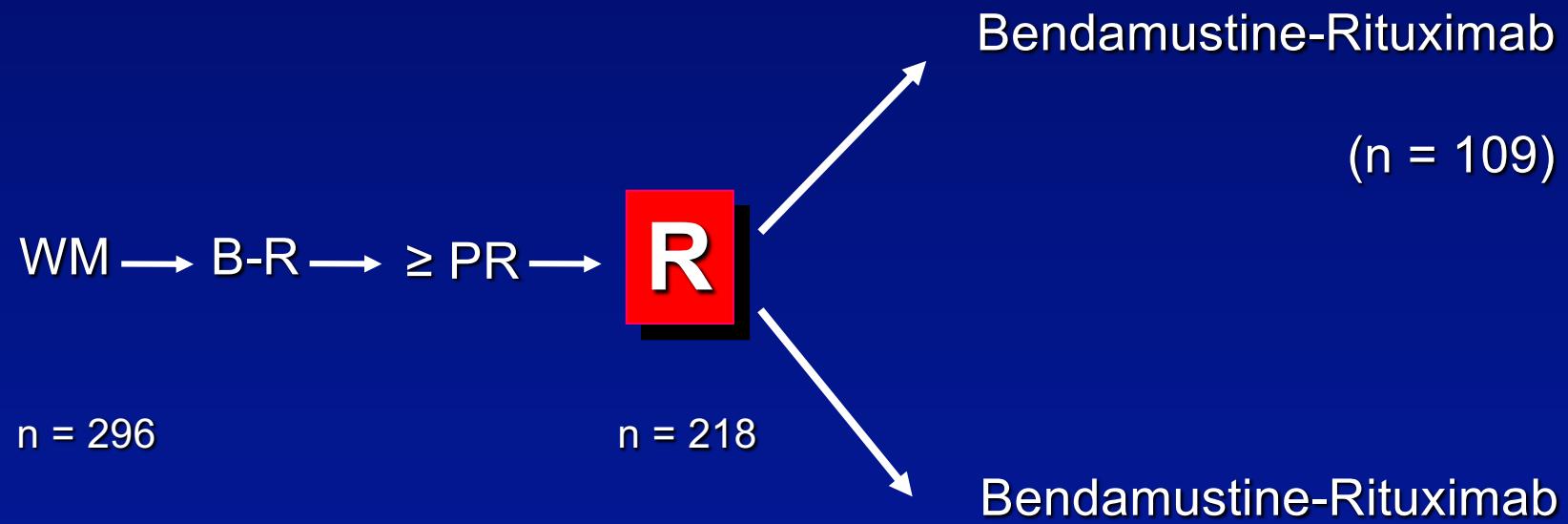
Suzanne Arulogun, UC London Hospitals NHS, UK

Answers and conclusions

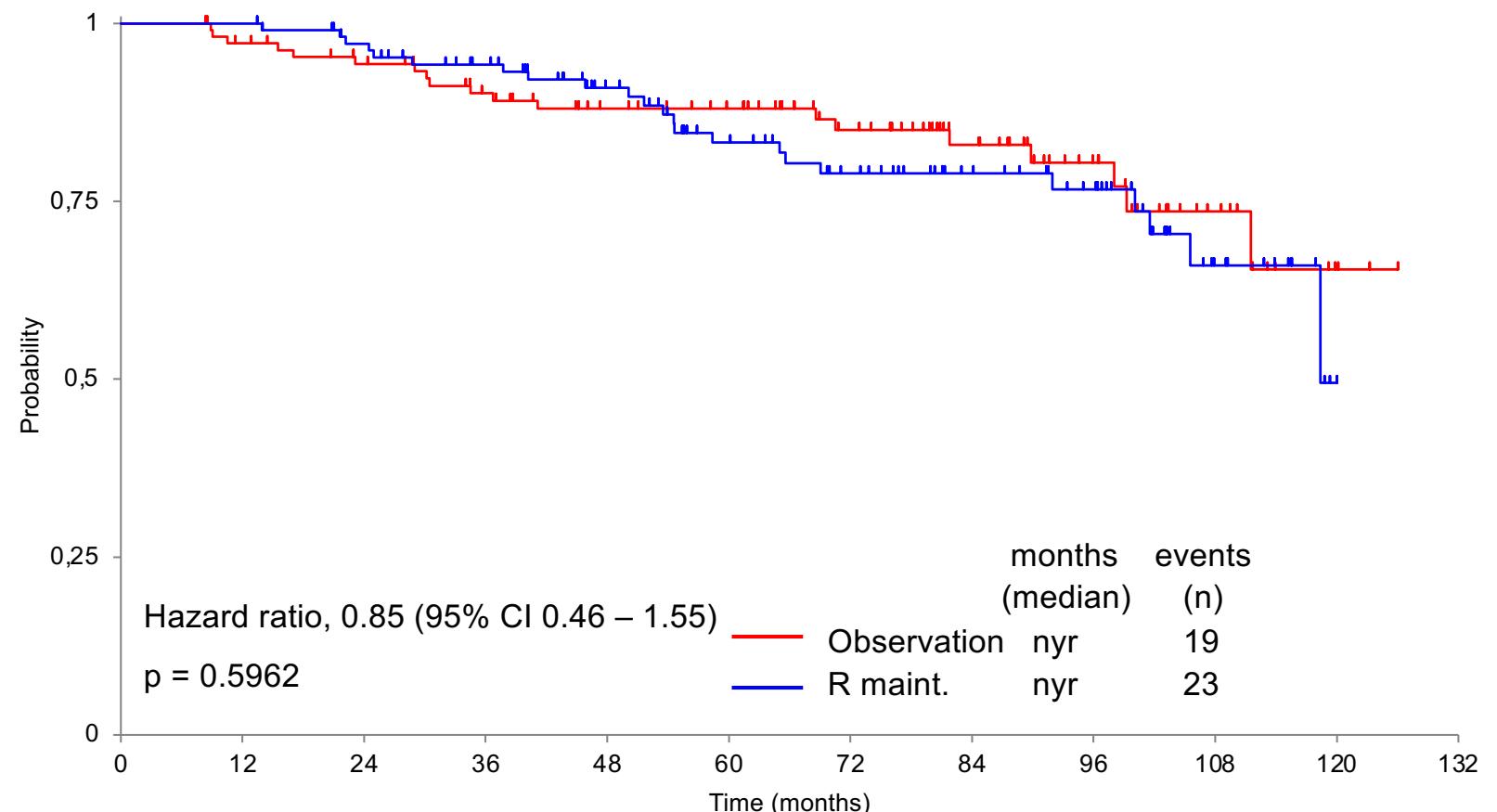
- BR is a tolerable, fixed duration option in WM and produces deep and durable responses, especially when used frontline
- Superior response, PFS and OS are seen in the frontline setting
- Deeper response (CR/VGPR) confers survival advantage
- Frontline: Bendamustine dose of $\geq 1000\text{mg}/\text{m}^2$ ($90\text{mg}/\text{m}^2$ for 6 cycles) produces best PFS
- Relapse: Bendamustine dose of $70\text{mg}/\text{m}^2$ for 6 cycles (or $90\text{mg}/\text{m}^2$ for 4 cycles) appears sufficient for best PFS

B-R + Watch & Wait vs. B-R + 2 years Rituximab

StiL NHL 7-2008 - MAINTAIN



Lebensdauer nach Beginn der Erhaltungstherapie



Pts at risk												
Observ.	109	103	96	86	75	69	55	40	26	12	3	
R maint.	109	109	101	91	75	61	51	40	32	12	12	1

Erhaltungstherapie nicht Standard!

Friday, 28.10.22



STIL Maintenance Rituximab

Mathias Rummel, University of Giessen, Germany

Kernaussagen:

- B-R sehr wirksam
- B-R Wirkdauer 7-10 Jahre Median (PFS) mit/ohne Erhaltung
- Erste Wahl!

A photograph of a presentation slide titled "Summary and conclusion" in green text at the top left. The slide contains a bulleted list of findings in white text on a blue background. The text discusses the high activity of B-R in Waldenström patients, the lack of improvement in PFS or OS with R-maintenance, the median PFS of 69 months for B-R without maintenance, and the excellent disease control with a median PFS of 10 or 7 years with or without R-maintenance. It also notes that age (>65 yrs) appears to be a critical factor for a potential benefit of R-maintenance, and concludes by recommending B-R as 1st-line treatment for WM based on the data.

Summary and conclusion

- High activity of B-R in Waldenström patients confirmed
- R-maintenance did not improve PFS or OS after B-R
- B-R without R-maintenance achieves a median PFS of 69 months (6 yrs)
- Patients responding to B-R have an excellent disease control with a median PFS of 10 or 7 years with or without R-maintenance
- Exploratory subgroup analyses suggest that age (>65 yrs) appears to be a critical factor for a potential benefit of R-maintenance
- Based on our data we can recommend B-R as 1st-line treatment for WM

Welche Therapieform?



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- Chemoimmuntherapie:
 - Rituximab-Bendamustin (R-B)
 - Rituximab-Cyclophosphamid-Dexamethason (RCD)
- Kinaseinhibitoren
 - Ibrutinib (Imbruvica[©])
 - Zanubrutinib (Brukinsa[©])
 - Acalabrutinib, Venetoclax



Friday, 28.10.22

[13:30-14:30] Session X

BTK-Inhibitors II

Alessandra Tedeschi, Constantine Tam [Chairs]

Long Term Follow-up-Acalabrutinib Phase II

Roger Owen, Leeds Hospital NHS Trust, UK

Long Term Follow-Up Zanubrutinib-Phase II

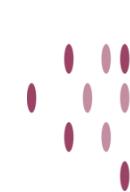
Judith Trotman, University of Sydney, Australia

Phase II Zanubrutinib in relapsed/refractory WM: Chinese experience

Lugui Qui, National Clinical Research Center for Blood Diseases, China

Phase II study of Zanubrutinib, Ixazomib and Dexamethasone

Shuhua Yi, Institute of Hematology and Blood Diseases Hospital
Chinese Academy of Medical Sciences



Friday, 28.10.22

[14:30-15:30] Session: XI

Plenary Session II

M.J. Kersten, Christian Buske [Chairs]

WM004 Final results of the Phase I/II Hovon 124/ECWM-R2 Study including 2 year rituximab maintenance after induction with ixazomib, rituximab and dexamethasone in relapsed Waldenstrom's Macroglobulinemia.

Karima Amaador, UMC Medical Center, University of Amsterdam, Netherlands

WM042 ASPEN: Long term follow-up results of a Phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenstrom Macroglobulinemia.

Meletios Dimopoulos, University of Athens, Greece

WM041 ASPEN Biomarker analysis: Response to BTK inhibitor treatment in patients with Waldenstrom Macroglobulinemia harboring CXCR4, TP53, and TERT mutations.

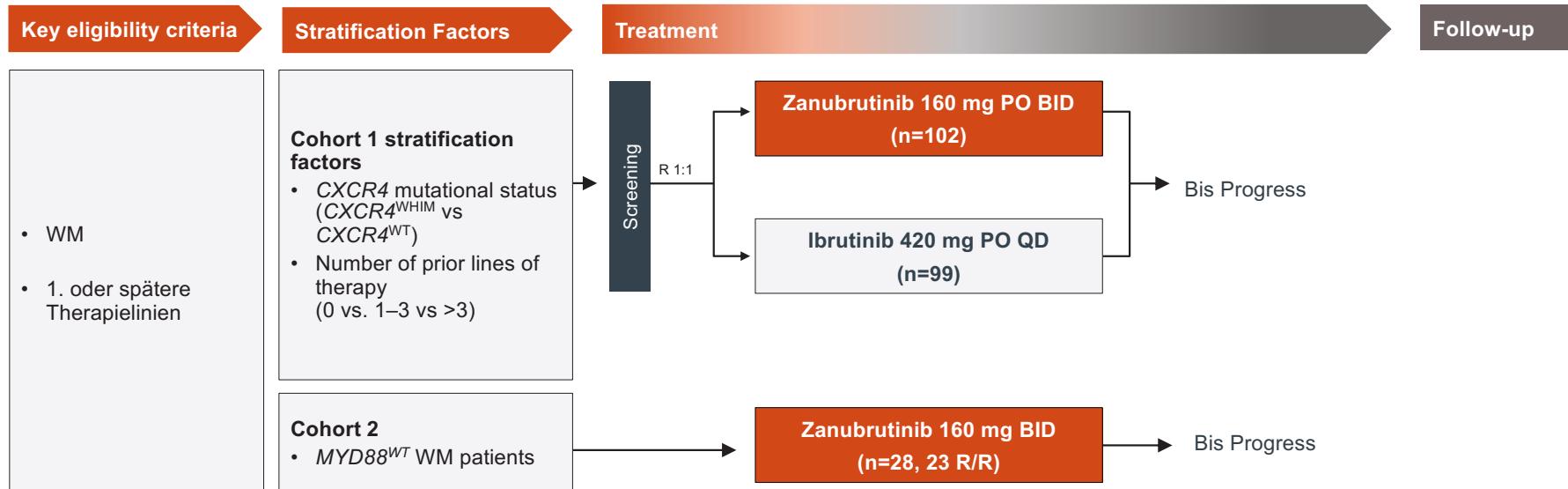
Constantine Tam, Peter MacCallum Cancer Center, Australia

WM024 Identification of robust predictors for ibrutinib response by multi-omic genomics in MYD88 mutated Waldenstrom's Macroglobulinemia.

Kris Richardson, Dana Farber Cancer Institute, USA

ASPEN Studie

Phase 3



Ergebnisse:

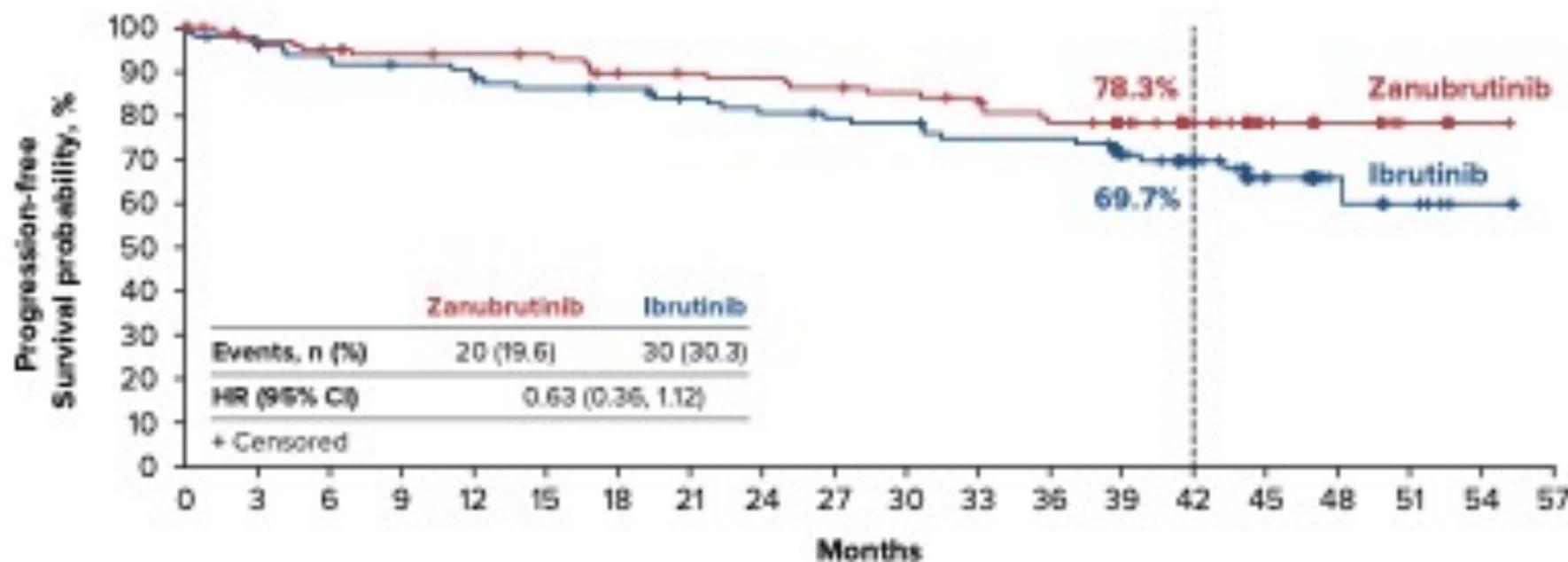
- Ibrutinib und Zanubrutinib ähnlich effektiv
- höhere Rate an VGPR, Gesamtansprechen gleich
- Dauer bis zum Rückfall in beiden Armen fast gleich
- leicht verminderte Rate an Nebenwirkungen, insbesondere Vorhofflimmern (18 vs.3%) und Blutungen (60 vs. 50%)



WM042 ASPEN: Long term follow-up results of a Phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenstrom Macroglobulinemia.

Meletios Dimopoulos, University of Athens, Greece

A. Progression-Free Survival*



No. of Patients at Risk:

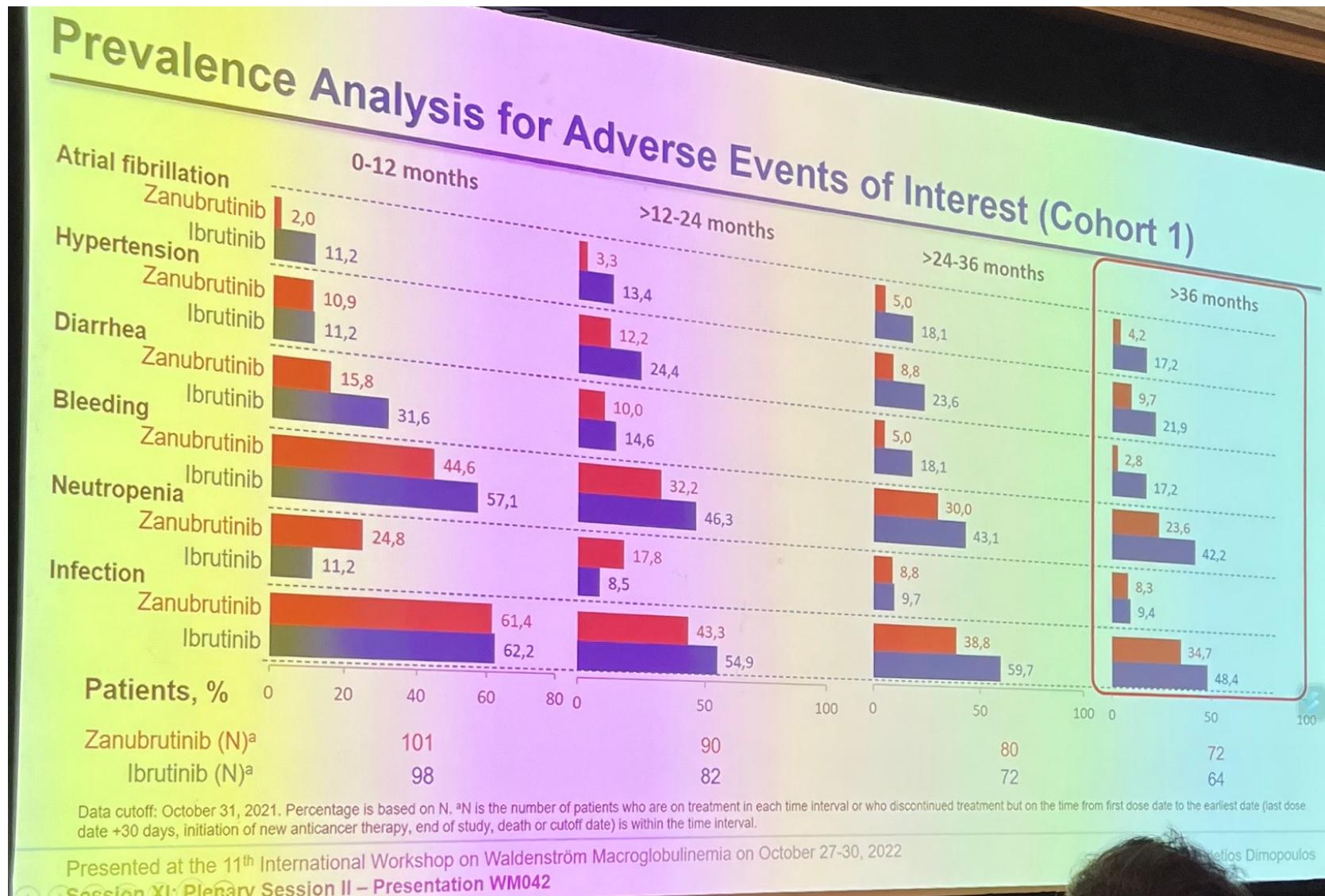
Zanubrutinib	102	96	93	90	89	88	82	81	80	78	76	74	68	60	43	25	15	8	1	0
Ibrutinib	99	92	88	85	83	79	78	74	71	69	68	64	64	52	41	27	11	6	2	0

last cutoff: October 31, 2021.

by investigator assessment.

WM042 ASPEN: **Nebenwirkungen**

Meletios Dimopoulos, University of Athens, Greece



Auswirkung von Dosisreduktion Ibrutinib auf die Krankheit

Shayna Sarosiek, Dana Farber Cancer Institute, US

Conclusions

- $\frac{1}{4}$ of patients with WM required a dose reduction
- More dose reductions in women and in those ≥ 65 years
- Most patients (65%) had improvement in symptoms with dose reduction
- Most patients (73%) had maintained/improved hematologic response

Falls Ibrutinib nicht vertragen wird: Zanubrutinib?

Mazyar Shadman, Fred Hutchinson Cancer Res Center, USA

CONCLUSIONS

- Consistent with a more selective BTK inhibition, zanubrutinib demonstrated few AEs associated with off-target kinase activity in patients with WM intolerant to ibrutinib and/or acalabrutinib
- Most AEs that led to ibrutinib and/or acalabrutinib treatment discontinuation did not recur with zanubrutinib
- All efficacy evaluable patients with WM maintained (n=1; 9.1%) or improved (n=10; 90.9%) their disease status from baseline on study entry
- Our safety data demonstrate that zanubrutinib was well tolerated in patients with WM previously intolerant to ibrutinib and/or acalabrutinib
 - Few patients discontinued zanubrutinib due to AEs
 - Cardiovascular AEs were less common in patients receiving zanubrutinib compared with ibrutinib
- Designed to minimize side effects associated with off-target binding, zanubrutinib is a viable treatment option for patients with WM intolerant to other BTK inhibitors

Samstag, 29.10.22, Tag der Debatten!

[8:00-11:15] Session XIII

Great Debates in WM

Eva Kimby, Jesus San Miguel [Chairs]

[8:00-8:30] Great Debate I

Should we treat smoldering WM? -No

Prashant Kapoor, Mayo Clinic, USA

Should we treat smoldering WM? -Yes

Irene Ghobrial, Dana Farber Cancer Institute

[8:30-9:00] Great Debate II

Should BTK-I or Benda-R be the standard frontline induction regimen? -for Benda-R

Christian Buske, University Hospital Ulm, Germany

Should BTK-I or Benda-R be the standard frontline induction regimen? -for BTK-I

Meletios Dimopoulos, University of Athens, Greece

[9:00-9:45] Great Debate III

Does the choice of BTK-inhibitor matter? -for Ibrutinib

Ranjana Advani, Stanford University Medical Center, USA

Does the choice of BTK-inhibitor matter? -for Acalabrutinib

Roger Owen, Leeds Hospital NHS Trust, UK

Does the choice of BTK-inhibitor matter? -for Zanubrutinib

Judith Trotman, University of Sydney, Australia

Sollen asymptomatische Patienten schon behandelt werden?



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[8:00-8:30] Great Debate I

No

Prashant Kapoor, Mayo Clinic, USA

smouldering MW hat normale Lebenserwartung,
Kein Überlebensvorteil durch frühe Therapie,

Yes

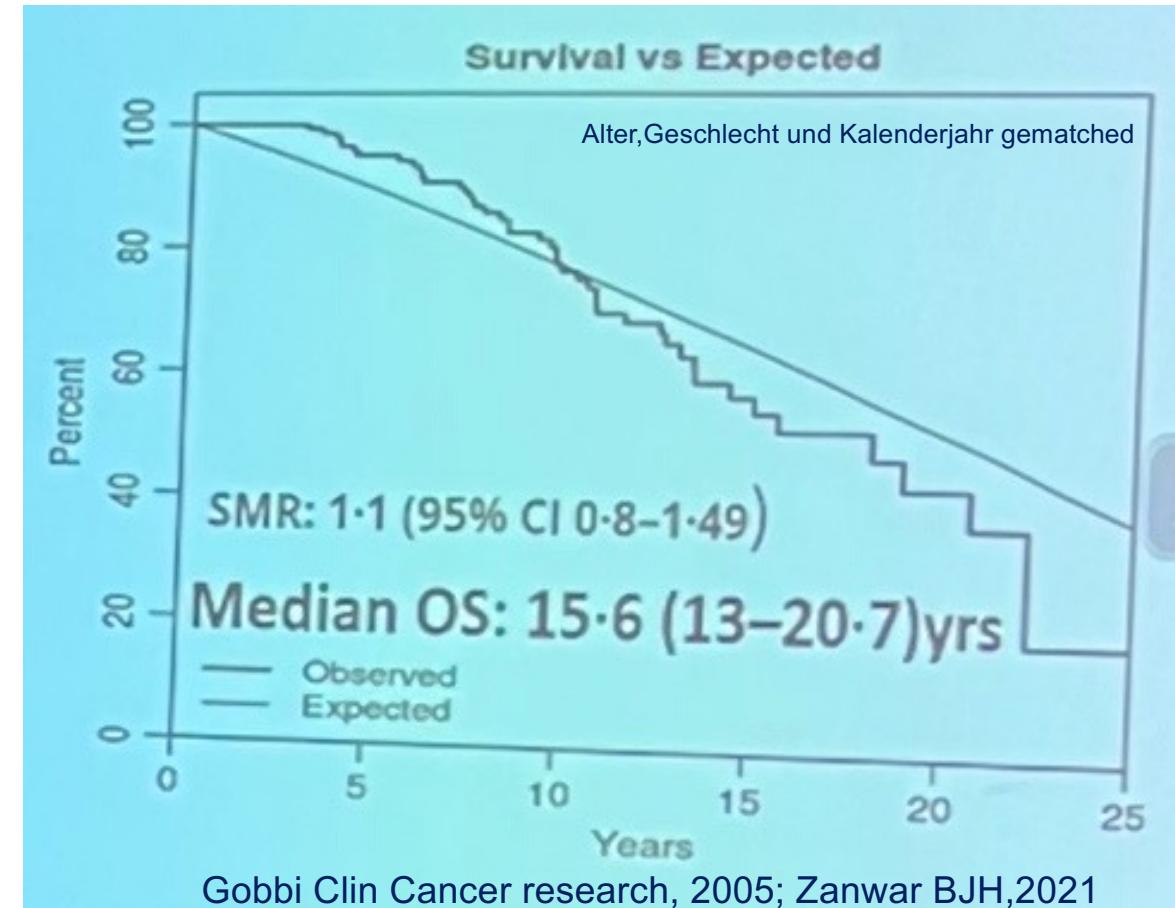
Irene Ghobrial, Dana Farber Cancer Institute

früh die besten Chancen auf Heilung
mit den besten Medikamenten:
bispezifische Antikörper,
CAR-T-Zellen

Abstimmung:

Gewinnerin: Kapoor: Abwarten

Aber: Ghobrial: Trials for early treatment



BTK-I oder Benda-R die beste Erstlinientherapie?



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[8:30-9:00] Great Debate II

für BTK-I

Meletios Dimopoulos, University of Athens, Greece#

Conclusions

- BTK-I and BR have at least similar efficacy but ...
- BTKi-based therapy is a reasonable approach for patients who
 - Have bulky disease
 - Have poor bone marrow reserve / cytopenias
 - Need immediate reduction of IgM
 - Are at risk for “IgM flare”
 - Are of advanced age
 - Prefer oral therapy
 - Do not wish to receive chemotherapy
 - Have no objections to continuous therapy

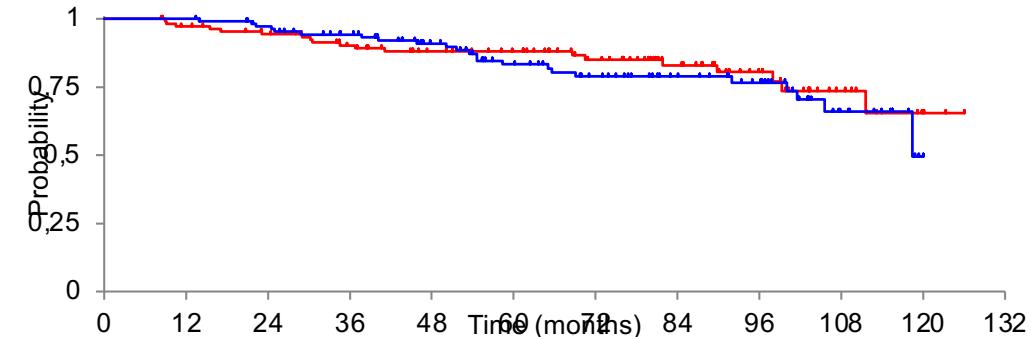
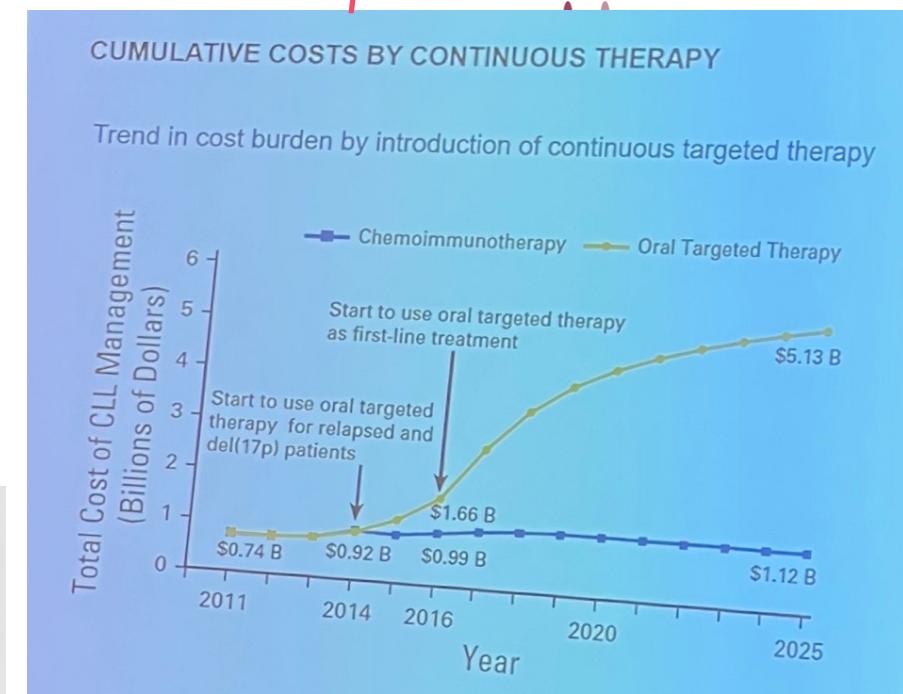
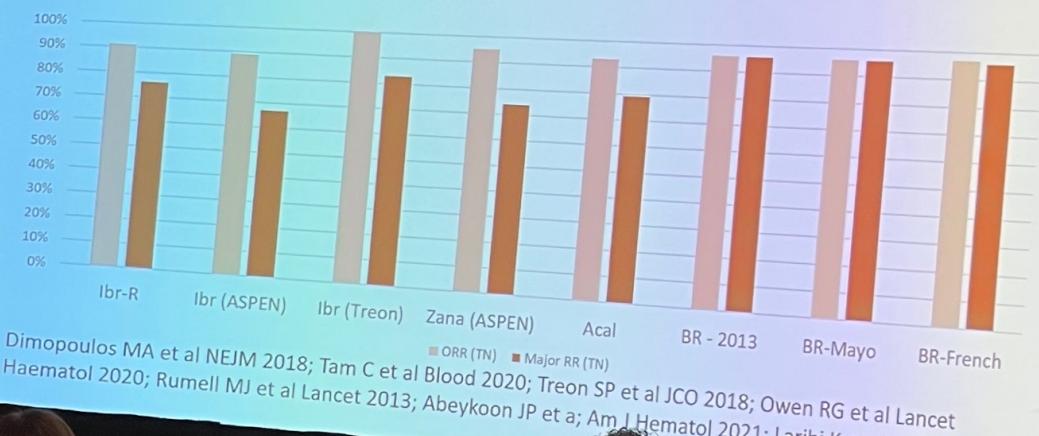
BTK-I oder Benda-R die beste Erstlinientherapie?

für Benda-R

Christian Buske, University Hospital Ulm, Germany

treatment-related factors to consider: activity

BTK-i based therapy vs Benda-R (TN) (Best response)



Abstimmung:
Gewinner: Buske (R-Benda)



Samstag, 29.10.22

[11:15-12:15] Session XIV

Novel Treatment Approaches to WM-Clinical I

Sheeba Thomas, Moshe Gatt [Chairs]

Venetoclax in combination with ibrutinib for WM

Jorge Castillo, Dana Farber Cancer Institute, USA

Zu toxisch, Studienabbruch

Targeting mutated CXCR4 in WM

Steven Treon, Dana Farber Cancer Institute, USA

Vielversprechend, ganz neue Substanzen

Obinutuzumab and Idelalisib in WM

Véronique Leblond, Hôpital Pitié Salpêtrière, France

m.E. keine Zukunft

Acalabrutinib and Rituximab for WM and IGM RD PN

Shayna Sarosiek, Dana Farber Cancer Institute, USA

Studie bei Polyneuropathie, startet gerade



Samstag, 29.10.22

[14:00-15:00] Session XVI

Novel Treatment Approaches to WM-Clinical III

Bispecifics in WM-CD3XCD20 RGN1979

Stephen Ansell, Mayo Clinic, USA

Phase II Study of Loncastuximab in WM

Shayna Sarosiek, Dana Farber Cancer Institute, USA

Idiotype DNA Vaccine Therapy for WM

Sheeba Thomas, MD Anderson, USA

CD20 CAR-T therapy for WM and other B-NHLs

Mazyar Shadman, Fred Hutchinson Cancer Res Center, USA

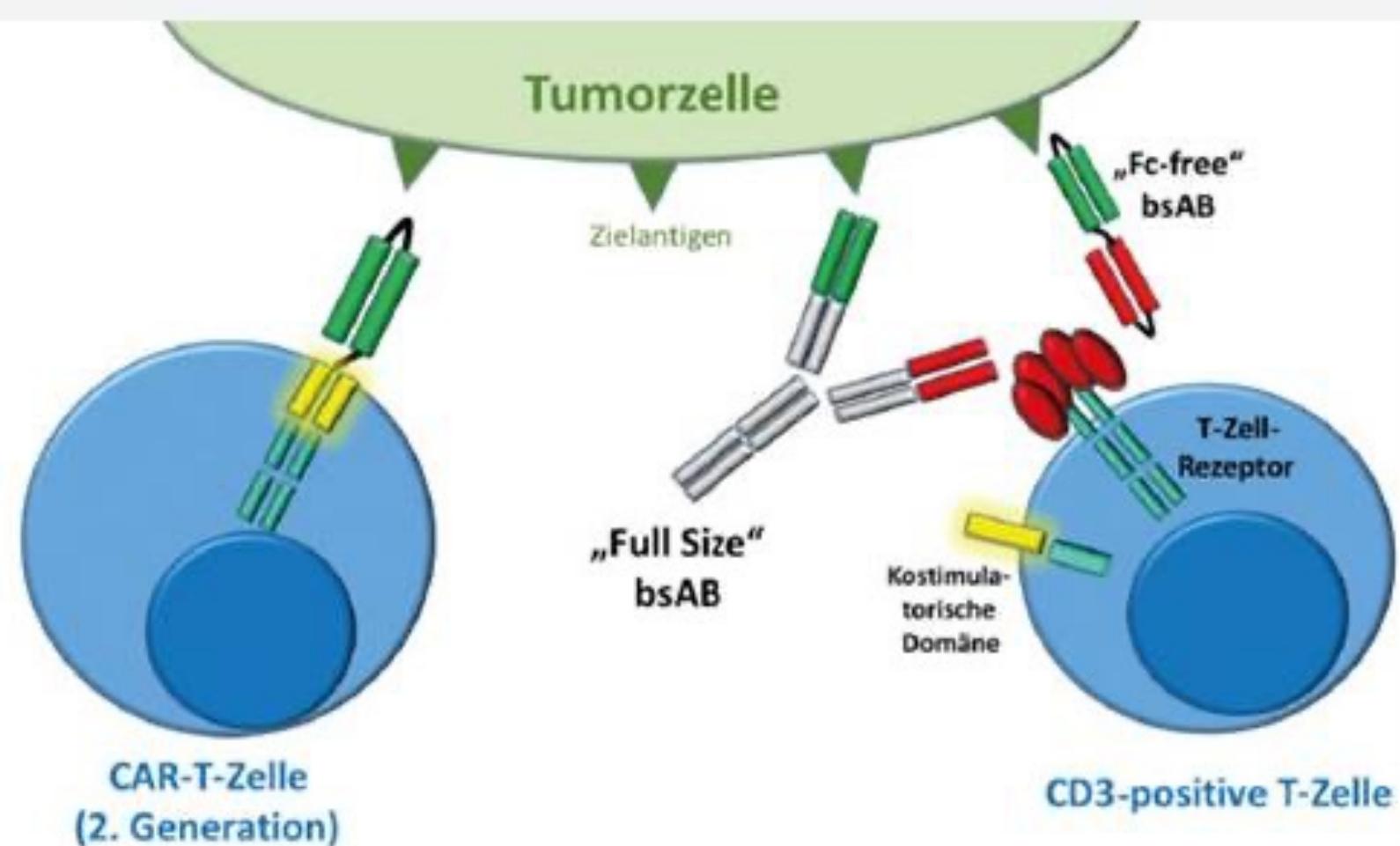
Bispezifische Antikörper und CAR-T-Zellen



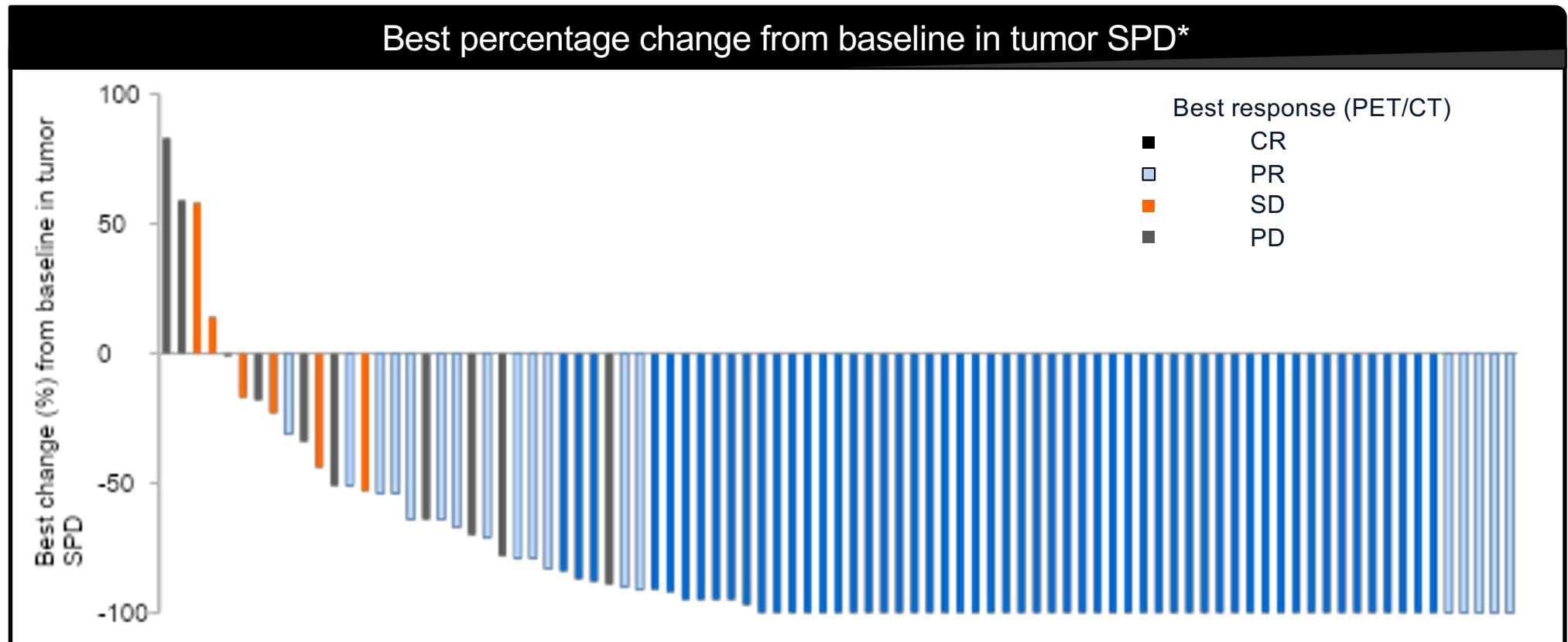
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Trillium GmbH



Anti-tumor efficacy



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



Bispecifics in WM-CD3XCD20 RGN1979

Stephen Ansell, Mayo Clinic, USA

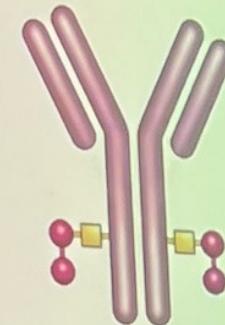
Conclusions

- Data on CD20 x CD3 bispecific antibodies in patients with Waldenstrom macroglobulinemia are very limited
- Bispecific antibodies are effective in other indolent lymphomas, particularly follicular lymphoma
- They are generally well tolerated with low rates of severe CRS or ICANS
- Ramp up dosing mitigates many of the AEs
- Where bispecific antibodies will fit in the treatment of WM remains to be determined.

Phase II Study of Loncastuximab in WM

Shayna Sarosiek, Dana Farber Cancer Institute, USA

Loncastuximab tesirine



- Antibody drug conjugate
- Humanized monoclonal antibody directed against CD19, attached with a cleavable linker to SG3199, a pyrrolobenzodiazepine dimer cytotoxin
- Binds to the DNA minor groove and forms cytotoxic interstrand cross-links
- FDA approved for relapsed/refractory large B-cell lymphoma



Samstag, 29.10.22

[15:00-15:30] Keynote Lectures

Bi-specifics and Conjugated Antibodies: MM Experience

Keynote Speaker: Kenneth C. Anderson, Dana Farber Cancer Institute, USA

Bringing CART to WM: Which One?

Keynote Speaker: Nikhil Munshi, Dana Farber Cancer Institute, USA

Zusammenfassung



Mannheimer Onkologie Praxis

Dr. phil. nat. Jürgen Brust

Prof. Dr. Manfred Hensel

Dr. med. Christoph Plöger

Dr. med. Dieter Schuster

Onkopedia-Leitlinien sind aktualisiert und einsehbar

Mehrere sehr gute Therapien für die Primärtherapie zur Auswahl:

Rituximab und Bendamustin, 6 Zyklen, alle 4 Wochen
RCD
Ibrutinib +/- Rituximab
Zanubrutinib

Meine erste Wahl ist weiterhin Rituximab und Bendamustin

Bei Rückfall gegebenenfalls Wiederholung der Primärtherapie (bei langer Remissionsdauer, z.B. >3 J.) oder eine der anderen Substanzen

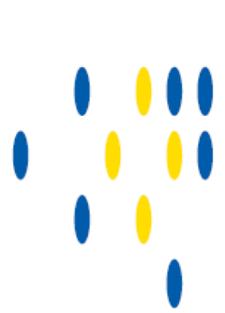
Viele neue Substanzen in der Erprobung

Wissenschaftliche Community ist sehr aktiv!



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Dr. med. Christoph Plöger
PD. Dr. med. Roger Vogelmann



Onkologische Tagesklinik
am Diakonissenkrankenhaus
OTD

Vielen Dank für Ihre Aufmerksamkeit