Lymphom
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Expert:innen berichten zu
Lymphomen & Leukämien

Kompetenznetz
Maligne Lymphome

EHA2023 HYBRID

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Prof. Dr. med. Georg Heß
Universitätsmedizin Mainz

Mantelzell-Lymphom (MCL)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – EHA2023 HYBRID wird in Kooperation mit sieben unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

- Consultancy: Abbvie, ADC-Therapeutics, AstraZenaeca, Genmab, Gilead/Kite, Incyte, Janssen, Morphosys, Novartis, Roche, Takeda
- Honoraria: Abbvie, AstraZeneca, Beigene, BMS, Genmab, Gilead/Kite, Incyte, Janssen, Roche
- Research Funding: Celgene, Gleade/Kite, Incyte, Janssen, Morphosys, Pfizer, Roche
- Patents and Royalties: not applicable
- Membership on an entity's Board of Directors or advisory committees: not applicable
- Discussion of off-label drug use: not applicable
- Travel grants: Gilead/Kite, Janssen

Kapitel 1

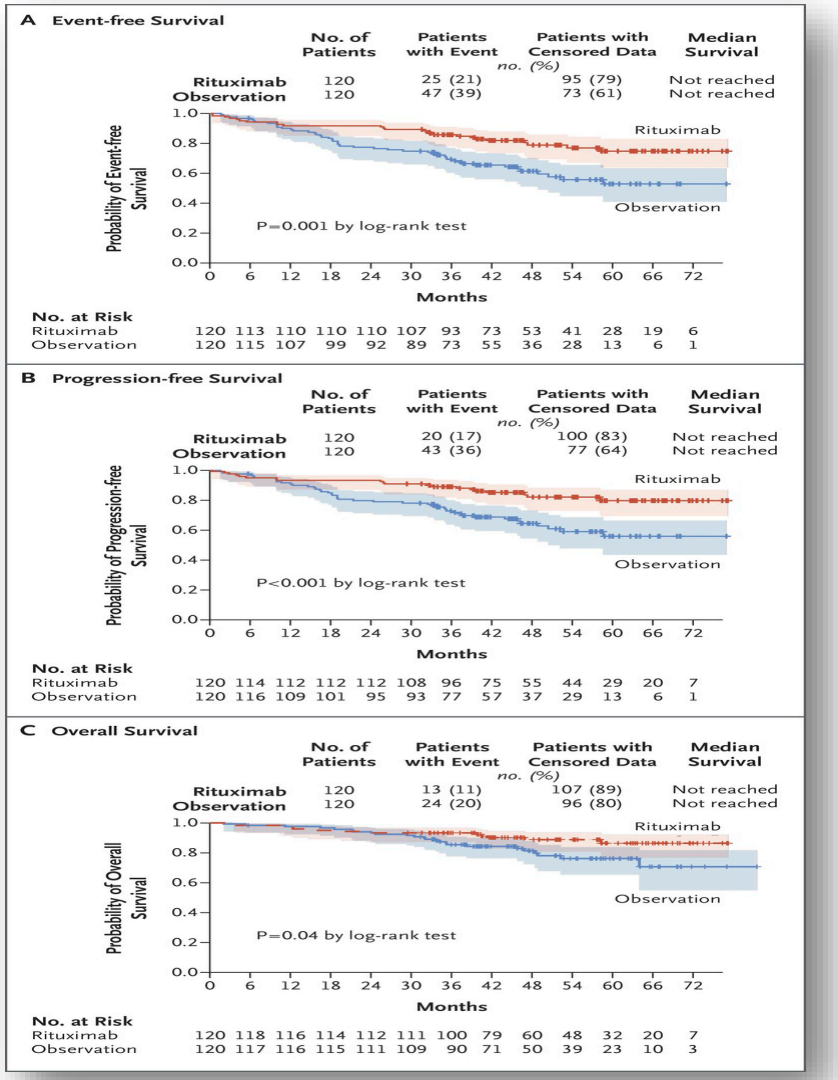
Langzeitergebnisse einer Erhaltungstherapie beim MCL

VERY LONG-TERM FOLLOW-UP OF RITUXIMAB MAINTENANCE IN YOUNG PATIENTS WITH MANTLE CELL LYMPHOMA INCLUDED IN THE LYMA TRIAL, A LYSA STUDY

1079

C. Sarkozy

Hintergrund



LeGouill, NEJM, 2017

Sind die Resultate in der Langzeitbeobachtung stabil?

Medianes follow up: 7 Jahre

- The median EFS and PFS were still statistically superior in favor of RM (not reached (NR), versus 5.8 years, p<.0001 for EFS and NR versus 6.1 years for PFS in RM and observation arm respectively).
- In the RM arm, 22 patients had died (18.3%) versus 33 (27.5%) in the observation arm with a 7-year OS estimate of 83.2% (95% CI: 74.7.7%-89.0%) and 72.2% (95% CI 62.9%- 79.5%) in RM and observation arm, respectively (p=0.087)
- Causes of death were not significantly distinct between the 2 groups, lymphoma being the leading cause in both (50% in both arm), with less than 10% of infectious related death.

Sind die Resultate in der Langzeitbeobachtung stabil?

Medianes follow up: 7 Jahre

- Post relapse OS was significantly impacted by previous RM, with a median OS-2 of 1.1 years (95%CI 0.7-2.1) for the 21 relapsing patients in the RM arm versus 4.6 years (95%CI 2-NA) for the 53 relapsing patients in the observation arm. Given the timing of relapses in RM arm, this reflects the aggressiveness of early disease progression during RM.

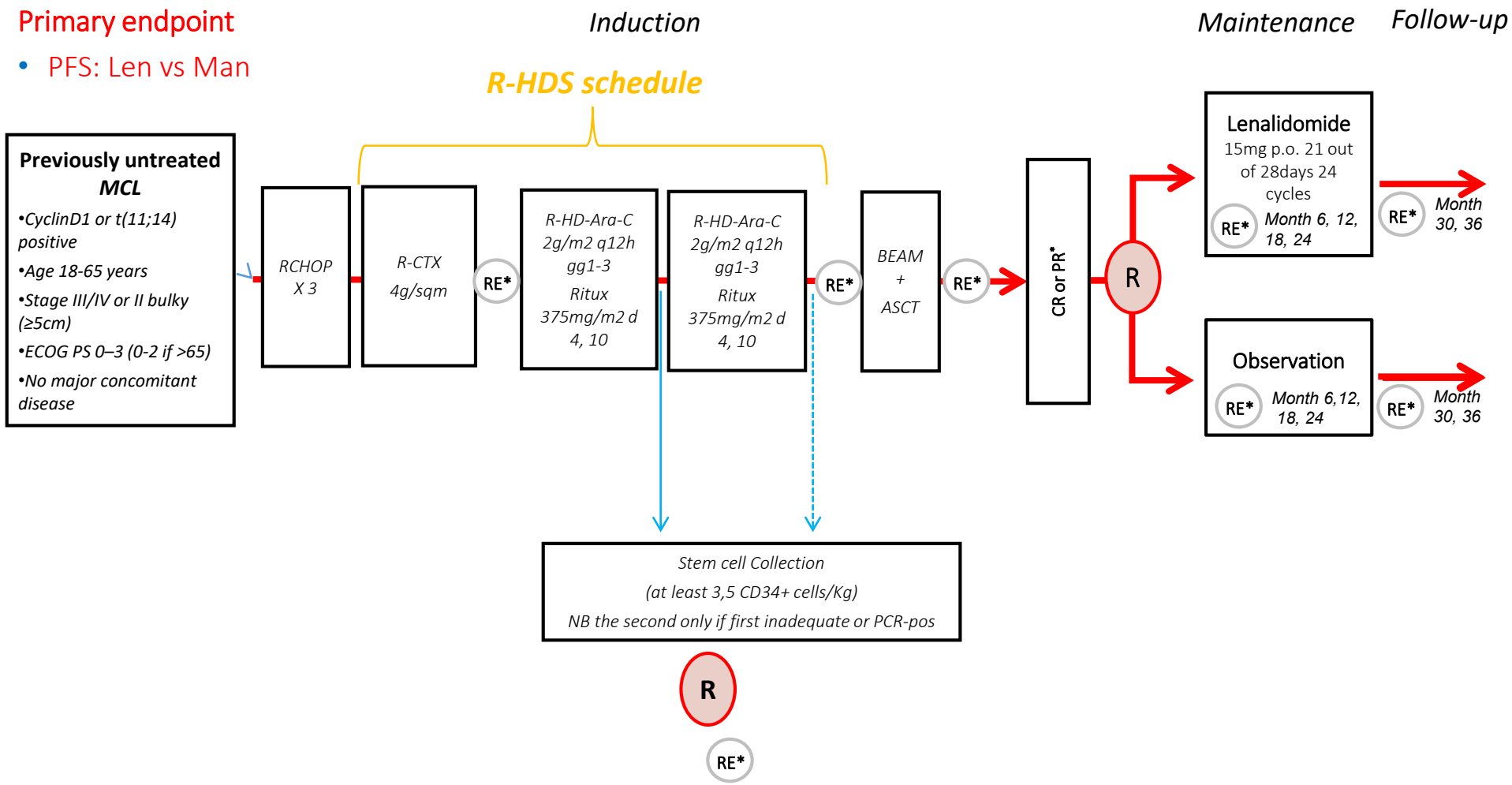
LONG-TERM RESULTS OF THE FIL MCL0208 TRIAL COMPARING LENALIDOMIDE MAINTENANCE (LEN) VS OBSERVATION (OBS) AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN MANTLE CELL LYMPHOMA (MCL)

221

M. Ladetto

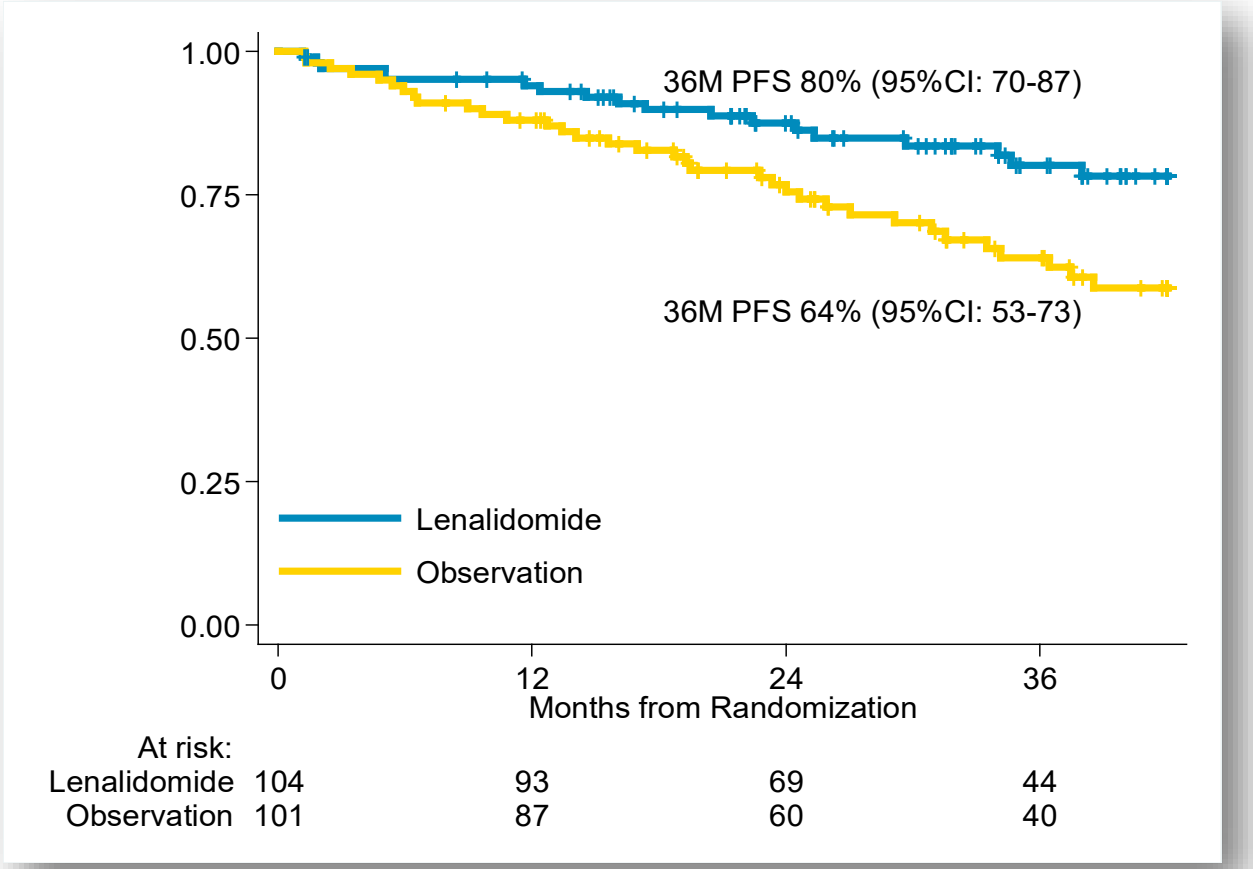
Primary endpoint

- PFS: Len vs Man



Ladetto ASH 2018

- RANDOM 1:1 (stratified by Clinical and molecular response and…..)
- Response evaluation


1.00
0.75
0.50
0.25
0.00
36M PFS 80% (95%CI: 70-87)
36M PFS 64% (95%CI: 53-73)
Lenalidomide
Observation
0
12
24
36
Months from Randomization
At risk:
Lenalidomide 104 93 69 44
Observation 101 87 60 40

Kernaussagen

- The two-year LEN program provided an early PFS benefit
- not maintained once LEN was interrupted with no OS advantage
  - 72 mo PFS 55 vs 50 mo (+Len vs –Len/p=0.175)
  - 72 mo OS 77 vs 75 mo (+Len vs –Len/p=0.189)

- Long-term MRD results stress the predictive value of this tool (BM > PB) for PFS and OS
  - particularly in the context of kinetic modeling

Kapitel 2 – CAR-T-cells in MCL

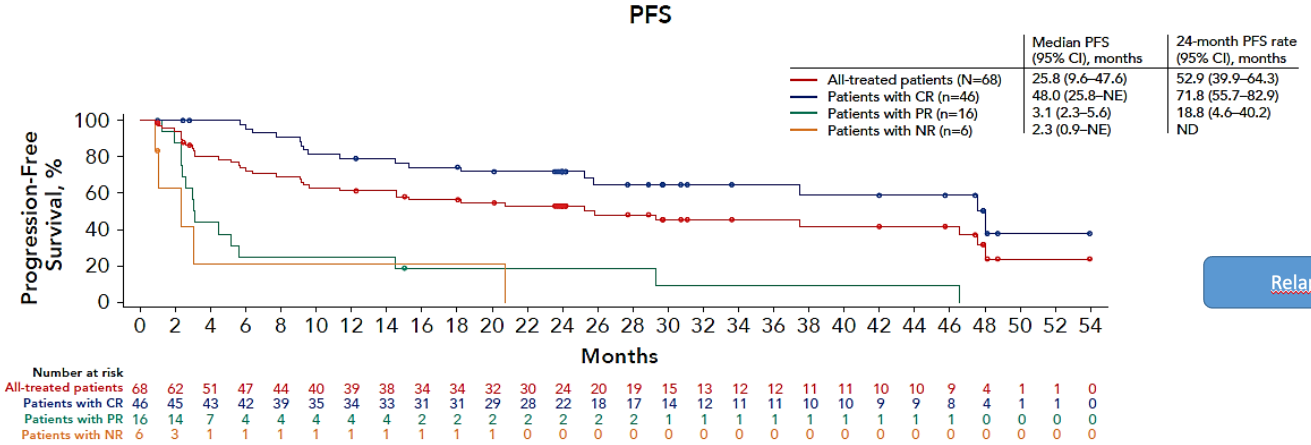
Ergebnisse im Behandlungsalltag

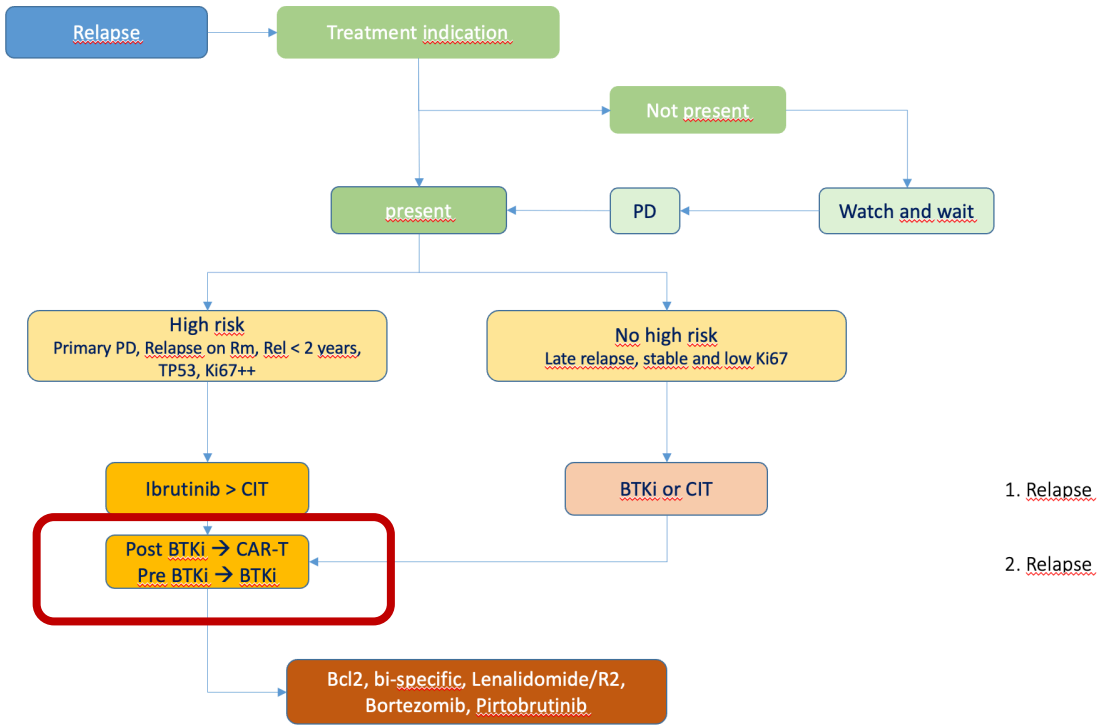
REAL-WORLD OUTCOMES OF BREXUCABTAGENE AUTOLEUCEL (BREXU-CEL) FOR RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA: A CIBMTR SUBGROUP ANALYSIS BY PRIOR TREATMENT

220

Nausheen Ahmed

Hintergrund





Wang et al., EHA 2022; P1117 (poster presentation)

Baseline Patient Characteristics

Characteristics[a]	Overall N=380	BTKi		Bendamustine		ASCT		Prior Therapies	
		Prior n=329	No prior n=51	Prior n=211	No prior n=169	Prior n=114	No prior n=266	1–2 Lines n=87	≥3 Lines n=293
Median age (range), years	66.8 (34.1–84.9)	66.9 (34.1–84.9)	65.5 (44.2–83.7)	**69.2 (44.2–84.9)**	**64.3 (34.1–83.7)**	**65.4 (34.1–82.3)**	**67.7 (34.3–84.9)**	66.9 (34.3–83.0)	66.5 (34.1–84.9)
ECOG PS ≥2, n (%)[b,c]	21 (6)	20 (7)	1 (2)	12 (6)	9 (6)	7 (6)	14 (6)	1 (1)	20 (7)
Ki-67 proliferation index ≥50%, n (%)[c,d]	97 (44)	**88 (47)**	**9 (28)**	**44 (37)**	**53 (52)**	23 (37)	74 (47)	27 (47)	70 (43)
TP53/17p deletion, n (%)[c,d]	40 (20)	32 (19)	8 (25)	16 (16)	24 (25)	6 (12)	34 (23)	13 (30)	27 (18)
Extranodal CNS involvement, n (%)[b,c]	17 (5)	17 (6)	0	11 (6)	6 (4)	7 (7)	10 (4)	1 (1)	16 (6)
Median no. of prior lines of therapy before leukapheresis (min–max)	4 (1–12)	**4 (1–12)**	**2 (1–7)**	**4 (1–12)**	**3 (1–10)**	**4 (1–12)**	**3 (1–11)**	**2 (1–2)**	**4 (3–12)**
Bridging therapy (any type), n (%)[c]	170 (46)	**159 (50)**	**11 (23)**	99 (48)	71 (44)	52 (47)	118 (46)	**29 (35)**	**141 (50)**

- Older patients were more likely to have had prior bendamustine and less likely to have received prior ASCT
- Patients with no prior BTKi therapy tended to receive brexu-cel in earlier lines and were less likely to receive bridging therapy

[a]In the overall population, 76% of patients were male, 79% were Non-Hispanic white, 4% Non-Hispanic black, 11% Hispanic, and 6% were other races, 30% of patients were chemosensitive prior to infusion, 76% had clinically significant comorbidities, 8% were planned outpatient infusions, and median time from leukapheresis to infusion was 28 days; these baseline characteristics were consistent across all subgroups. [b]Prior to infusion. [c]Percentages are based on the number of patients with available data. [d]At diagnosis.
Values in bold text denote statistically significant difference within a subgroup.

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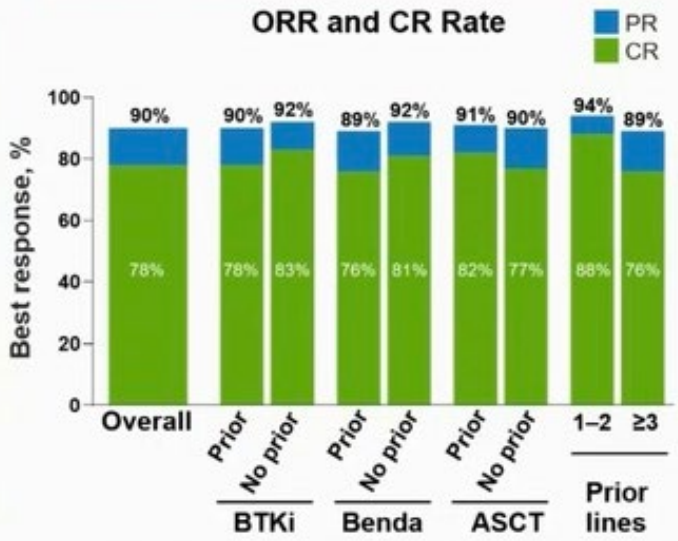
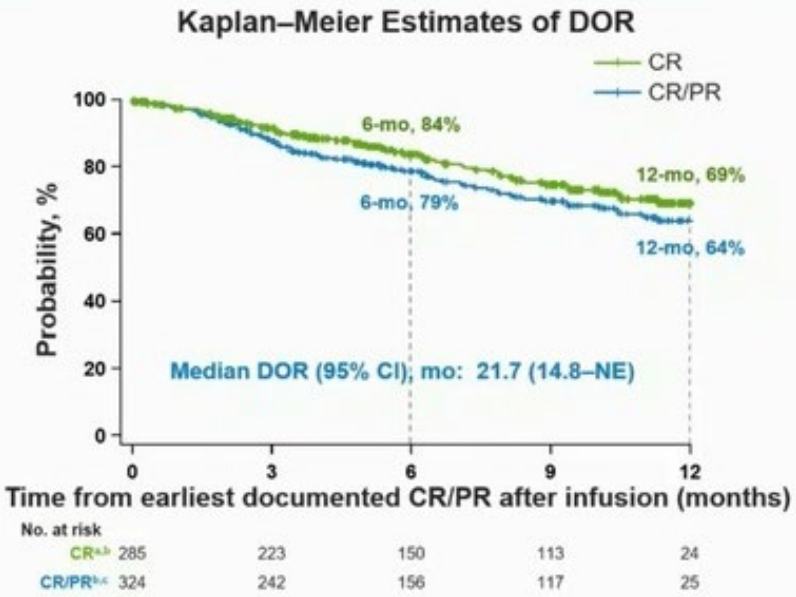
7

ORR, CR Rate, and DOR — Overall Population





- ORR and CR rates in ZUMA-2 were 91% and 68%, respectively[1]

[a]Among patients who achieved CR as a best response. [b]Subsequent cellular therapy and HCT without previously documented relapse or disease progression were censored; median follow-up was 12.0 months (range, 0.0–26.3). [c]Among patients who achieved CR/PR as a best response. NE, not estimable.

1. Wang M, et al. *J Clin Oncol*. 2023;41(3):555–567.

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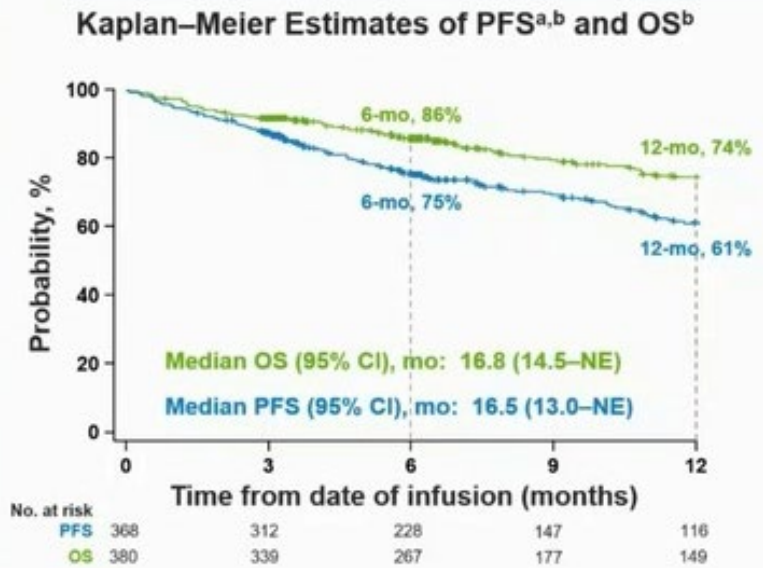
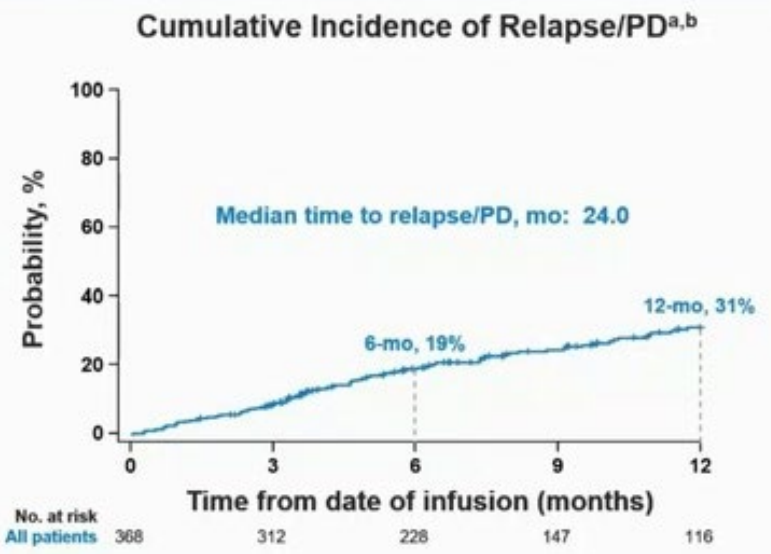
8

PFS, OS, and Relapse/PD — Overall Population





- In the ZUMA-2 primary analysis, the 12-month PFS and OS rates were 61% and 83%, respectively[1]

[a]Subsequent cellular therapy and HCT without previously documented relapse or PD were censored. [b]Median follow-up was 12.0 months (range, 0.0–25.3). NE, not estimable.

1. Wang M, et al. *N Engl J Med*. 2020;382(14):1331–1342.

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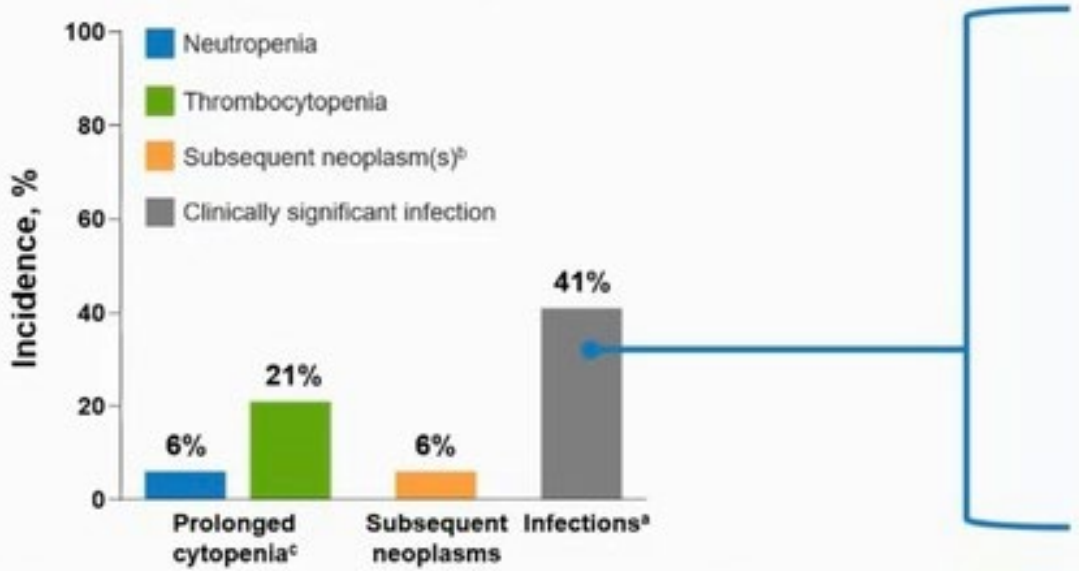
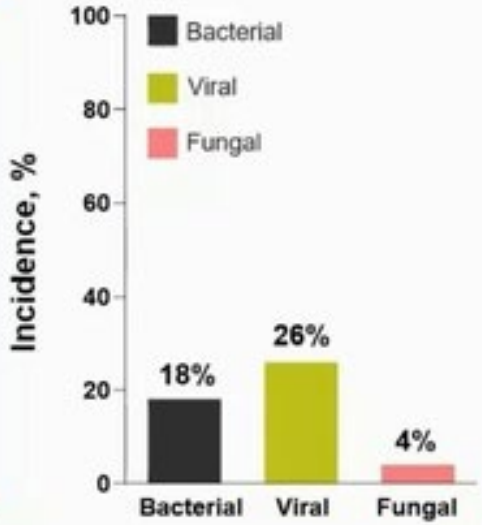
9

Other Safety Outcomes — Overall Population

Prolonged Cytopenia, Subsequent Neoplasms, and Infections[a]



Types of Infections[d]



- Prolonged neutropenia and thrombocytopenia occurred in 6% and 21% of patients, respectively
- The most common clinically significant infections were bacterial (18%) and viral (26%)

[a]Infection was defined according to CIBMTR Forms Instruction Manual: https://www.manula.com/manuals/cibmtr/flm/1/en/topic/4100q180-183. [b]Defined as the diagnosis of a new or secondary malignancy that is not a recurrence, progression, or transformation of the primary disease after initial brexu-cel infusion. [c]Prolonged neutropenia (failure to recover absolute neutrophil count ≥0.5 × 10^9/L and/or sustain 3 lab values) or thrombocytopenia (failure to recover platelet count ≥20 × 10^9/L) among patients who survived 30 days after infusion. [d]Types of infections were not mutually exclusive; percentages are based on the overall analysis population (N=380).

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12

Kapitel 3

Neue Therapieoptionen?

PIRTOBRUTINIB IN COVALENT BTK-INHIBITOR PRE-TREATED MANTLE CELL LYMPHOMA: UPDATED RESULTS AND SUBGROUP ANALYSIS FROM THE PHASE 1/2 BRUIN STUDY WITH >3 YEARS FOLLOW-UP FROM START OF ENROLLMENT

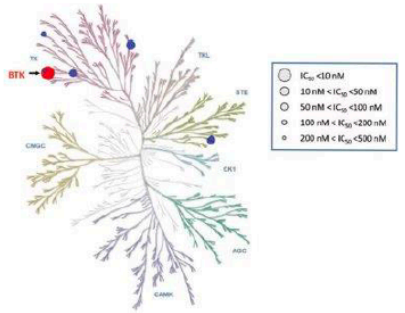
1087

W. Jurczak

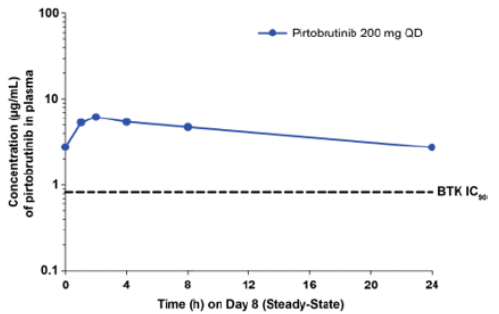
Hintergrund

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

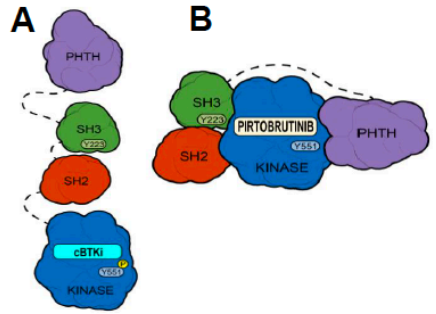
Highly Selective for BTK[2,3]



Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



Pirtobrutinib may stabilize/ maintain BTK in a closed inactive conformation

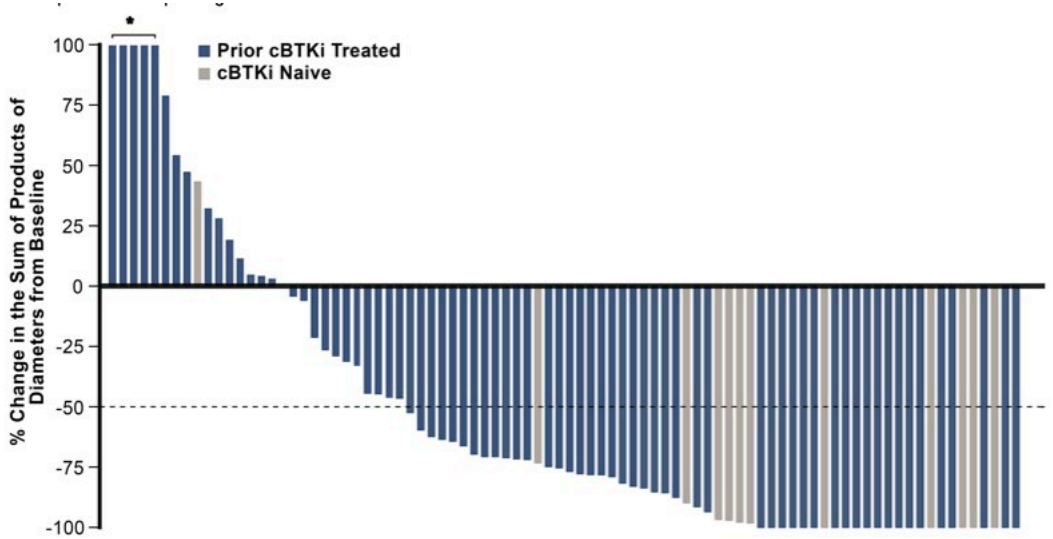


- Inhibits both WT and C481-mutant BTK with equal low nM potency[4]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[4]

MCL Patient Characteristics

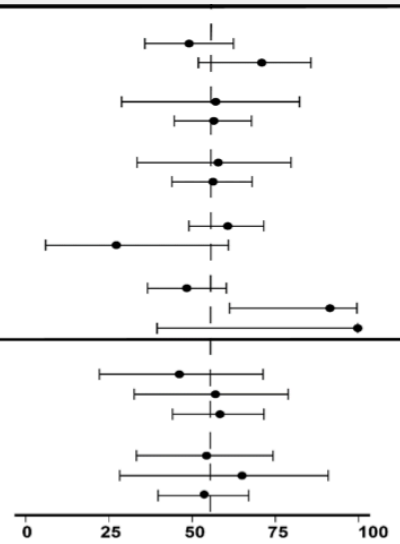
Characteristics	Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Median age, years (range)	70.0 (46.0-87.0)	67.0 (60.0-86.0)
Male, n (%)	72 (80.0)	10 (71.4)
Histology, n (%)		
Classic	70 (77.8)	11 (78.6)
Pleomorphic/Blastoid	20 (22.2)	3 (21.4)
ECOG PS, n (%)		
0	61 (67.8)	5 (35.7)
1	28 (31.1)	8 (57.1)
2	1 (1.1)	1 (7.1)
sMIPI Score, n (%)		
Low risk (0-3)	20 (22.2)	3 (21.4)
Intermediate risk (4-5)	50 (55.6)	5 (35.7)
High risk (6-11)	20 (22.2)	6 (42.9)
Tumor bulk (cm), n (%)		
<5[a] / ≥5	66 (73.3) / 24 (26.7)	9 (64.3) / 5 (35.7)
Bone marrow involvement, n (%)		
Yes	46 (51.1)	4 (28.6)
No	44 (48.9)	10 (71.4)
Median number of prior lines of systemic therapy, n (range)	3 (1-8)	2 (1-3)
Reason discontinued any prior cBTKi[b], n (%)		
Progressive disease	74 (82.2)	-
Toxicity / Other	16 (17.8)	-
Prior therapy, n (%)		
BTK inhibitor	90 (100.0)	0 (0.0)
Anti-CD20 antibody	86 (95.6)	14 (100.0)
Chemotherapy	79 (87.8)	14 (100.0)
Immunomodulator	19 (21.1)	1 (7.1)
Stem cell transplant	19 (21.1)	7 (50.0)
Autologous	17 (18.9)	7 (50.0)
Allogeneic	4 (4.4)	0 (0.0)
BCL2 inhibitor	14 (15.6)	0 (0.0)
CAR-T	4 (4.4)	0 (0.0)
PI3K inhibitor	3 (3.3)	1 (7.1)
***TP53* status**, n (%)		
Yes	17 (18.9)	3 (21.4)
No	19 (21.1)	4 (28.5)
Missing	54 (60.0)	7 (50.0)
Ki-67 index, n (%)		
<30%	9 (10.0)	2 (14.3)
≥30%	25 (27.8)	6 (42.9)
Missing	56 (62.2)	6 (42.9)

Data cutoff date of 29 Jul 2022. . [a]<5 cm includes 7 prior cBTKi patients and 1 cBTKi-naïve patient without a measurable lymph node. [b]In the event more than one reason was noted for discontinuation, disease progression took priority.

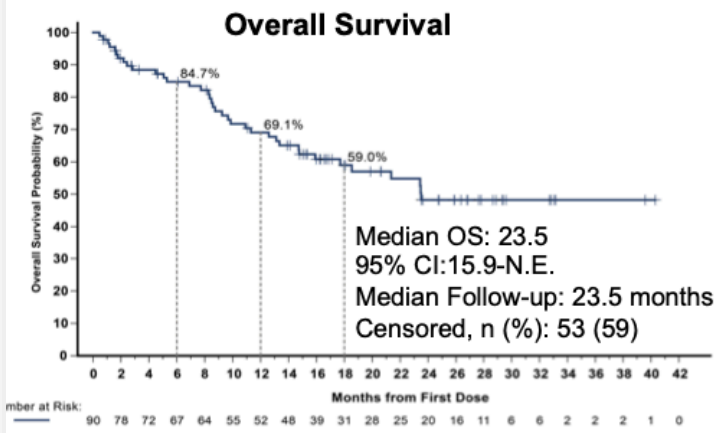


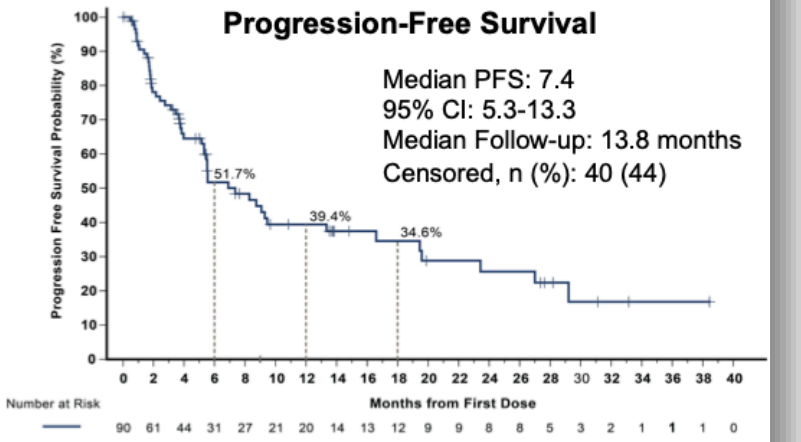
Overall Response Rate in Prior cBTKi MCL Subgroups

	Responders/Patients	ORR % (95% CI)
All Patients	51/90	56.7 (45.8 - 67.1)
Age (years)		
< 65	17/24	70.8 (48.9 - 87.4)
≥ 65	34/66	51.5 (38.9 - 64.0)
Sex		
Male	39/72	54.2 (42.0 - 66.0)
Female	12/18	66.7 (41.0 - 86.7)
Race		
White	42/76	55.3 (43.4 - 66.7)
Non-White	9/14	64.3 (35.1 - 87.2)
Region		
US	38/68	55.9 (43.3 - 67.9)
Outside US	13/22	59.1 (36.4 - 79.3)
ECOG PS at Baseline		
0	36/61	59.0 (45.7 - 71.4)
1-2	15/29	51.7 (32.5 - 70.6)
Ann Arbor Staging for Lymphoma		
Stage I - III	12/20	60.0 (36.1 - 80.9)
Stage IV	39/70	55.7 (43.3 - 67.6)
Simplified MCL IPI		
Low Risk [0 to 3]	16/20	80.0 (56.3 - 94.3)
Intermediate Risk [4 to 5]	30/50	60.0 (45.2 - 73.6)
High Risk [6 to 11]	5/20	25.0 (8.7 - 49.1)
Tumor Bulk (largest diameter)		
< 5 cm	35/59	59.3 (45.7 - 71.9)
≥ 5 cm	10/24	41.7 (22.1 - 63.4)
Extranodal Disease		
Yes	24/35	68.6 (50.7-83.1)
No	27/55	49.1 (35.4 - 62.9)
Bone Marrow Involvement		
Yes	25/46	54.3 (39.0 - 69.1)
No	26/44	59.1 (43.2 - 73.7)
Gastrointestinal Involvement		
Yes	4/7	57.1 (18.4 - 90.1)
No	47/83	56.6 (45.3 - 67.5)
MCL Histology		
Classic/Leukemic	41/70	58.6 (46.2 - 70.2)
Blastoid	4/8	50.0 (15.7 - 84.3)
Pleomorphic	6/12	50.0 (21.1 - 78.9)
Prior Lines of Systemic Therapies		
≤ 3	29/59	49.2 (35.9 - 62.5)
> 3	22/31	71.0 (52.0 - 85.8)
Prior BCL2 Inhibitor		
Yes	8/14	57.1 (28.9 - 82.3)
No	43/76	56.6 (44.7 - 67.9)
Prior Stem Cell Transplant		
Yes	11/19	57.9 (33.5 - 79.7)
No	40/71	56.3 (44.0 - 68.1)
Prior Anti-CD20 and Chemotherapy		
Yes	48/79	60.8 (49.1 - 71.6)
No	3/11	27.3 (6.0 - 61.0)
Discontinuation from any Prior BTKi		
Disease Progression	36/74	48.6 (36.9 - 60.6)
Toxicity	11/12	91.7 (61.5 - 99.8)
Other	4/4	100.0 (39.8 - 100.0)
TP53 Status		
Positive	8/17	47.1 (23.0 - 72.2)
Negative	11/19	57.9 (33.5 - 79.7)
Missing	32/54	59.3 (45.0 - 72.4)
Ki-67 Index		
≥ 30%	14/25	56.0 (34.9 - 75.6)
< 30%	6/9	66.7 (29.9 - 92.5)
Missing	31/56	55.4 (41.5 - 68.7)

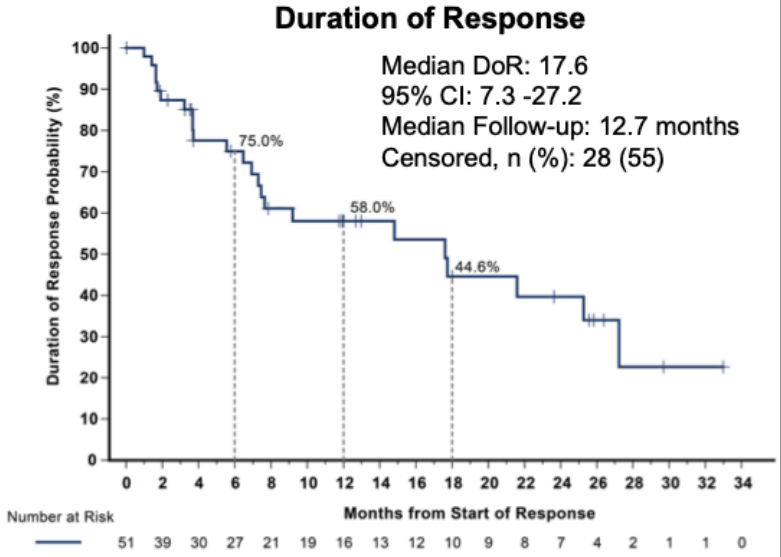


DoR, PFS, and OS in Pre-Treated MCL Patients Based on IRC Assessment





- cBTKi-naïve cohort, median DoR, PFS, and OS (95% CI) were not reached
  - 18-month DoR rate was 100% (95% CI: 100%)
  - 18-month PFS rate was 92.3% (95% CI: 56.6-98.9%)
  - 18-month OS rate was 92.3% (95% CI: 56.6-98.9%)



Data cutoff date of 29 Jul 2022. Response status per Lugano 2014 criteria based on IRC assessment.

Zusammenfassung | Take-Home-Messages

Eine Erhaltungstherapie ist beim Mantelzelllymphom mit einem verbesserten progressionsfreien Überleben assoziiert. Der Effekt kann jedoch nach dem Absetzen verschwinden.

Es wird wichtig sein, die Patienten zu identifizieren, die von einer verlängerten Therapie profitieren.

CAR-T-Zell-Therapie beim MCL ist auch im Routineinsatz sicher und effektiv in allen Patientengruppen.

Pirtobrutinib verspricht eine weitere Option für Patienten mit BTK—Versagen mit guter Verträglichkeit zu werden. Der Stellenwert im Vergleich zu anderen BTKi in der Inhibitor-naiven Situation muss noch evaluiert werden.

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2023

Für den Inhalt verantwortlich:

Prof. Dr. med. Georg Heß

Universitätsmedizin Mainz

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

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