Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

63rd ASH Meeting 2021

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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Klinik für Innere Medizin II | Universitätsklinikum Schleswig-Holstein (Kiel)

Mantelzell Lymphom (MCL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2021 wird in Kooperation mit sechs unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	
Beratungs-/ Gutachtertätigkeit	Abbvie, Roche, Lilly, Gilead, Novartis, Incyte
Besitz von Geschäftsanteilen, Aktien oder Fonds	
Patent, Urheberrecht, Verkaufslizenz	
Honorare	
Finanzierung wissenschaftlicher Untersuchungen	Morphosys, Roche
Andere finanzielle Beziehungen	
Immaterielle Interessenkonflikte	

Themenauswahl

Verbesserung der Erstlinienbehandlung beim MCL

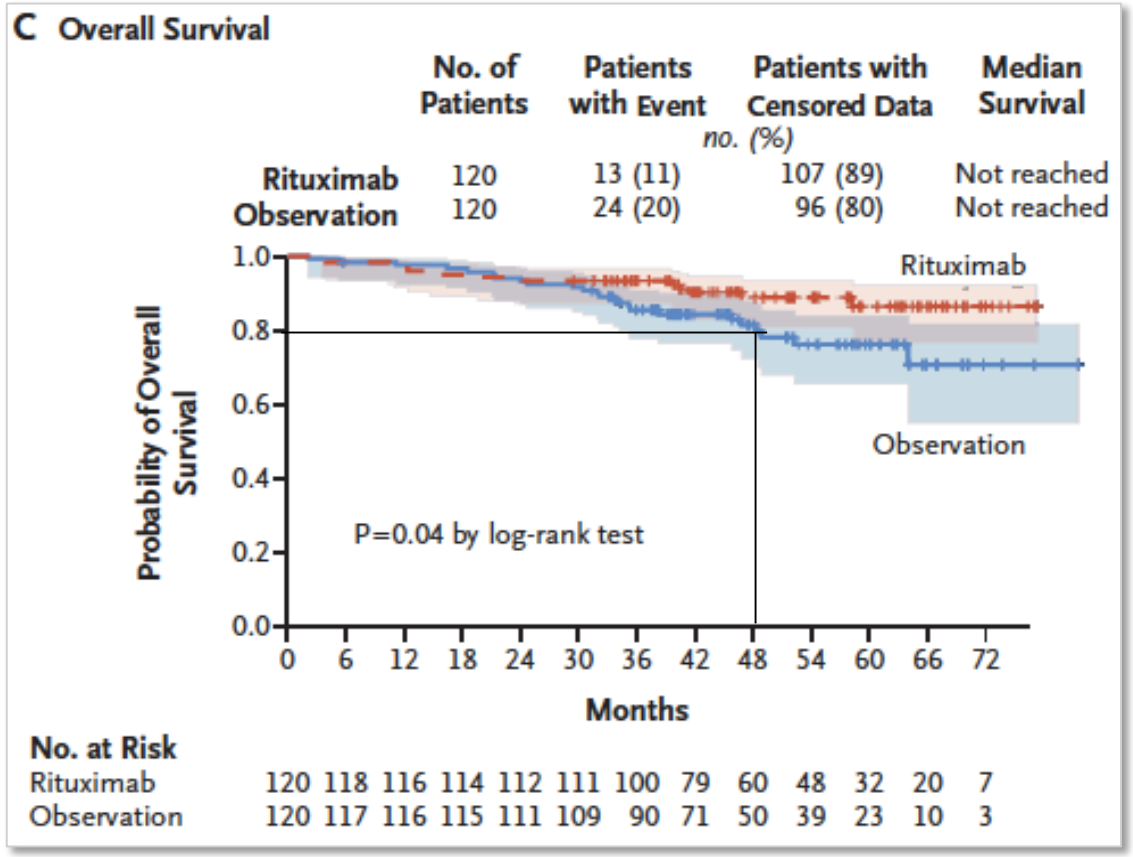
- Jüngere Patienten
- Ältere Patienten

Neue therapeutische Möglichkeiten im Rezidiv

- bispezifische Antikörper
- Nicht kovalente BTKi
- Pi3K Inhibitoren
- RWE Analyse CAR-T-Zellen

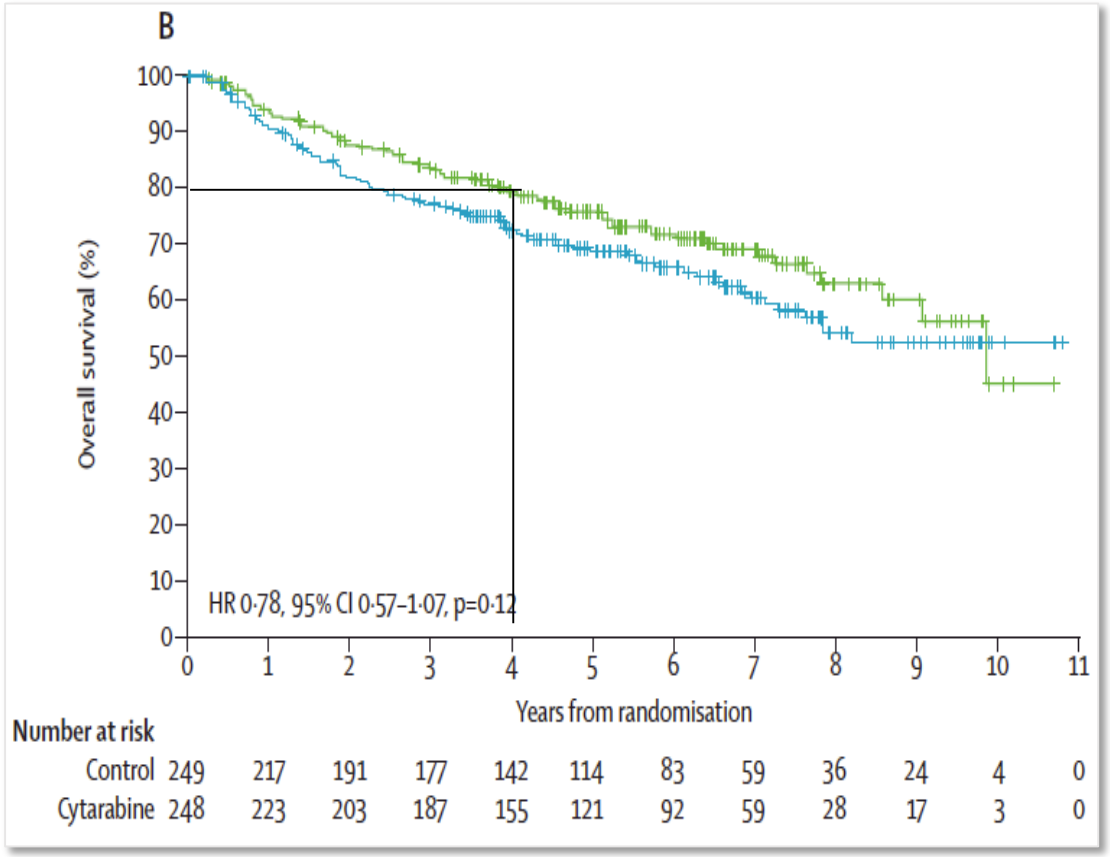
Standard of care for younger pats.: HiDAC induction, ASCT followed by Rituximab maintenance

Survival rates from Randomization after ASCT



OS 89% vs 80%

Le Gouill, NEJM 2017



Hermine Lancet 2016

Erstlinienbehandlung jüngerer Patienten mit MCL (transplantierbar)

#380 Addition of High-Dose Cytarabine to Immunochemotherapy before Autologous Stem-Cell Transplantation in Patients Aged 65 Years or Younger with Mantle Cell Lymphoma (MCL Younger): A Long-Term Follow-up of the Randomized, Open-Label, Phase 3 Trial of the European Mantle Cell Lymphoma Network

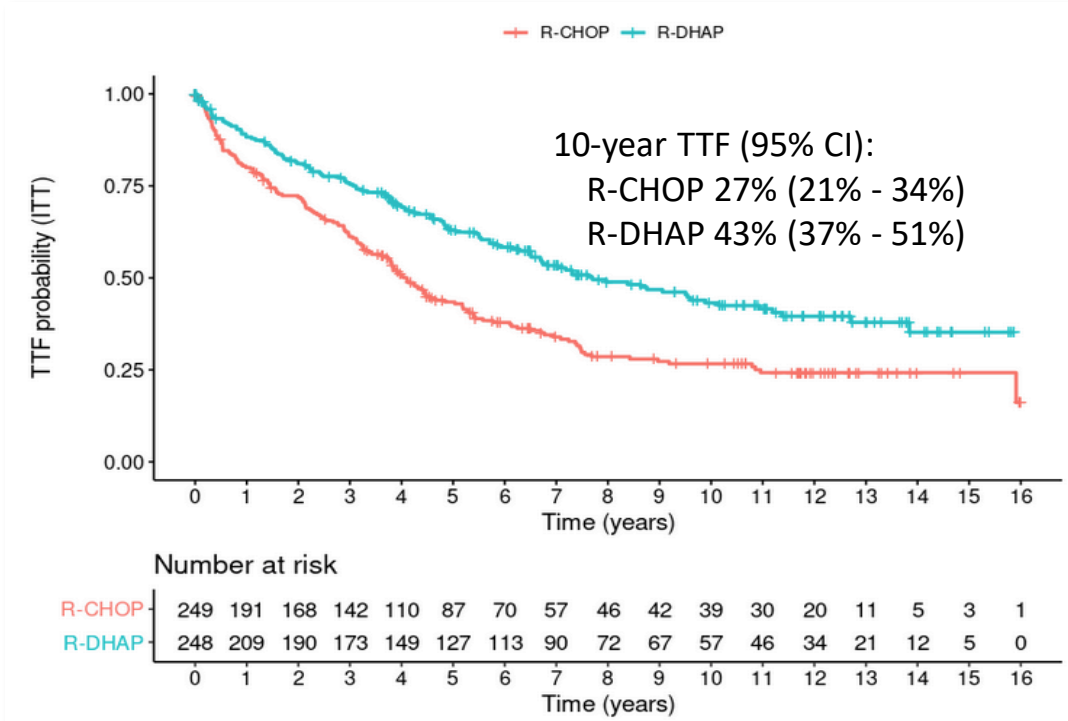
Olivier Hermine, Linmiao Jiang, Jan Walewski, André Bosly, Michal Szymczyk, Catherine Thieblemont, Christiane Pott, Gilles Salles, Pierre Feugier, Kai Hübel, Barbara Burroni, Wolfram Klapper, Michael Unterhalt, Eva Hoster, Martin Dreyling

Survival according to treatment arm

N=497 ITT

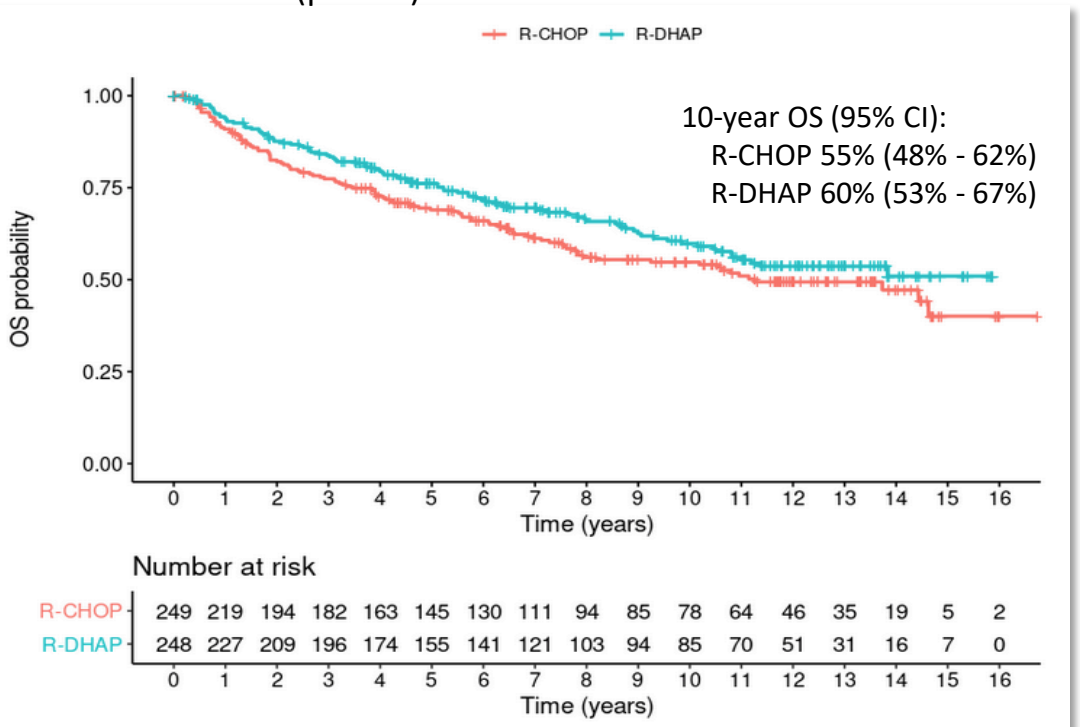
Median follow-up 10.6 years

P<0.0001, HR: 0.6



Median follow-up 11 years

Median OS was not reached in the R-DHAP arm vs 11.3 years in R-CHOP (p=0.12)

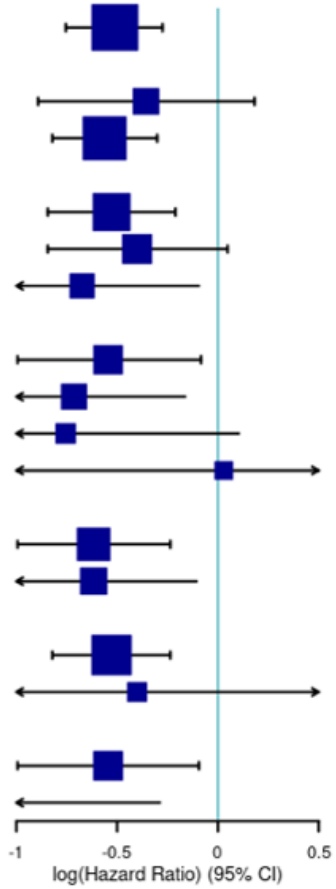


adjusted for MIPI score and Ki-67, OS was significantly superior in the R-DHAP arm (HR 0.60, 95% CI 0.41-0.87, p=0.0066)

Updated Results 2021 – Subgroups

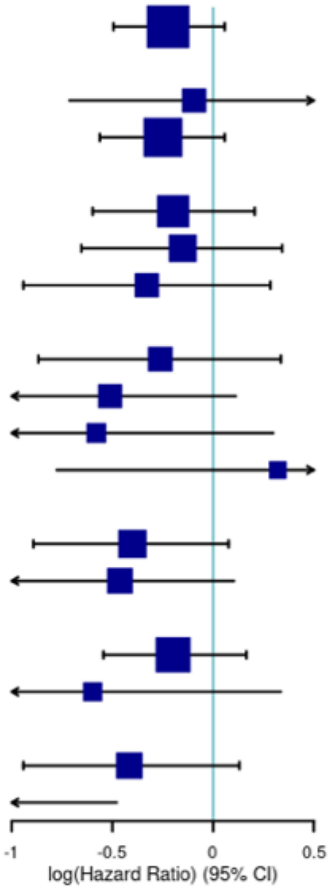
TTF

Subgroup	No. of patients	Hazard ratio (95% CI)
Full	497	0.60 (0.47 - 0.76)
Sex		
Female	105	0.70 (0.41 - 1.20)
Male	392	0.57 (0.44 - 0.74)
MIPI		
Low	307	0.59 (0.43 - 0.81)
Intermediate	119	0.67 (0.43 - 1.05)
High	71	0.51 (0.28 - 0.91)
MIPI-c (n=297)		
low	158	0.58 (0.37 - 0.92)
low intermediate	91	0.49 (0.28 - 0.85)
high intermediate	32	0.47 (0.20 - 1.11)
high	16	1.03 (0.36 - 3.00)
Ki-67 (n=297)		
low	211	0.54 (0.37 - 0.79)
high	86	0.54 (0.32 - 0.90)
Cytology (n=333)		
Non-blastoid	305	0.59 (0.44 - 0.79)
Blastoid	28	0.67 (0.27 - 1.69)
p53 expression (n=159)		
low	137	0.58 (0.37 - 0.91)
high	22	0.20 (0.05 - 0.75)

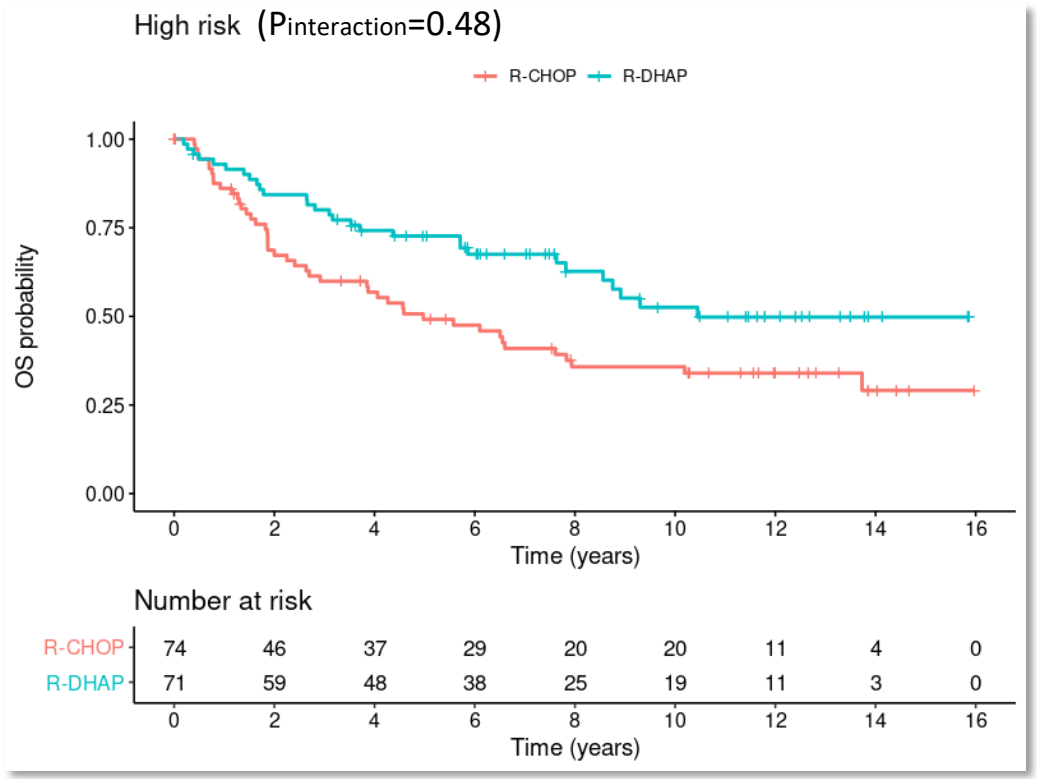


OS

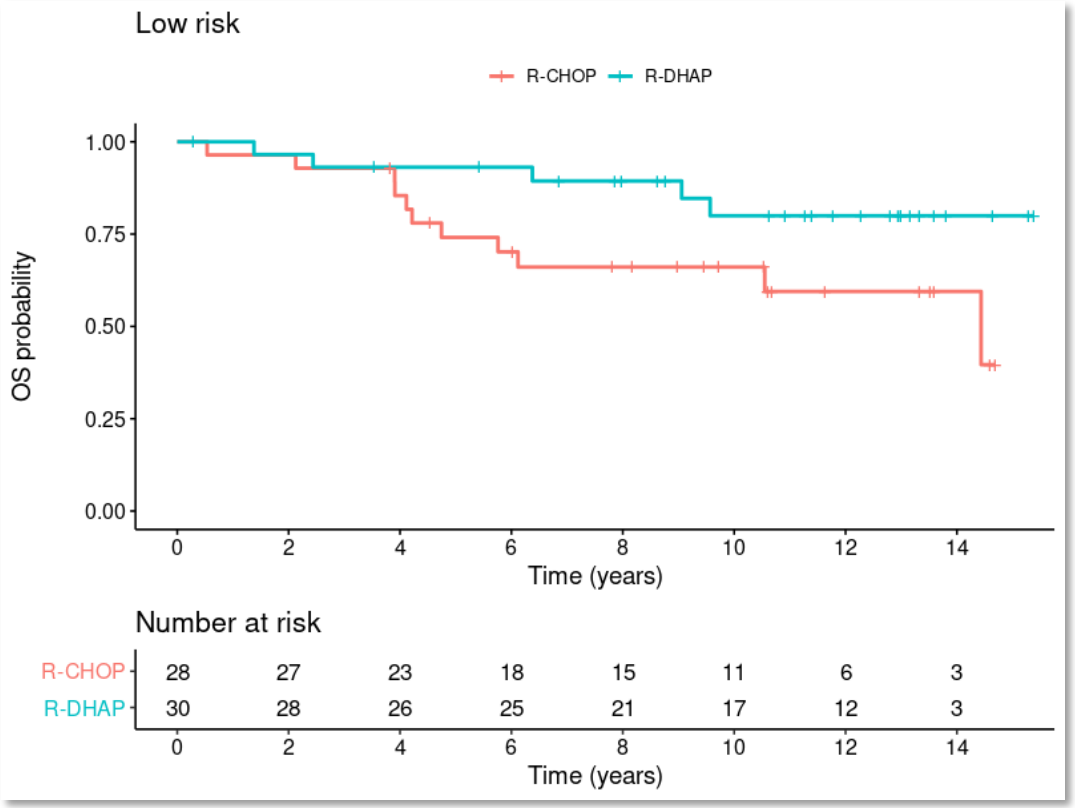
Subgroup	No. of patients	Hazard ratio (95% CI)
Full	497	0.80 (0.61 - 1.06)
Sex		
Female	105	0.91 (0.49 - 1.70)
Male	392	0.78 (0.57 - 1.06)
MIPI		
Low	307	0.82 (0.55 - 1.23)
Intermediate	119	0.86 (0.52 - 1.41)
High	71	0.72 (0.39 - 1.33)
MIPI-c (n=297)		
low	158	0.77 (0.42 - 1.40)
low intermediate	91	0.60 (0.32 - 1.12)
high intermediate	32	0.56 (0.23 - 1.35)
high	16	1.38 (0.46 - 4.21)
Ki-67 (n=297)		
low	211	0.67 (0.41 - 1.08)
high	86	0.63 (0.36 - 1.11)
Cytology (n=333)		
Non-blastoid	305	0.82 (0.58 - 1.18)
Blastoid	28	0.55 (0.21 - 1.40)
p53 expression (n=159)		
low	137	0.66 (0.39 - 1.14)
high	22	0.16 (0.04 - 0.62)



Updated Results 2021 – risk groups



- High risk: high intermediate or high MIPI-c/high p53/blastoid
- Median OS
  R-CHOP 5.0 years
  R-DHAP 10.4 years
  p=0.011
- HR 0.55 (0.35-0.88), p=0.013



- Low risk: low intermediate or low MIPI-c, low p53, non-blastoid
- Median OS
  R-CHOP 14.4 years
  R-DHAP not reached
  p=0.054
- HR 0.37 (0.13-1.06), p=0.064

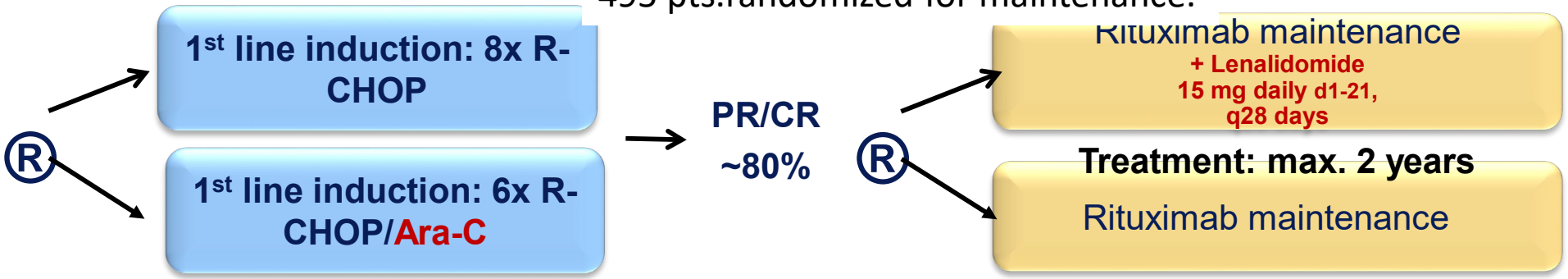
Erstlinienbehandlung älterer Patienten mit MCL (nicht transplantierbar)

#379 Rituximab-Lenalidomide(R2) Maintenance Is Superior to Rituximab Maintenance after First Line Immunochemotherapy in Mantle Cell Lymphoma: Results of the MCL R2 Elderly Clinical Trial

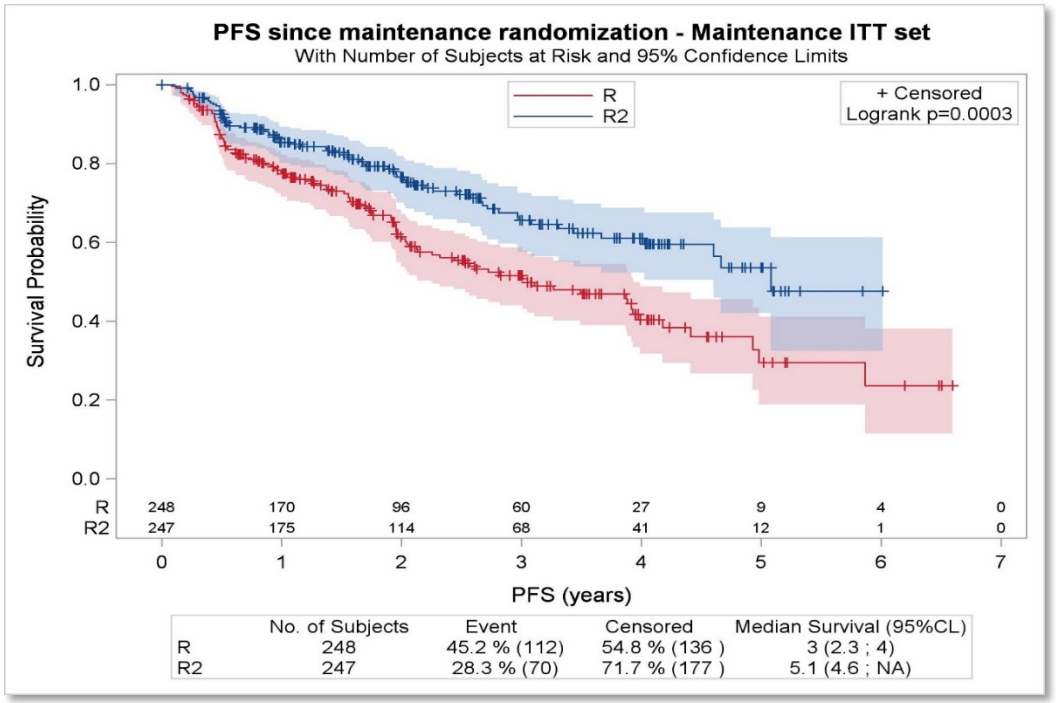
V. Ribrag, V. Safar, Hanneke C. Kluin-Nelemans, L.Oberic4, P.Feugier, O.Casasnovas, C. Thieblemont, N.Daguindau, G. Damaj , W. Klapper, E. Hoster, L. Fischer von Weikersthal, M.Hänel , M. André , M. Gomes Da Silva , F. Carnicero , A. Marin-Niebla, M. Taszner , J. Walewski , R. Boersma , I. Houtenbos , MH. Delfau-Larue , S. Le Gouill, M. Dreyling

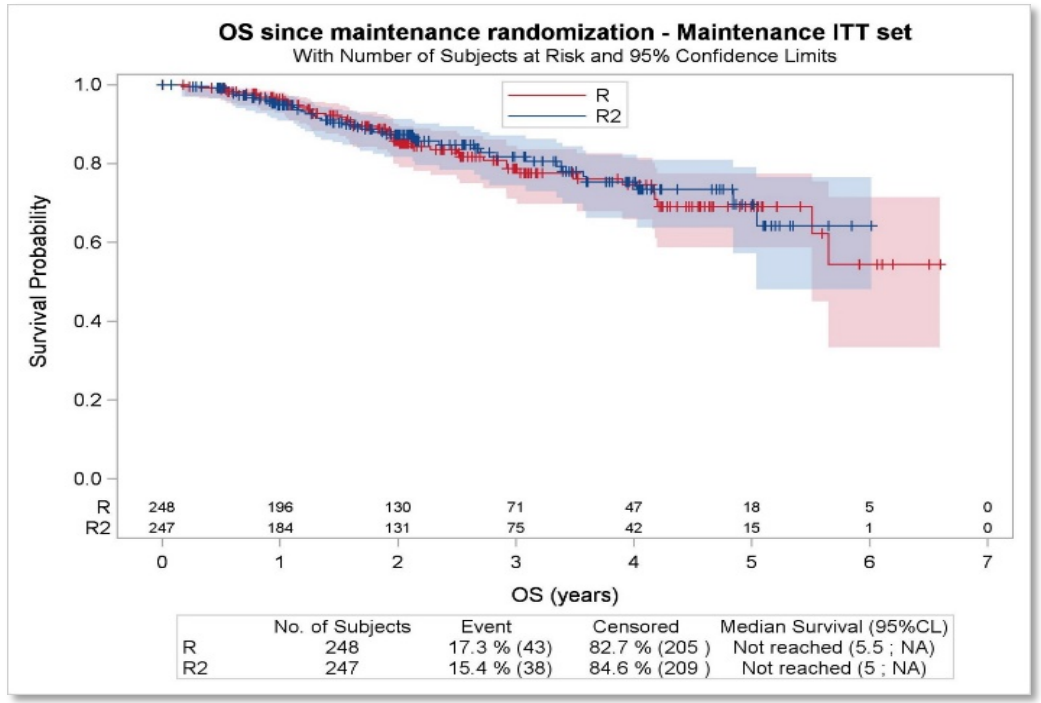
Results of the MCL R2 Elderly Clinical Trial

495 pts.randomized for maintenance.



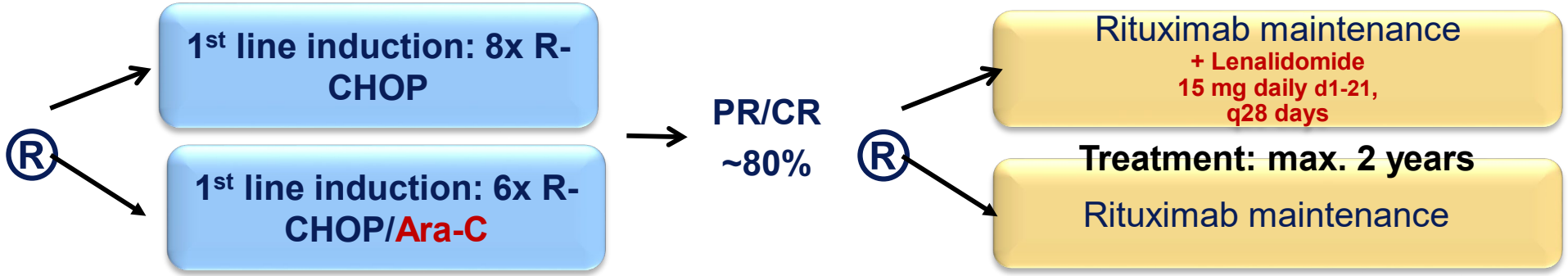
Median observation 25,2 mos





2-yrs PFS 76,8% and 60,8%

Results of the MCL R2 Elderly Clinical Trial



495 pts.randomized for maintenance.

- AEs of grade ≥ 3 were: neutropenia (50.0% vs 18.8%),
- respiratory tract infection (5.5% vs. 0.8%),
- skin cancer (5.5% vs 2.0%).

	R N=250	R2 N=238
Blood and Lymphatic System Disorders	68 (117 events)	140 (471 events)
Neutropenia > grade 2	47 (64 events)	119 (315 events)
Anemia > grade 2	1 (1 event)	7 (7 events)
Infections and Infestations	6 (7 events)	26 (33 events)

Erstlinienbehandlung älterer Patienten mit MCL (nicht transplantierbar)

#40 Impact of Maintenance Arm on Prognostic Value of MRD after Induction Treatment in MCL R2 Elderly Trial , a Mantle Cell Lymphoma Network Study

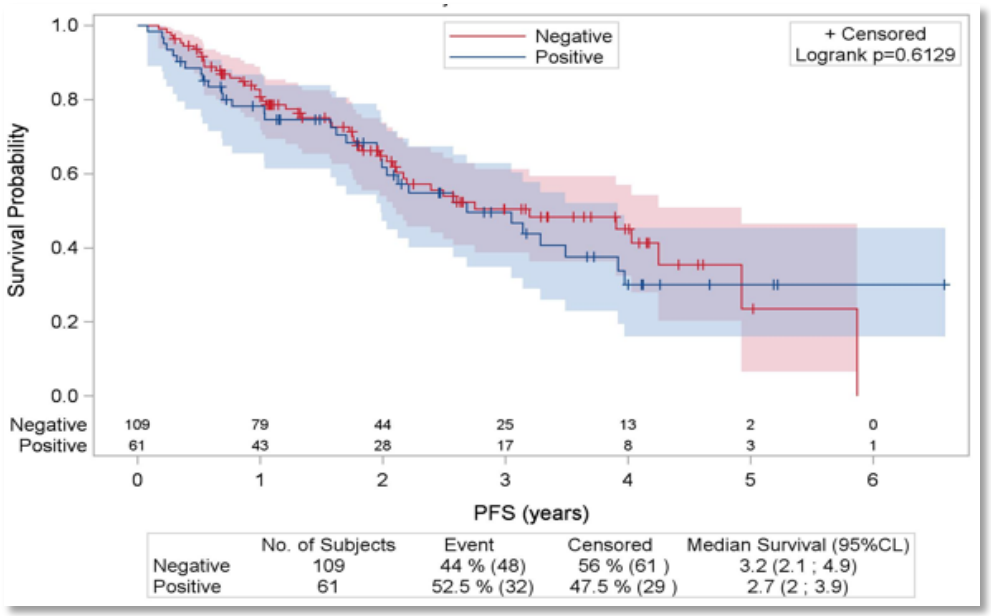
Marie-Helene Delfau, Elizabeth A. Macintyre, Mary B. Callanan, Christiane Pott, Vincent H.J. Van Der Velden, Christa Homburg, Ramon Garcia-Sanz, Paula Gameiro, Maria Gomes Da Silva, Wolfram Klapper, Lucie Oberic, , Pierre Feugier, Violaine Safar, Olivier Casasnovas, Martin H. Dreyling and Vincent Ribrag.

Survival according to MRD response after end of induction

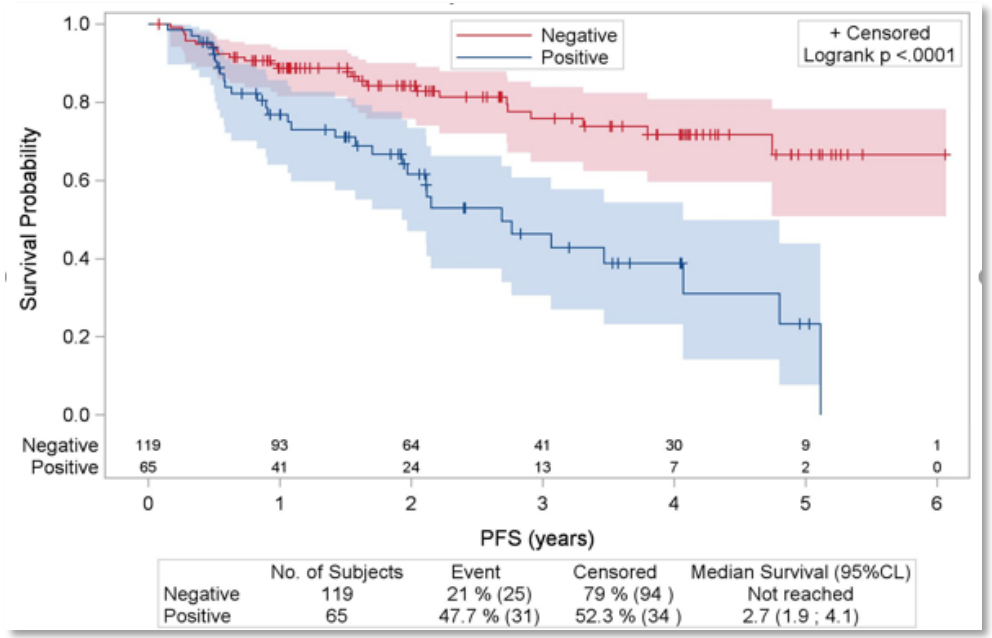
MRD assessment by standardized Euro-MRD QPCR in 231 patients
EOI MRD negativity 61% HR 3.034 (1.779-5.174) p<.0001

survival analysis according to MRD status in PB or BM at end of induction

Rituximab maintenance



R2 maintenance



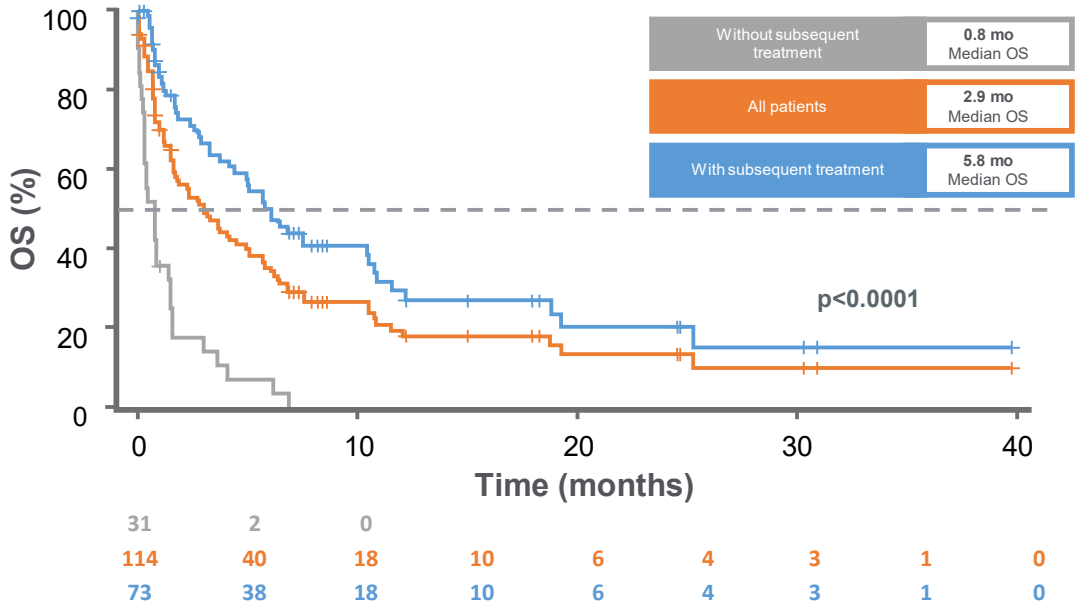
MRD conversion MRD+ to MRD - during first year maintenance 50% and 55% respectively

Thema 2

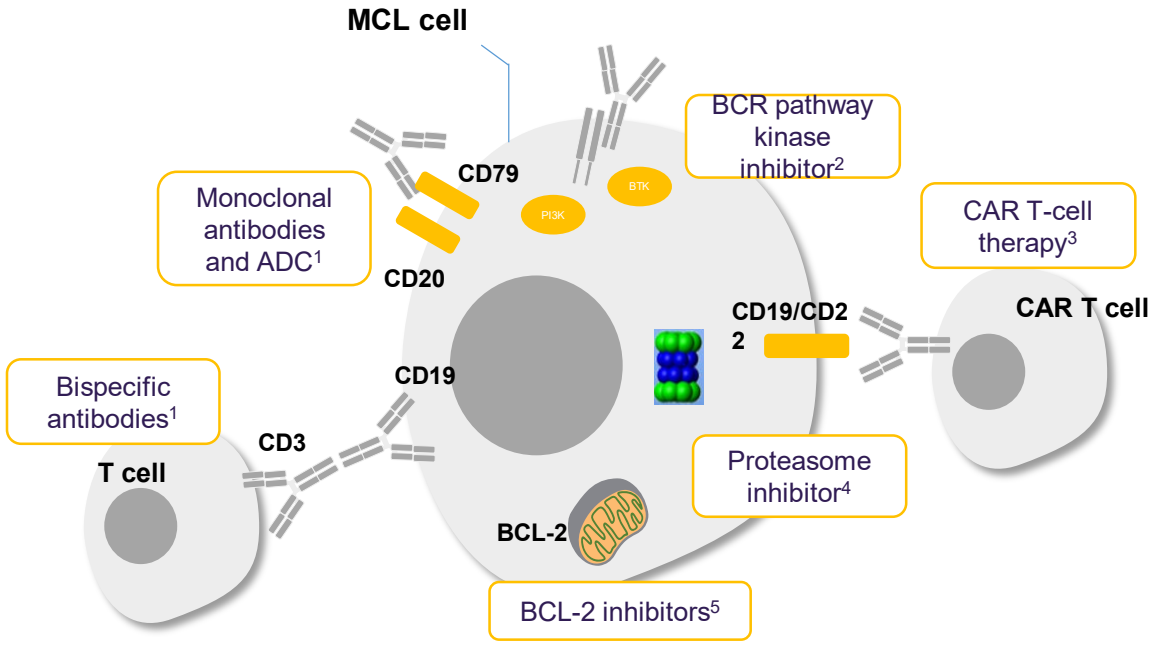
Neue therapeutische Möglichkeiten im Rezidiv des MCL

Treatment at relapse in MCL

Overall survival of patients with MCL after ibrutinib cessation (± subsequent therapy) (N=114)[2]



Patients had a median of 3 (range 0–10) prior therapies



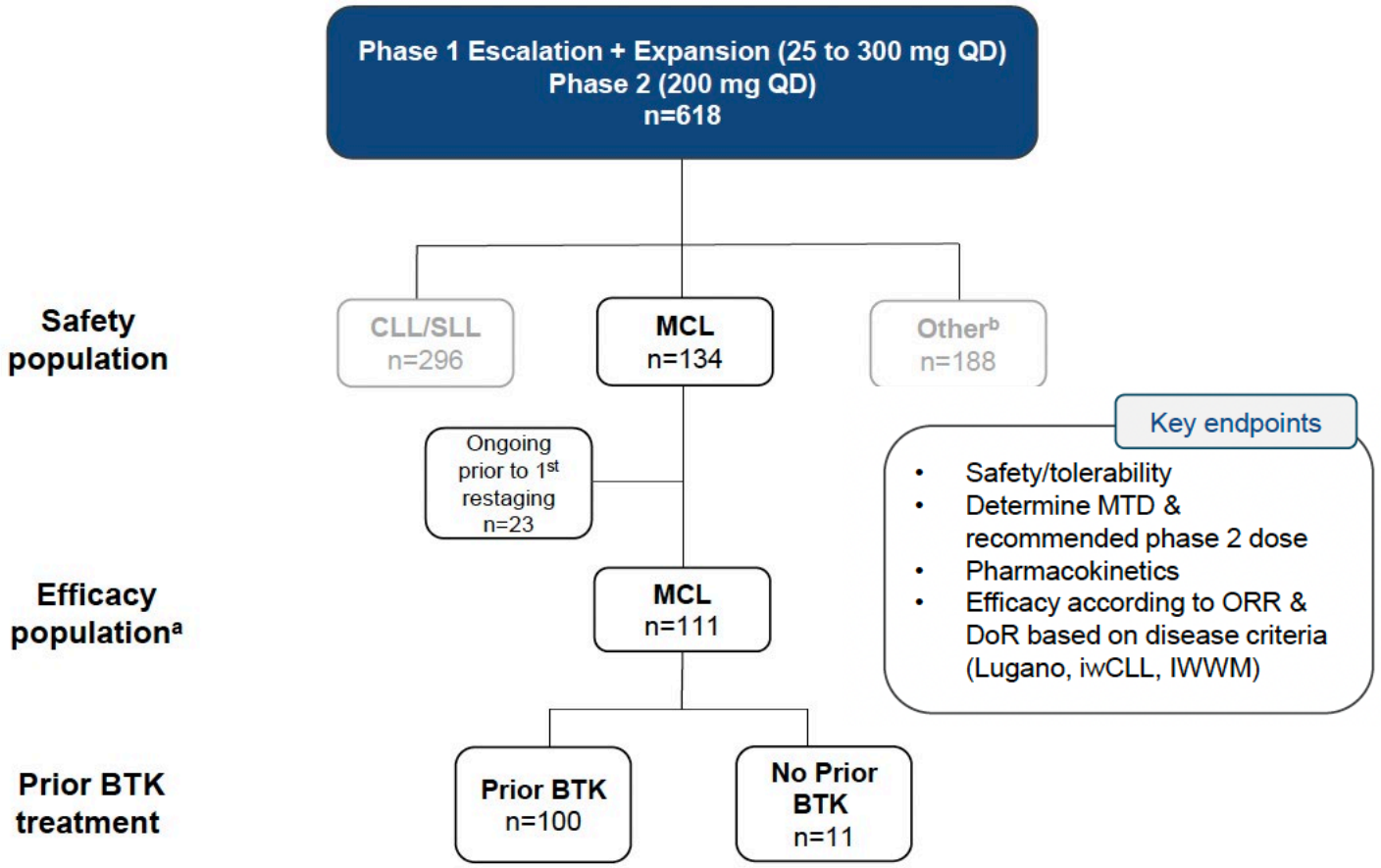
Martin P, *et al. Blood* 2016; 127:1559–1563

Rezidivtherapie mit BTKi

#381 Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

Michael L. Wang1, Nirav N. Shah2, Alvaro J. Alencar3, James N. Gerson4, Manish R. Patel5, Bita Fakhri6, Wojciech Jurczak7, Xuan Tan8, Katharine Lewis8, Timothy Fenske2, Catherine C. Coombs9, Ian W. Flinn10, David J. Lewis11, Steven Le Gouill12, M. Lia Palomba13, Jennifer A. Woyach14, John M. Pagel15, Nicole Lamanna16, Jonathon B. Cohen17, Minal A. Barve18, Paolo Ghia19, Toby A. Eyre20, Pier Luigi Zinzani21, Chaitra S. Ujjani22, YoungilKoh23, Koji Izutsu24, EwaLech-Maranda25, Constantine S. Tam26, Suchitra Sundaram27, Ming Yin28, Binoj Nair28, Donald E. Tsai28, Minna Balbas28, Anthony R. Mato13, Chan Y. Cheah8

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment

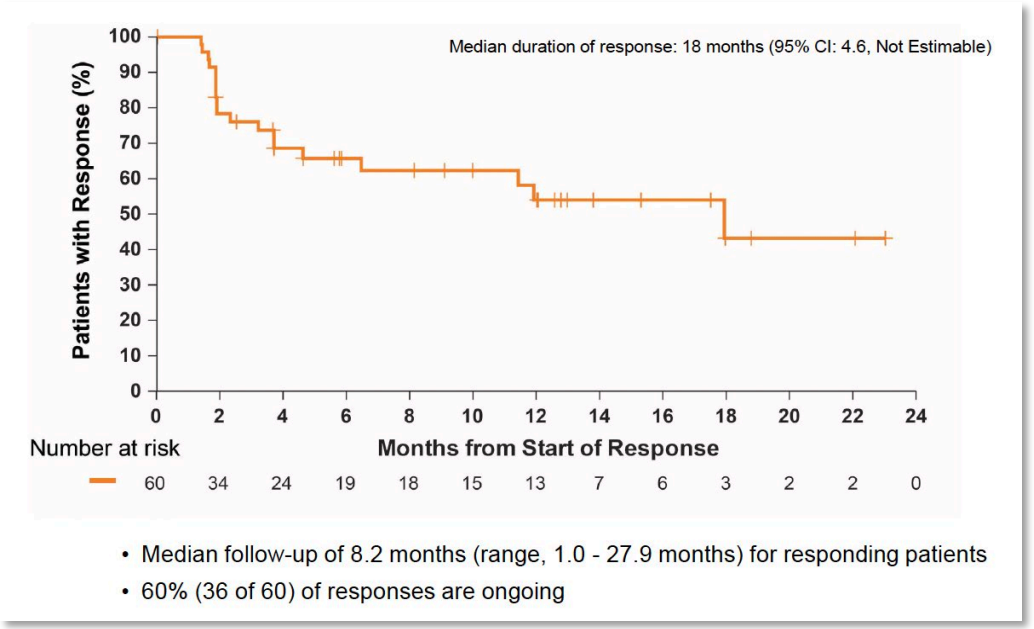


Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

Phase 1/2 BRUIN Study: Efficacy and DOR

BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:
- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Toxicity grade ¾: Neutropenia 8%, Hypertension 2%, Hemorrhage 2%, AF<1%
5 of 323 patients (1.5%) discontinued due to treatment-related Aes,
No DLTs reported and MTD not reached

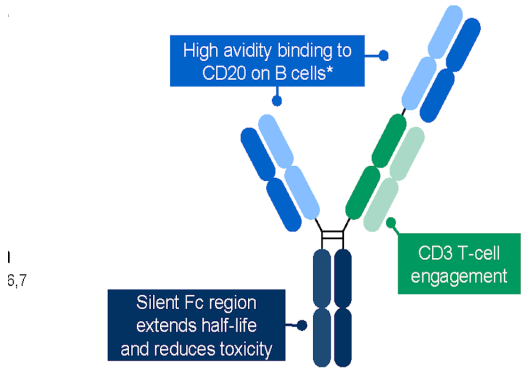
Rezidivtherapie mit bispezifischen Antikörpern

#130 Glofitamab Step-up Dosing Induces High Response Rates in Patients (pts) with Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL), Most of Whom Had Failed Prior Bruton's Tyrosine Kinase Inhibitor (BTKi) Therapy

Tycel Phillips, MD1, Michael Dickinson, MBBS2, Franck Morschhauser, MD, PhD3*, Emmanuel Bachy, MD, PhD4*, Michael Crump5, Marek Trněný, MD6, Nancy L. Bartlett, MD7, Jan Zaucha8*, Kathryn Humphrey9*, David Perez-Callejo10*, Linda Lundberg10*, James Relf9*, Audrey Filézac de L'Étang10*, David Carlile9*, Emma Clark9* and Carmelo Carlo-Stella, MD11

Phase I/II trial in pts with R/R MCL who received a 1000mg or 2000mg dose of Gpt prior to glofitamab monotherapy

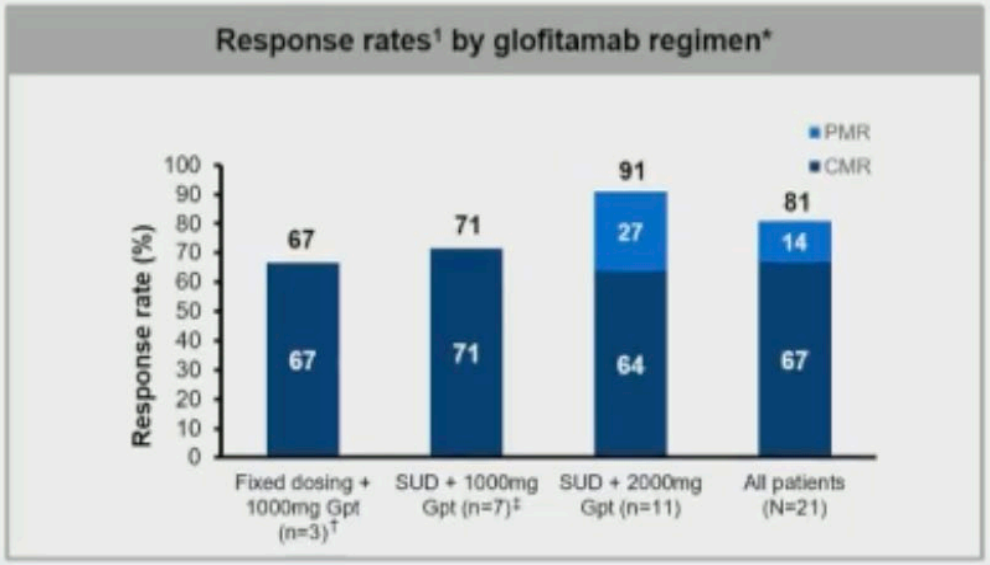
Glofitamab: *CD20xCD3 bispecific antibody with 2:1 configuration for increased potency vs 1:1 configuration*[4]

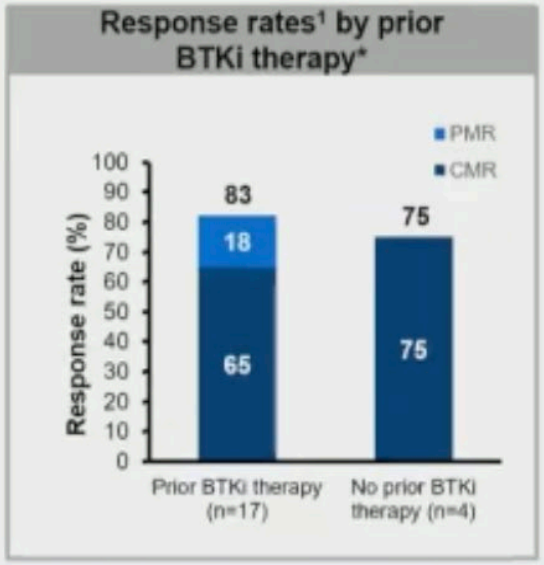


N=27 patients
Median prior lines of therapy 3 (range, 1–6), 69% (n=20) had prior BTKi therapy and 14% (n=4) had prior lenalidomide therapy.

Glofitamab: fixed dosing after 1000mg Gpt (n=3);
SUD after 1000mg Gpt (n=7; 1 pt received SUD starting at 0.5mg) or 2000mg Gpt (n=19).

Response rates





Glofitamab resulted in high response rates in patients with R/R MCL

*21/29 patients were efficacy-evaluable; the secondary efficacy-evaluable population includes all patients who had a response assessment performed (investigator-assessed), or who were still on treatment at the time of their first scheduled response assessment (Lugano 2014 criteria)[1]. †Due to a data issue, the response (CR) from one patient is reported as missing, and two patients treated with a combination of glofitamab and obinutuzumab (G-combo); ‡One patient treated with G-combo. CMR, complete metabolic response; PMR, partial metabolic response.

1. Cheson, BD et al. J Clin Oncol 2014

Phase I/II trial in pts with R/R MCL who received a 1000mg or 2000mg dose of Gpt prior to glofitamab monotherapy

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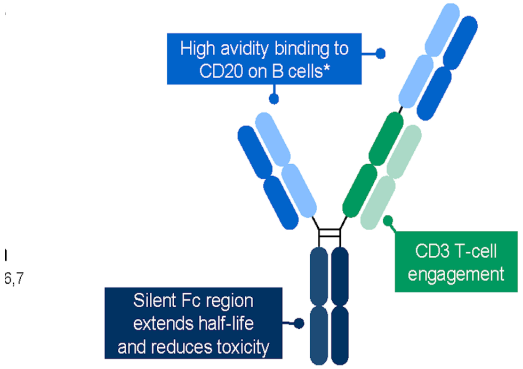
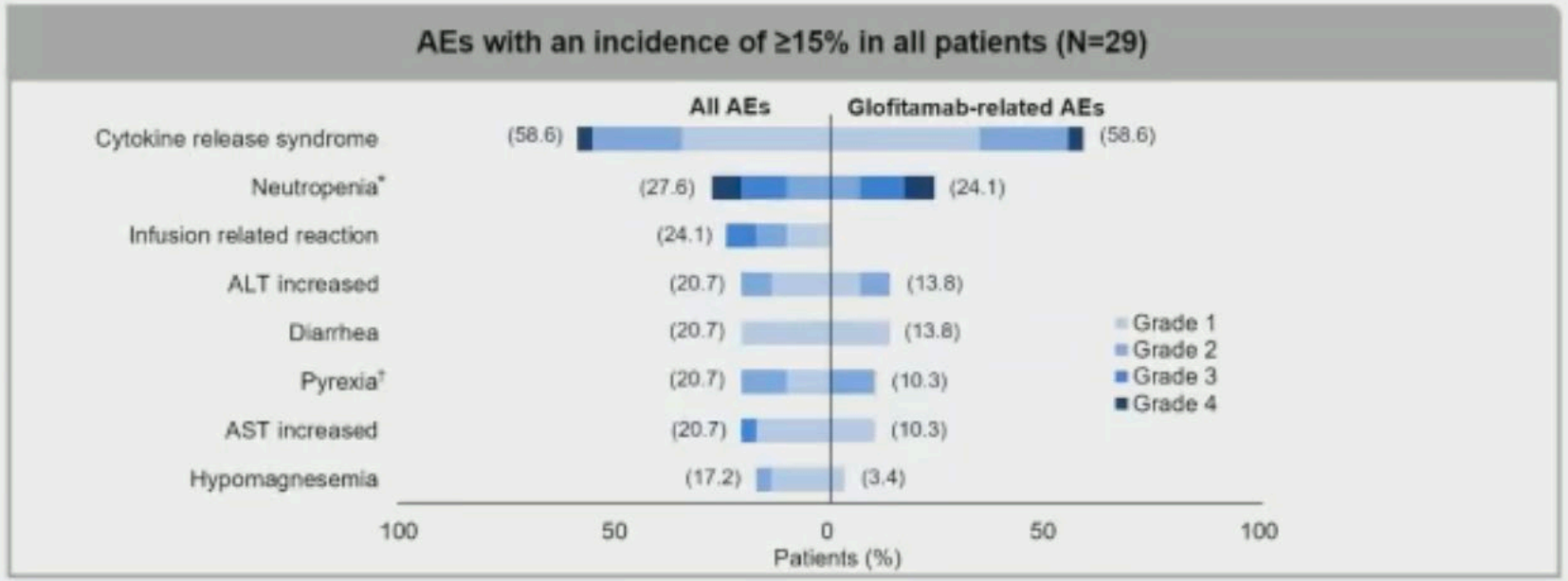
Glofitamab: *CD20xCD3 bispecific antibody with 2:1 configuration for increased potency vs 1:1 configuration*[4]



5,7

Common adverse events



*Incidence of neutropenia includes neutrophil count decrease. †Events occurred separately from CRS. ALT, Alanine aminotransferase; AST, aspartate aminotransferase.

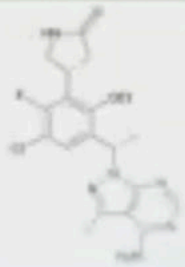
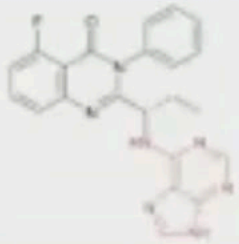
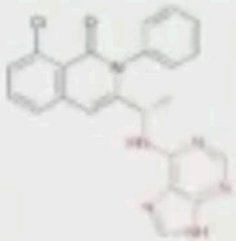
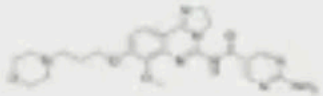
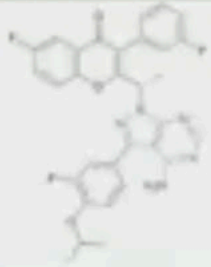
most common adverse events (AEs) were CRS (58.6%) and infusion-related reactions (24.1%). All CRS events were Grade (Gr) 1–2 (by ASTCT criteria), except for 1 Gr 4

#382 Efficacy and Safety of Parsaclisib in Patients with Relapsed or Refractory Mantle Cell Lymphoma Not Previously Treated with a BTK Inhibitor: Primary Analysis from a Phase 2 Study (CITADEL-205)

Amitkumar Mehta, MD1, Marek Trněný, MD2, Jan Walewski, MD, PhD3, Vincent Ribrag, MD4, Caroline Dartigeas, MD5*, Jacob Haaber Christensen, MD, PhD6*, Fabrizio Pane, MD7, Guillermo Rodriguez, MD8*, Michal Taszner, MD9*, Parameswaran Venugopal, MD10, Vittorio Ruggero Zilioli, MD11*, Fred Zheng, MD12*, Douglas J DeMarini, PhD12*, Wei Jiang, PhD12* and Pier Luigi Zinzani, MD13

Phase 2 study parsaclisib in rr MCL

Parsaclisib is a potent, highly selective, next-generation inhibitor of phosphatidylinositol 3-kinase (PI3K) δ.

	Parsaclisib[1]	Idelalisib[2]	Duvelisib[3]	Copanlisib[4]	Umbralisib[5,6]
Structure					
PI3Kδ IC_{50}, nM	1	2.5	2.5	0.7	22.2
Fold selectivity					
PI3Kα	>20,000	>300	1602	1	>1500
PI3Kβ	>20,000	>200	85	5	>1500
PI3Kγ	19,000	>35	27	10	225

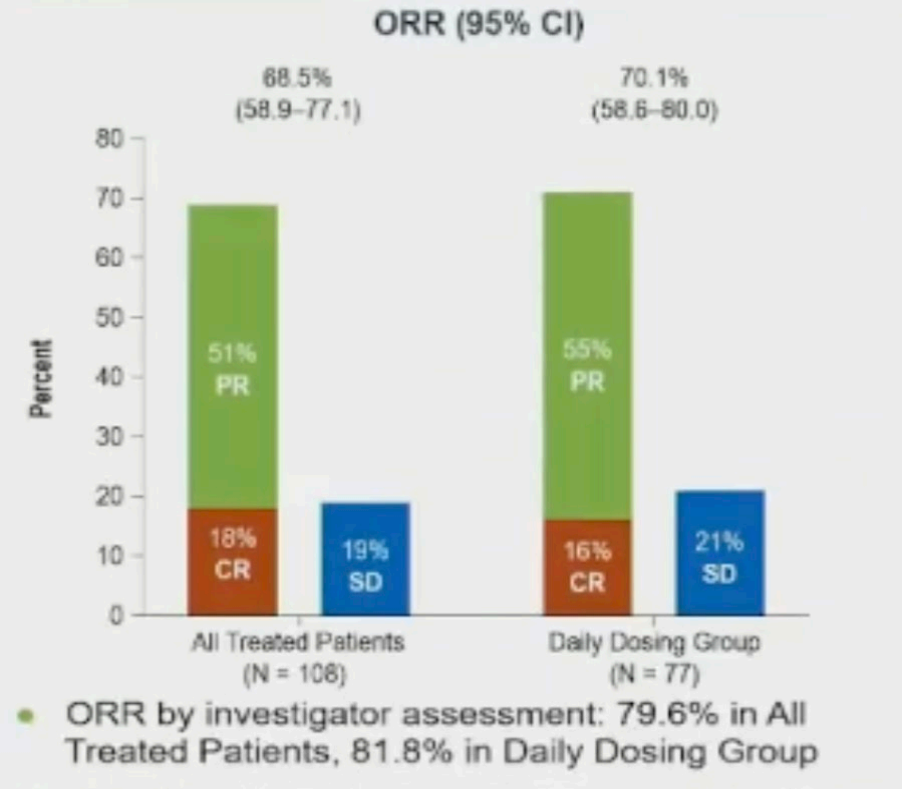
Inclusion criteria:
rrMCL with 1–3 prior systemic therapies and no BTK and/or PI3K inhibitor

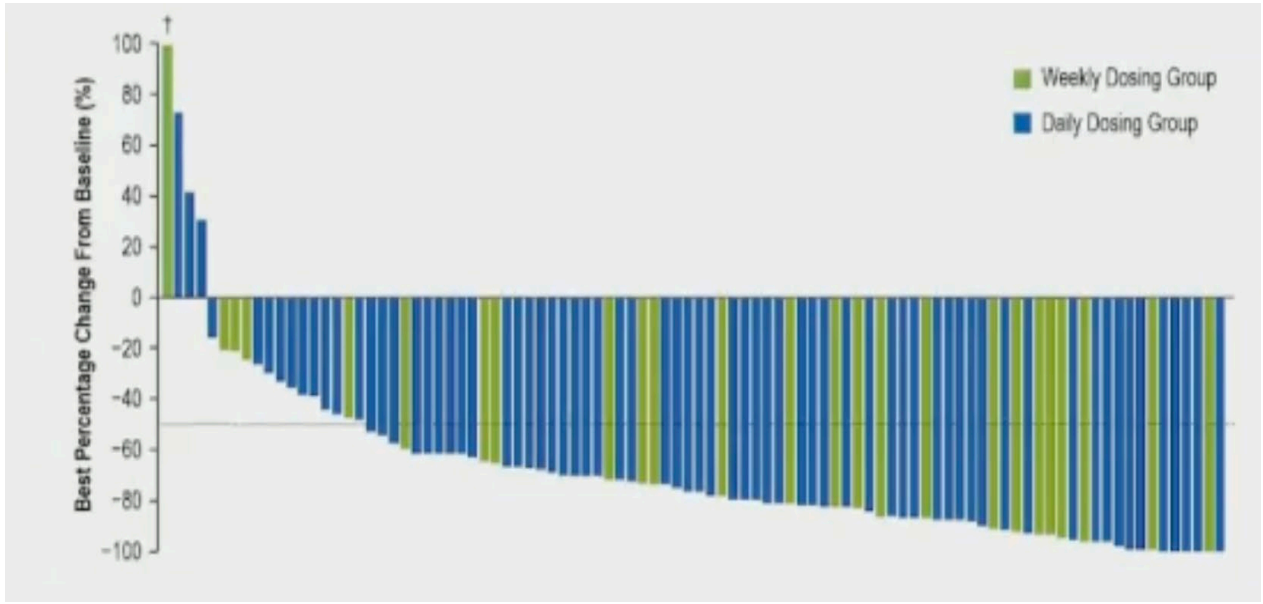
Parsaclisib 20 mg once daily (QD) for 8 weeks followed by either 20 mg once weekly (weekly-dosing group [WG]) or 2.5 mg QD

Phase 2 study parsaclisib in rr MCL

N=108

96% regression at target lesions, 84%> 50%





	All Treated Patients (N = 108)	Daily Dosing Group (N = 77)
Median PFS (95% CI), months	12.0 (8.3–16.9)	13.6 (10.0–16.9)

Toxicity: any TEAE 40% , Diarrhoe 8%, Colitis 4,5%
Events leding to dose discontinuation 16% diarrhoe, colitis 6,5%

#743 Kte-X19 in Relapsed or Refractory Mantle-Cell Lymphoma, a “Real-Life” Study from the Descar-T Registry and Lysa Group

Charles Herbaux, MD1, Caroline Bret, PhD, PharmD2*, Roberta Di Blasi, MD, PhD3*, Emmanuel Bachy, MD, PhD4*, David Beauvais, MD5*, Elodie Gat6*, Thomas Gastinne, MD7*, Florence Broussais8*, Guillaume Cartron, MD, PhD9*, Alexis Cuffel10*, Loic Ysebaert, MD, PhD11*, Mikael Roussel, MD, PhD12*, Krimo Bouabdallah13*, Julien Guy, MD14*, Arnaud Campidelli15*, François Van Laethem16*, Rene-Olivier Casasnovas, MD17*, Remy Dulery18*, Franck Morschhauser, MD, PhD19*, Sophie Caillat-Zucman, MD, PhD20*, Roch Houot21* and Steven Le Gouill22

ZUMA-2 Study: KTE-X19 in Patients With R/R MCL

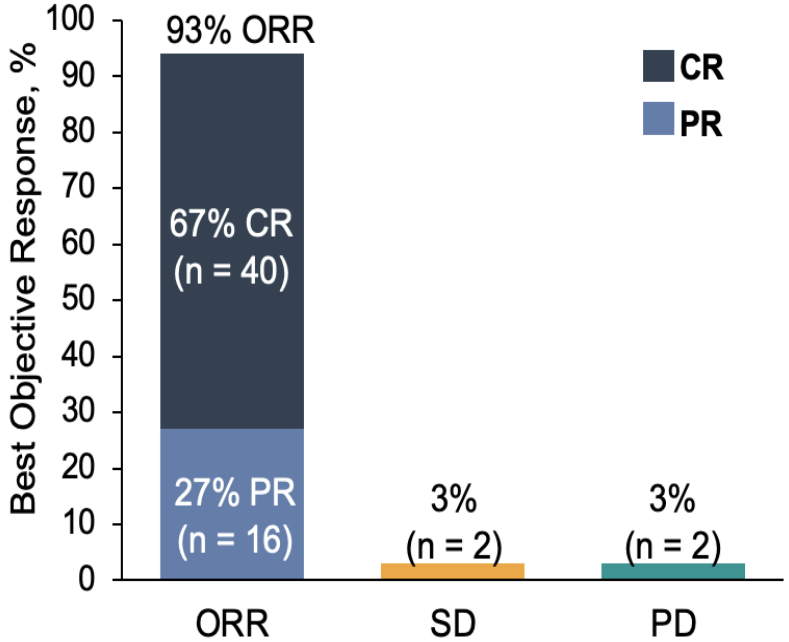
Phase 2

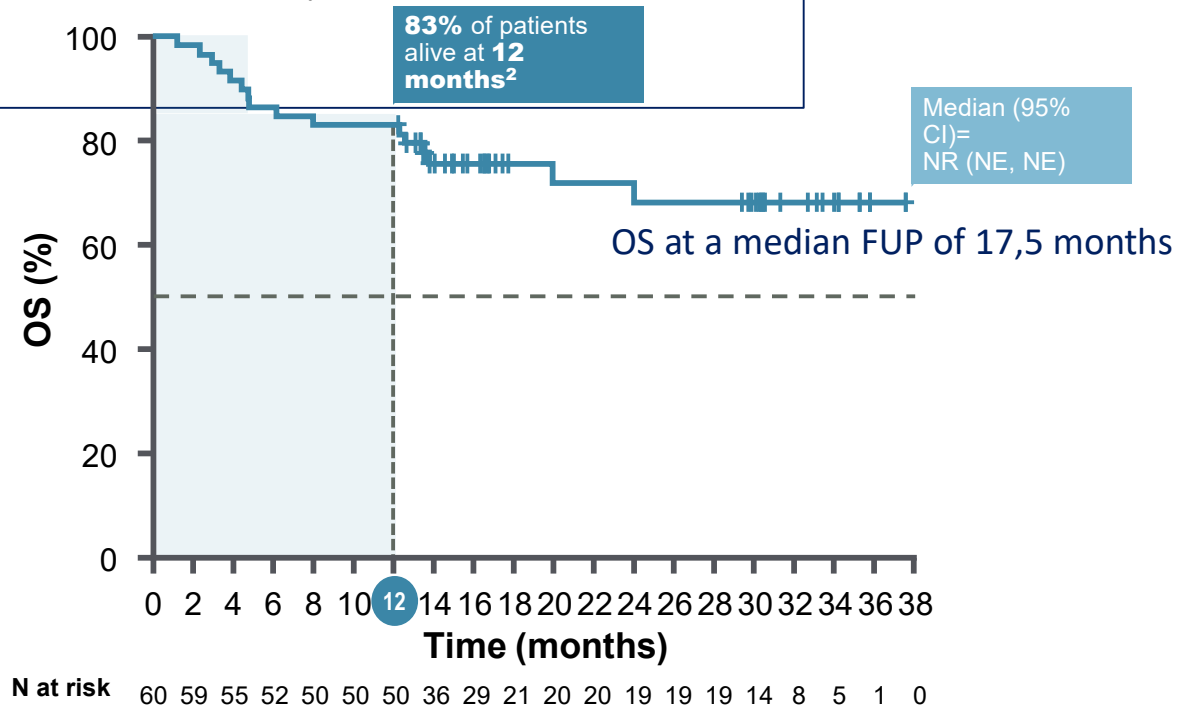
Enrollment/ Leukapheresis	Optional Bridging Therapy[a]	Conditioning Chemotherapy	CAR T Cell Dose	**Follow-Up Period**
R/R MCL	Dexamethasone 20 – 40 mg or equivalent PO or IV daily for 1 – 4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily	Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3	2 × 10^6 KTE-X19 cells/kg single IV infusion on Day 0	First tumor assessment on Day 28[b]

R/R MCL defined as
- Disease progression after last regimen or
- Failure to exhibit a CR or PR to the last regimen

1 – 5 Prior therapies that must have included
- An anthracycline- or bendamustine-containing chemotherapy and
- Anti-CD20 monoclonal antibody therapy and
- Ibrutinib or acalabrutinib

Enrolled/Leukapheresis manufactured for 71/74 patients (96%) and administered to 68 (92%



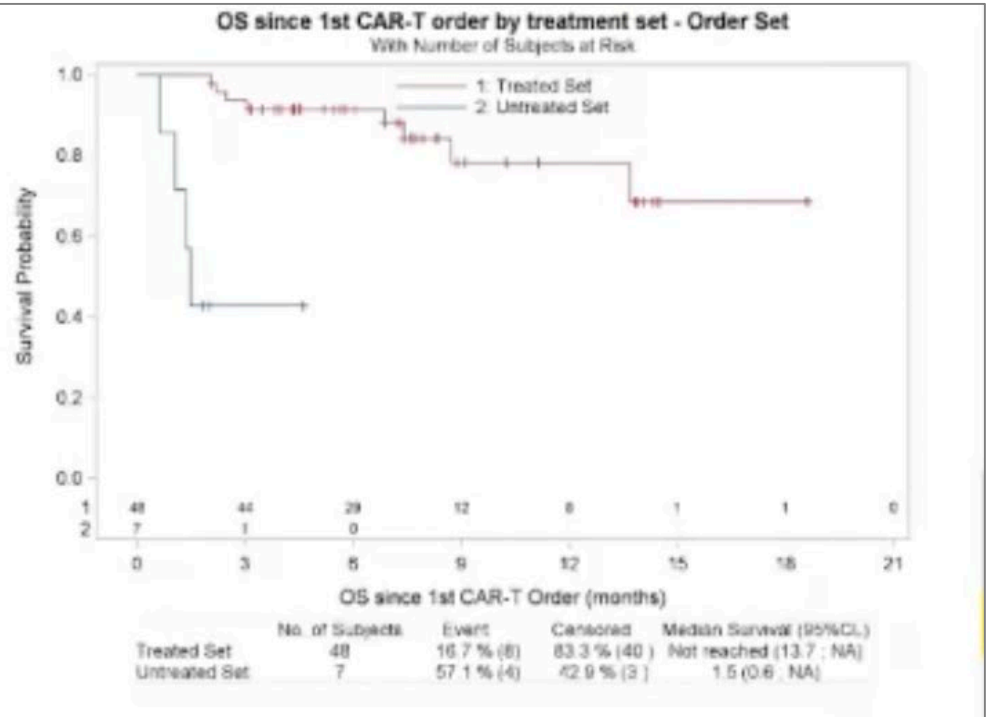


Wang ML, et al. ASH 2020. Abstract #1120.

CAR-T “Real-Life” Study from the Descar-T Registry

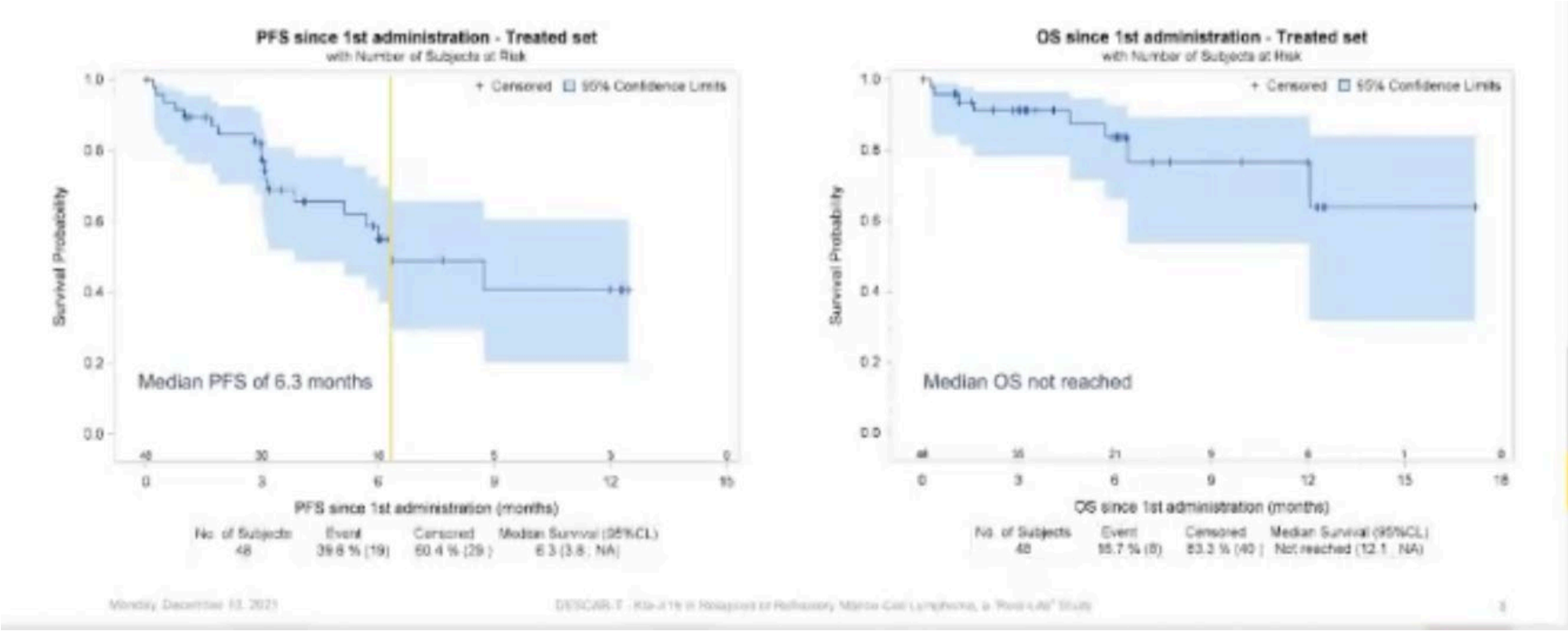
N=57 pats. registered in DESCART, 48 infused

- Median time between CAR-T order and infusion was **56 days** (range 35-134)
- **42 patients (87.2%) had a bridging therapy:**
  - anti-CD20: 27 pts (64.3%)
  - chemotherapy: 24 pats (57.1%)
  - BTKi: 11 pts (26.2%)
  - IMiDs: 6 pts (14.3%)
- **ORR of 45.3% to bridging therapy** (14.3% of CR)
- Significantly **worse OS if TECARTUS was not administered**



CAR-T “Real-Life” Study from the Descar-T Registry

Best ORR for 48 patients 87,2% including CR in 63,8% (vs. 93% and 67% in ZUMA-2)



Side effects: CRS ≥3 8,7% and neurotoxicity ≥3 8,7% (vs. 15% and 31%)

Zusammenfassung | Take-Home-Messages

- Eine cytarabin-basierte Induktionstherapie gefolgt von autologer Stammzelltransplantationn führt zu einem verbesserten Gesamtüberleben und ist für Subgruppen des MCL möglicherweise sogar kurativ
- Die Kombination von Lenalidomid und Rituximab in der Erhaltungstherapie führt zu einem verbesserten PFS bei MRD negativen Patienten nach der Induktionstherapie
- Der MRD-Status nach der Induktion ist prädiktiv für die bessere Wirksamkeit von R2
- PI3K-Inhibitoren haben eine Wirksamkeit bei BTK-naiven MCL im Rezidiv
- Bispezifische Antikörper sind vielversprechend in der Rezidivbehandlung
- Die CAR-T Zell Therapie stellt auch ausserhalb von klinischen Studien eine hochwirksame Therapieoption für rezidivierte MCL nach BTKi Versagen dar

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2021

Für den Inhalt verantwortlich:

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Universitätsklinikum Schleswig-Holstein (Kiel)

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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