Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

61. ASH Annual Meeting
7. – 10. Dezember 2019

KML-Experten berichten vom ASH 2019 aus Orlando

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

Prof. Dr. med. Christian Buske

Indolente Lymphome

Direktor, CCC Ulm - Institut für Experimentelle Tumorforschung, Universitätsklinikum Ulm | Präsident der German Lymphoma Alliance e.V. | Vorstandsmitglied im KML

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2019 wird in Kooperation mit vier unterstützenden Firmen durchgeführt. Diese Firmen haben keinen Einfluss auf die Inhalte dieses Vortrags. Meine weiteren Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	--
Beratungs-/ Gutachtertätigkeit	Roche, AbbVie, Janssen, Celltrion, Hexal
Besitz von Geschäftsanteilen, Aktien oder Fonds	--
Patent, Urheberrecht, Verkaufslizenz	--
Honorare	Roche, Pfizer, AbbVie, Janssen
Finanzierung wissenschaftlicher Untersuchungen	Roche, Janssen, Bayer, MSD
Andere finanzielle Beziehungen	--
Immaterielle Interessenskonflikte	

Kapitel 1

Indolente Lymphome
Follikuläres Lymphom (FL)

Ist IFRT ausreichend um MRD-Negativität beim lokalisierten FL zu erreichen?

#124

EARLY STAGE FOLLICULAR LYMPHOMA: FIRST RESULTS OF THE FIL "MIRO" STUDY, A MULTICENTER PHASE II TRIAL COMBINING LOCAL RADIOTHERAPY AND MRD-DRIVEN IMMUNOTHERAPY

Saturday, December 7, 2019: 10:00 AM
Hall E2, Level 2 (Orange County Convention Center)

Alessandro Pulsoni, MD[1*], *Maria Elena Tosti, Statistician, Simone Ferrero, MD*[3], *Stefano Luminari, MD*[4], *Anna Marina Liberati*[5*] *et al.*

[1]*Hematology Section, Department of Translational and Precision Medicine, Sapienza University of Rome, Italy, Rome, Italy*

Kapitel 2

Indolente Lymphome
Follikuläres Lymphom (FL)

Ist der neue Ansatz der Blockade der EZH2 Mutation beim FL erfolgversprechend?

#123

PHASE 2 MULTICENTER STUDY OF TAZEMETOSTAT, AN EZH2 INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA

Saturday, December 7, 2019: 10:00 AM
Hall E2, Level 2 (Orange County Convention Center)

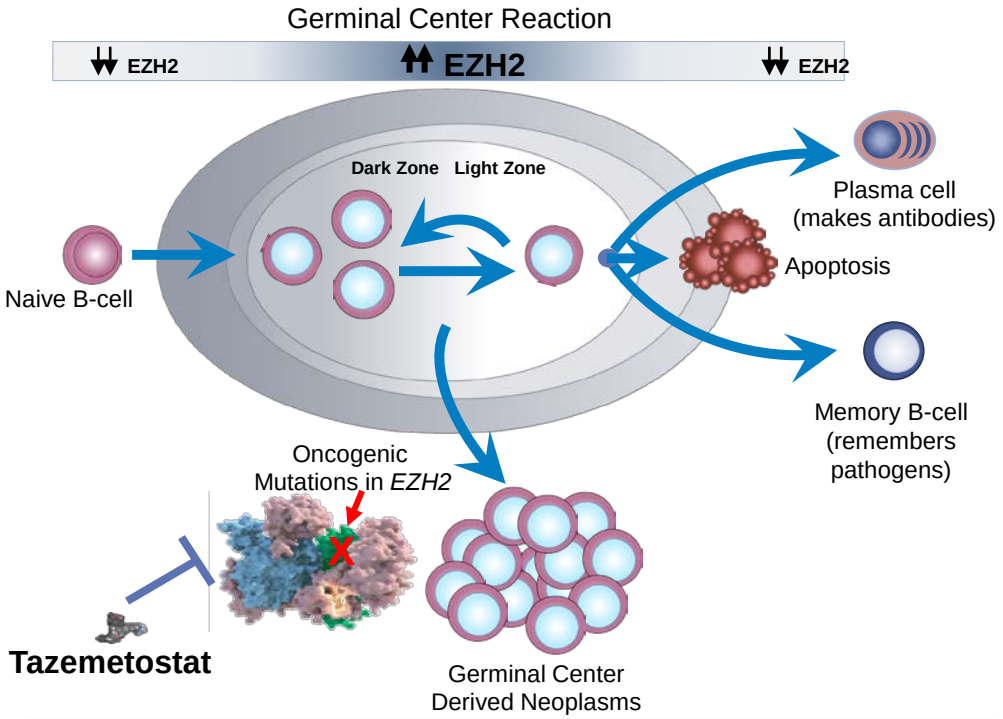
Franck Morschhauser, MD, PhD[1*], *Herve Tilly, MD, PhD*[2], *Aristeidis Chaidos*[3*], *Tycel J. Phillips, MD*[4], *Vincent Ribrag, MD*[5], *Philip Campbell, MBBS, FRACP, FRCPA*[6], *Damaj Gandhi Laurent, MD, PhD*[7*], *Wojciech Jurczak, MD, PhD*[8], *Pamela McKay, MD*[9*], *Stephen Opat*[10*], *John Radford*[11*], *Jennifer Whalen*[12*], *Anand Rajarethinam*[12*], *Susan Benedict Navia*[13*], *Deyaa Adib*[14*] *and Gilles A. Salles, MD, PhD*[15]

[1]*Department of Hematology, CHRU Lille, Lille, France*

Indolente NHL

Follicular Lymphoma and EZH2

- EZH2 is an epigenetic regulator of gene expression and cell fate decisions[1]
- EZH2 is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in EZH2 suppress exit from germinal state and “lock” B cells in this state, thereby transforming into a cancer[2]
- EZH2 biology relevant in both mutant (MT) and wild-type (WT) EZH2 FL
  - ~20% of patients with FL have EZH2 gain of function mutations[3]

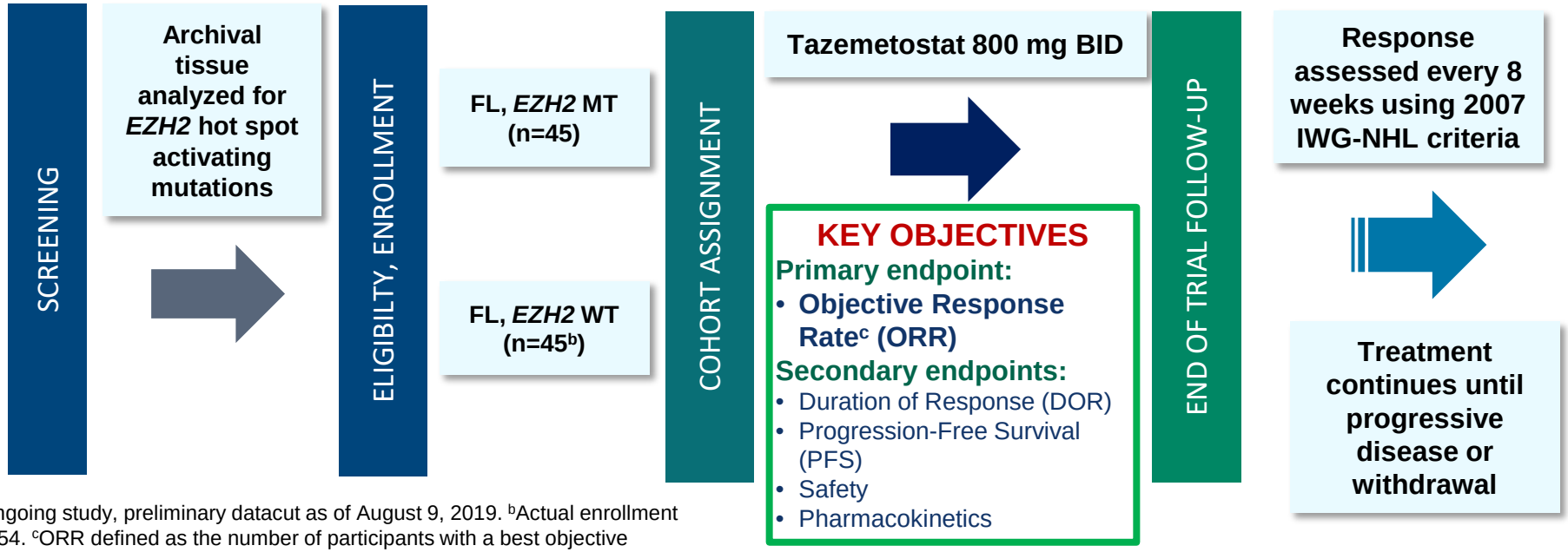


Tazemetostat, an investigational, first-in-class, selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin’s lymphoma patients with either MT or WT EZH2[4,5]

1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692. 3. Bödör C, et al. *Blood*. 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol*. 2018;19(5):649-59; 5. Morschhauser F, et al. *Hematol Oncol*. 2017;35:24-5. EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma.

Phase 2, Open-Label, Multicenter Study of Tazemetostat

- Enrollment initiated July 2015; last data cut for efficacy August 9, 2019[a]; for safety, May 24, 2019
- Conducted at 56 sites across North America, Europe, Asia, and Australia



[a]Ongoing study, preliminary datacut as of August 9, 2019. [b]Actual enrollment N=54. [c]ORR defined as the number of participants with a best objective response of complete response or partial response.

BID, twice-daily; EOT, end of treatment; FL, follicular lymphoma; IWG-NHL, International Working Group for non-Hodgkin's lymphoma; MT, mutant; WT, wild-type.

Indolente NHL

Tazemetostat is Well Tolerated in FL Patients

Adverse Events in ≥10% Patients[a]

Category, n (%)	All TEAEs (N=99)		Treatment-related TEAEs (N=99)	
	All Grades[b]	Grade ≥3	All Grades	Grade ≥3
Nausea	23 (23)	0 (0)	19 (19)	0 (0)
Asthenia	19 (19)	3 (3)	15 (15)	1 (1)
Diarrhea	18 (18)	0 (0)	12 (12)	0 (0)
Fatigue	17 (17)	2 (2)	12 (12)	1 (1)
Alopecia	17 (17)	0 (0)	14 (14)	0 (0)
Cough	16 (16)	0 (0)	2 (2)	0 (0)
Upper respiratory tract infection	15 (15)	0 (0)	1 (1)	0 (0)
Bronchitis	15 (15)	0 (0)	3 (3)	0 (0)
Anemia	14 (14)	5 (5)	9 (9)	2 (2)
Abdominal pain	13(13)	1 (1)	2 (2)	0 (0)
Headache	12 (12)	0 (0)	5 (5)	0 (0)
Vomiting	12 (12)	1(1)	6 (6)	0 (0)
Back pain	11 (11)	0 (0)	0 (0)	0 (0)
Pyrexia	10 (10)	0 (0)	2 (2)	0 (0)
Thrombocytopenia	10 (10)	5 (5)	8 (8)	3 (3)

- Treatment with tazemetostat was generally well tolerated
  - 8% of patients discontinued treatment due to TEAEs
  - 9% of patients had a dose reduction due to TEAEs
  - 27% of patients had a dose interruption due to TEAEs
  - Low rate of grade ≥3 treatment-related TEAEs
- There were no treatment-related deaths

[a]As of May 24, 2019; [b]All grade TEAEs reported as occurring in ≥10% of patients.

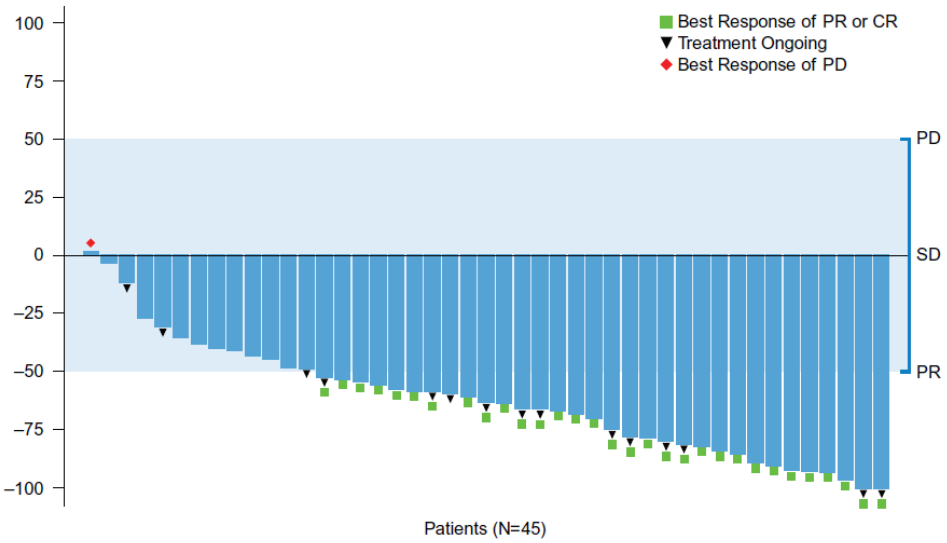
MT, mutant; TEAEs, treatment-emergent adverse events; WT, wild-type.

Indolente NHL

Response in the MT EZH2 Cohort

Parameter	MT EZH2 (n=45)	
	Investigator	IRC
Objective response rate, n (%)	35 (78)	31 (69)
95% CI[a]	62.9–88.8	53.4–81.8
Complete response, n (%)	4 (9)	6 (13)
Partial response, n (%)	31 (69)	25 (56)
Stable disease, n (%)	10 (22)	13 (29)
Progressive disease, n (%)	0	1 (2)[c]

[a]By Brookmeyer and Crowley method; [b]Best overall response based on Cheson (2007) criteria for lymphomas.



- **44 of 45[b] (98%) patients with evidence of tumor reduction by IRC**

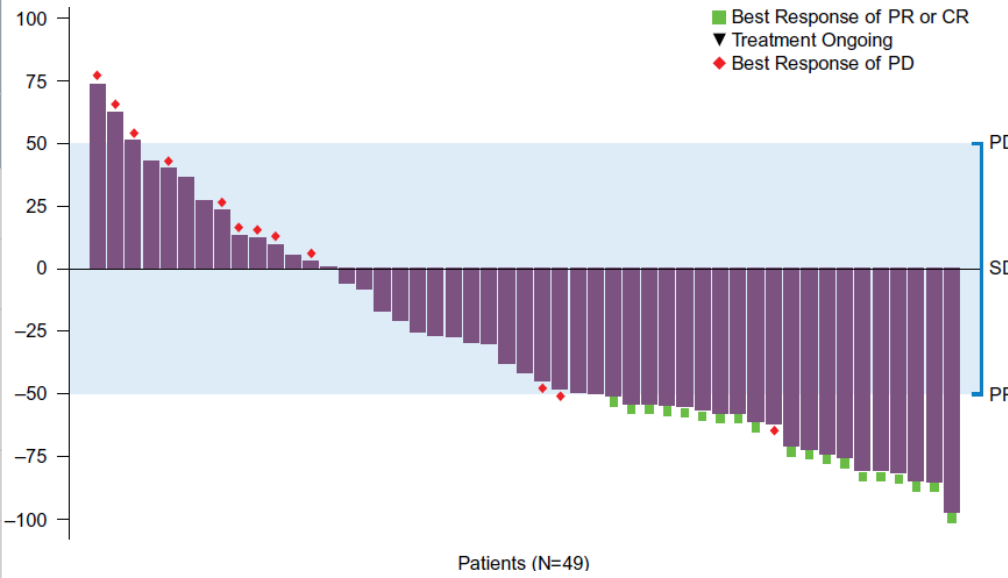
High Concordance Between IRC and Investigator Assessed Response

CI, confidence interval; DOR, duration of response; IRC, independent radiology committee; ITT, intent-to-treat; ORR, objective response rate; MT, mutant; NE, non-evaluable; WT, wild-type.

Indolente NHL

Responses in the WT EZH2 Cohort

Parameter	WT *EZH2* (n=54)	
	Investigator	IRC
Objective response rate, n (%)	18 (33)	19 (35)
95% CI[a]	21.1–47.5	22.7–49.4
Complete response, n (%)	3 (6)	2 (4)
Partial response, n (%)	15 (28)	17 (31)
Stable disease, n (%)	16 (30)	18 (33)
Progressive disease, n (%)	16 (30)	12 (22)
NE, missing, or unknown,[b] n (%)	4 (7)	5 (9)



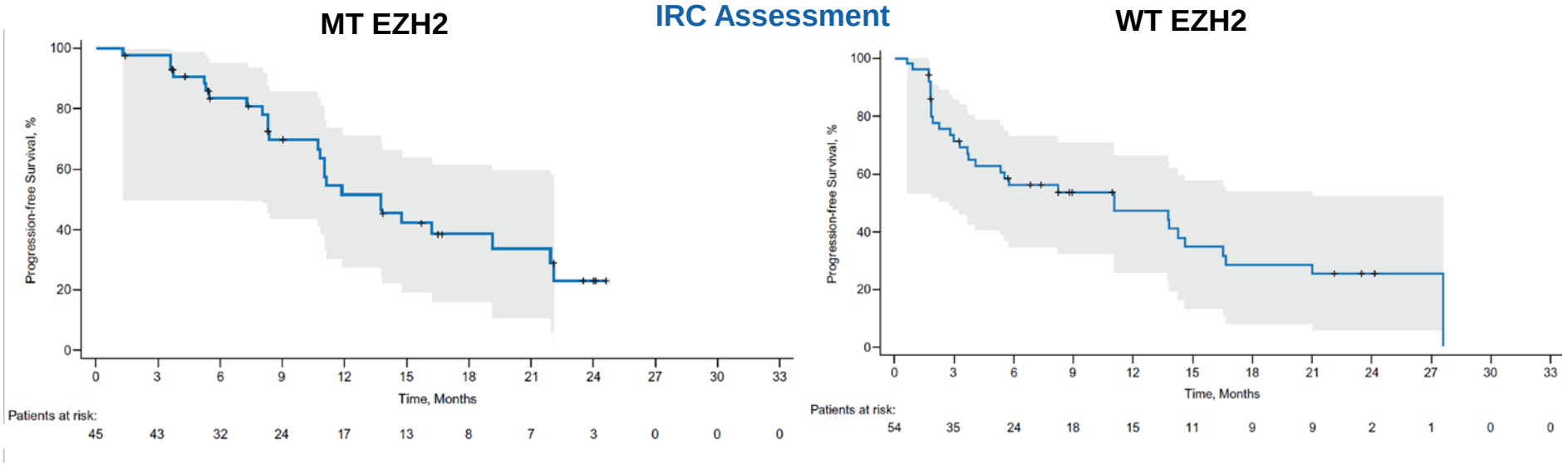
- **35 of 49[c] (71%) patients with evidence of tumor reduction by IRC**

High Concordance Between IRC and Investigator Assessed Response

[a]By Brookmeyer and Crowley method. [b]4 subjects with missing post-baseline values and 1 subject with poor image [c]Best overall response based on Cheson (2007) criteria for lymphomas.

CI, confidence interval; DOR, duration of response; IRC, independent radiology committee; ITT, intent-to-treat; ORR, objective response rate; MT, mutant; NE, non-evaluable; WT, wild-type.

Median PFS of 13.8 and 11.1 months was Observed in MT and WT EZH2 Cohorts



Endpoint	MT EZH2 Investigator (n=45)	MT EZH2 IRC (n=45)	WT EZH2 Investigator (n=54)	WT EZH2 IRC (n=54)
Median (95% CI) PFS, months,	13.8 (8.4, 16.4)	13.8 (10.7, 22.0)	5.6 (3.3, 11.1)	11.1 (3.7, 14.6)
K-M estimate of PFS (95% CI) at 6 months, %	83.3 (68.0, 91.7)	83.6 (68.6, 91.8)	46.4 (32.2, 59.4)	55.9 (40.7, 68.7)
K-M estimate of PFS (95% CI) at 12 months, %	53.2 (36.2, 67.6)	51.7 (34.4, 66.6)	35.8 (22.8, 49.0)	47.1 (31.6, 61.1)
K-M estimate of PFS (95% CI) at 18 months, %	31.0 (16.4, 46.8)	38.8 (22.7, 54.7)	22.5 (11.8, 35.)	28.3 (14.8, 43.4])

+, censored; CI, confidence interval; IRC, independent radiology committee; ITT, intent-to-treat; MT, mutant; NE, non-estimable; PFS, progression-free survival; WT, wild-type.

Treatment with Tazemetostat Demonstrated Clinical Activity in High-Risk Subgroups

IRC Assessment

Parameter	MT EZH2			WT EZH2		
	Refractory to rituximab (n=22)	POD24 (n=19)	Refractory to prior treatment (n=33)	Refractory to rituximab (n=32)	POD24 (n=32)	Refractory to prior treatment (n=42)
Objective response rate, n (%)	**13 (59)**	**12 (63)**	**21 (64)**	**10 (31)**	**8 (25)**	**12 (29)**
95% CI[a]	36.4–79.3	38.4–83.7	45.1–79.6	16.1–50.0	11.5–43.4	15.7–44.6
Complete response, n (%)	2 (9)	2 (11)	5 (15)	1 (3)	1 (3)	1 (2)
Partial response, n (%)	11 (50)	10 (53)	16 (49)	9 (28)	7 (22)	11 (26)
Stable disease, n (%)	8 (36)	7 (37)	11 (33)	8 (25)	11 (34)	13 (31)
Progressive disease, n (%)	1 (5)	0	1 (3)	10 (31)	9 (28)	12 (29)
NE, missing, or unknown, n (%)	0	0	0	4 (13)	4 (13)	5 (12)
Median DOR (95% CI), months	7.3 (2.9–12.0)	6.6 (2.1–NE)	8.3 (3.7–NE)	7.4 (1.0–NE)	13.0 (0.5–NE)	7.4 (3.4–19.3)

Best overall response based on Cheson (2007) criteria for lymphomas. [a] By Brookmeyer and Crowley method.

CI, confidence interval;. CR, complete response; IRC, independent radiology committee; MT, mutant; NE, non-evaluable; POD24, progression of disease within 24 months of prior therapy; WT, wild-type.

Summary

Tazemetostat, an investigational EZH2 inhibitor, demonstrated single agent, antitumor activity in patients with relapsed/refractory follicular lymphoma, with data from IRC indicating

- An ORR of 69% and 35% in MT and WT EZH2 cohorts, respectively
- Durable clinical activity across both MT and WT EZH2 cohorts, with patients on therapy up to 24 months, and responses continuing to deepen over time.
- A median PFS of 13.8 and 11.1 months in MT and WT EZH2 cohorts, respectively

Clinically meaningful responses were observed in high-risk subgroups particularly in MT EZH2 cohort

Tazemetostat was associated with a low frequency of treatment-related grade ≥3 TEAEs, and a low frequency of dose reduction or discontinuation due to AEs

Tazemetostat represents a potential therapeutic option for patients with relapsed/refractory follicular lymphoma

AE, adverse event; DOR, duration of response; FL, follicular lymphoma; IRC, independent radiology committee; MT, mutant; ORR, objective response rate; PFS, progression-free survival; POD24, progression of disease within 24 months of prior therapy; TEAE, treatment emergent adverse event; WT, wild-type

Kapitel 3

Indolente Lymphome
Follikuläres Lymphom (FL)

Können auch ältere Patienten mit FL von der Kombination Rituximab/Lenalidomid profitieren?

#347

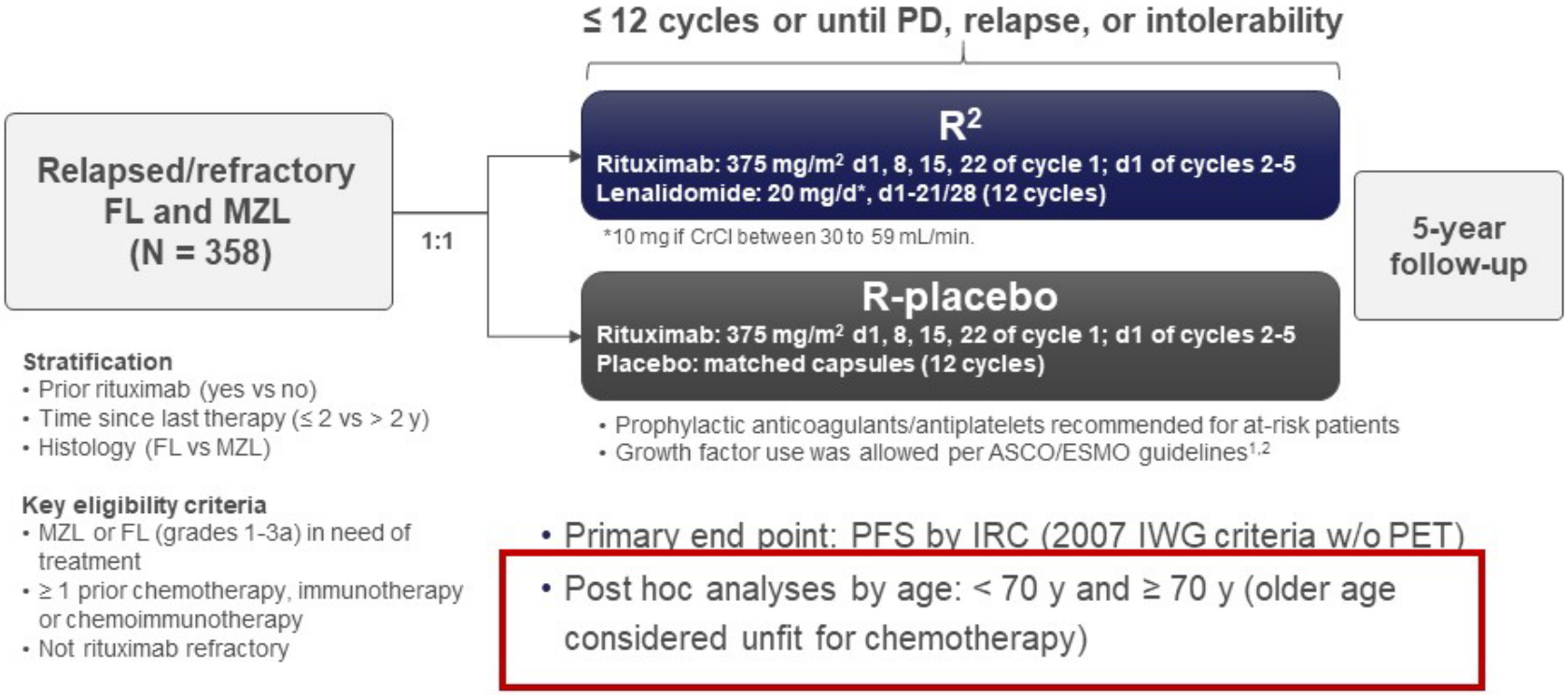
SUBGROUP ANALYSES OF ELDERLY PATIENTS AGED ≥ 70 YEARS IN AUGMENT: A PHASE III RANDOMIZED STUDY OF LENALIDOMIDE PLUS RITUXIMAB (R2) VS RITUXIMAB PLUS PLACEBO (R-PLACEBO) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) INDOLENT NON-HODGKIN LYMPHOMA (INHL)

Sunday, December 8, 2019: 8:30 AM
Tangerine 3 (WF3-4), Level 2 (Orange County Convention Center)

Marek Trněný, MD[1], *John P. Leonard, MD*[2], *Huilai Zhang*[3*], *Grzegorz Nowakowski, MD*[4], *Koji Izutsu, MD, PhD*[5*], *Nathan H. Fowler, MD*[6], *Catherine Thieblemont, MD PhD*[7], *Pier Luigi Zinzani, MD, PhD*[8], *Stacey Kalambakas, MD*[9*], *Myron Czuczman*[9*], *Pierre Fustier, PhD*[10*], *Chengqing Wu, PhD*[9*] *and John G. Gribben, MD, DSc*[11]

[1]*Charles University General Hospital, Prague, Czech Republic*

STUDY DESIGN: RANDOMIZED DOUBLE-BLIND PHASE III TRIAL



NCT01938001, EudraCT 2013-001245-14.
ASCO, American Society of Clinical Oncology; d, day; ESMO, European Society for Medical Oncology; FL, follicular lymphoma; IRC, independent review committee; IWG, International Working Group; MZL, marginal zone lymphoma; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; R², lenalidomide plus rituximab; R-placebo, rituximab plus placebo.
1. Crawford et al. *Ann Oncol.* 2010;21(suppl 5):248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212.

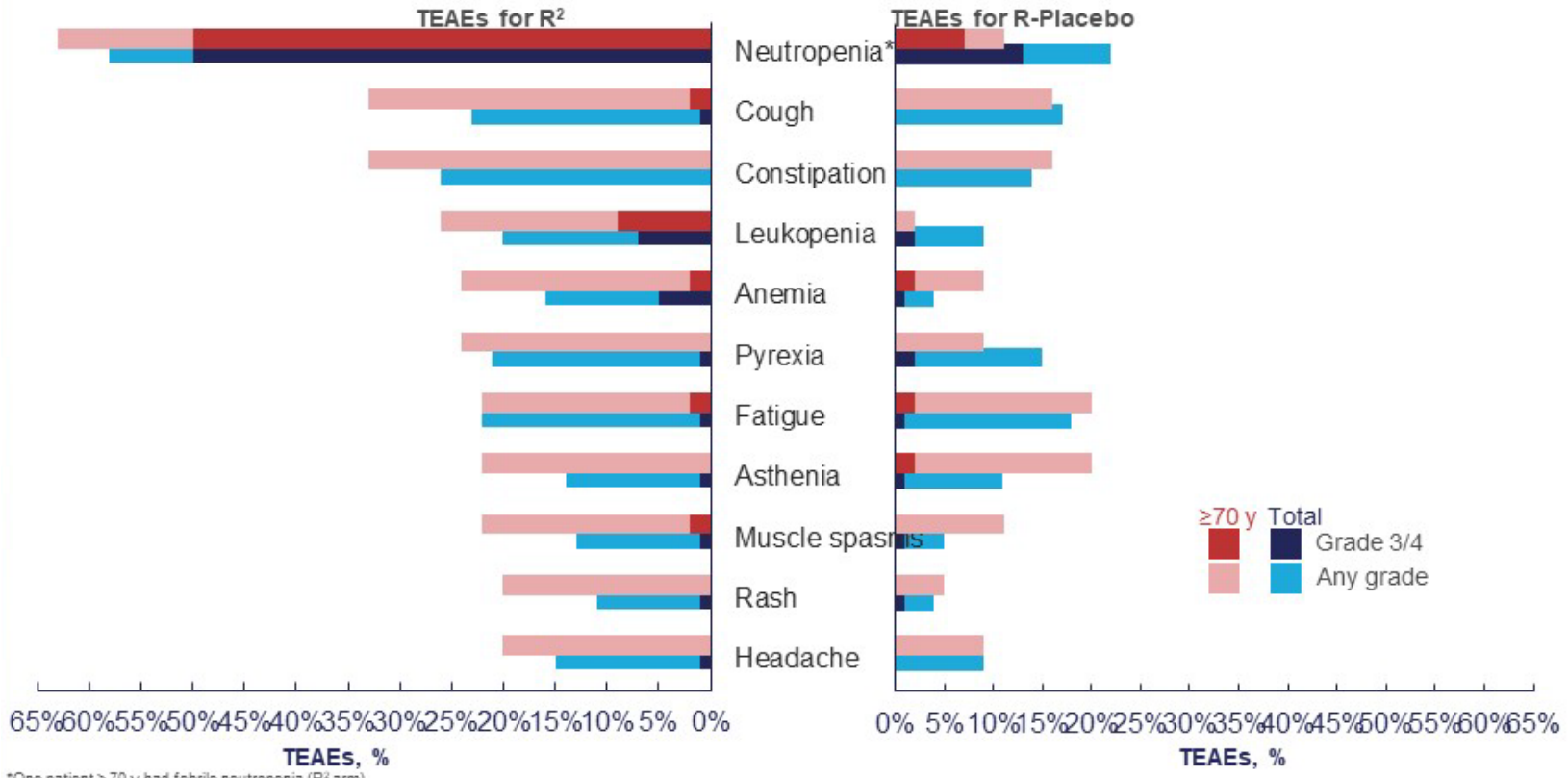
TREATMENT ADMINISTRATION AND MODIFICATIONS (SAFETY POPULATION)

	≥ 70 y		Total	
Treatment administration	**R² (n = 46)**	**R-Placebo (n = 44)**	**R² (n = 176)**	**R-Placebo (n = 180)**
Completed 12 cycles of lenalidomide/placebo, n (%)	26 (57)	29 (66)	125 (71)	111 (62)
Median no. of cycles of lenalidomide/placebo (min, max)	12 (1, 12)	12 (2, 12)	12 (1, 12)	12 (1,12)
Patients with lenalidomide/placebo dose modifications due to TEAE, n (%)	**R² (n = 46)**	**R-Placebo (n = 44)**	**R² (n = 176)**	**R-Placebo (n = 180)**
Dose reduction	16 (35)	1 (2)	63 (35)	13 (7)
Dose interruption	32 (70)	9 (20)	116 (66)	53 (29)
Discontinuation	9 (20)	5 (11)	15 (9)	9 (5)

- In the R² arm, the median number of treatment cycles was 12 for both ≥ 70 y subgroup and the total population; however:
  - Fewer patients aged ≥ 70 y completed 12 cycles of lenalidomide (57% vs 71%)
  - More patients aged ≥ 70 y started lenalidomide at the lower dose of 10 mg (35% vs 14%) because of low creatinine clearance
- In the R² ≥ 70 y subgroup vs total population, the average daily dose of lenalidomide was 14.4 mg/d (SD, 5.4) vs 17.0 mg/d (SD, 4.2), and median relative dose intensity was 86% vs 95%, respectively

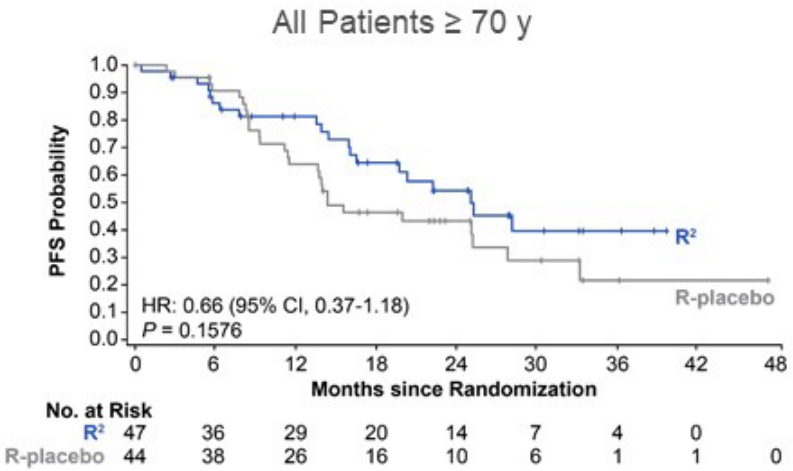
Data cutoff June 22, 2018.
R², lenalidomide plus rituximab; R-placebo, rituximab plus placebo; SD, standard deviation; TEAE, treatment-emergent adverse event.

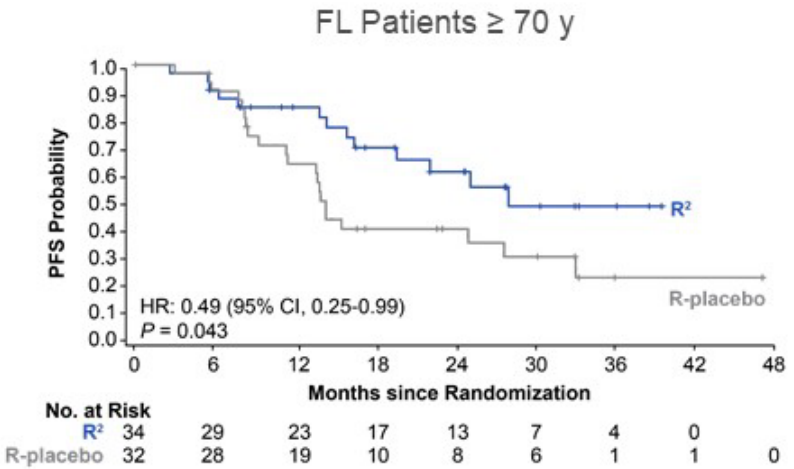
TEAEs IN ≥ 20% OF PATIENTS FOR EITHER GROUP (SAFETY POPULATION)



*One patient ≥ 70 y had febrile neutropenia (R² arm)
Data cutoff June 22, 2018.

PRIMARY END POINT: PROGRESSION-FREE SURVIVAL (ITT, IRC*)





	All ≥ 70 y		FL ≥ 70 y		Total	
	R² (n = 47)	R-Placebo (n = 44)	R² (n = 34)	R-Placebo (n = 32)	R² (n = 178)	R-Placebo (n = 180)
PFS, median (95% CI), mo	24.9 (16.4-NR)	14.3 (11.3-27.7)	28.0 (16.4-NR)	14.3 (11.3-27.7)	39.4 (22.9-NR)	14.1 (11.4-16.7)
HR (95% CI)	0.66 (0.37-1.18)		0.49 (0.25-0.99)		0.46 (0.34-0.62)	

Data cutoff June 22, 2018.
FDA, Food and Drug administration; FL, follicular lymphoma; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival; R², lenalidomide plus rituximab; R-placebo, rituximab plus placebo.
*Censoring rules based on FDA guidance.

CONCLUSIONS

- Similar to the results in the overall population,[1]
  - Median PFS in the ≥ 70 y vs overall population R^2 arms was 24.9 vs 39.4 months
  - R^2 showed trend to superior PFS vs R-placebo in ITT older patients aged ≥ 70 y (HR, 0.66, *P* = 0.1576)
  - R^2 showed superior PFS vs R-placebo in FL older patients aged ≥ 70 y (HR, 0.49, P=0.043)
- The safety profiles of R^2 and R-placebo in patients aged ≥ 70 y were similar to those reported in the overall population
- These data show that R^2 maintained efficacy improvements vs R-placebo in patients aged ≥ 70 y, despite higher unfit status and lower overall lenalidomide treatment/exposure (compared to the overall population)
- R^2 is an effective and available treatment option for patients with iNHL, including those with advanced age

CR, complete response; FDA, Food and Drug administration; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; PFS, progression-free survival; R^2, lenalidomide plus rituximab; R-placebo, rituximab plus placebo; R/R, relapsed/refractory.

1. Leonard et al. *J Clin Oncol*. 2019;37:1188-1199.

Kapitel 4

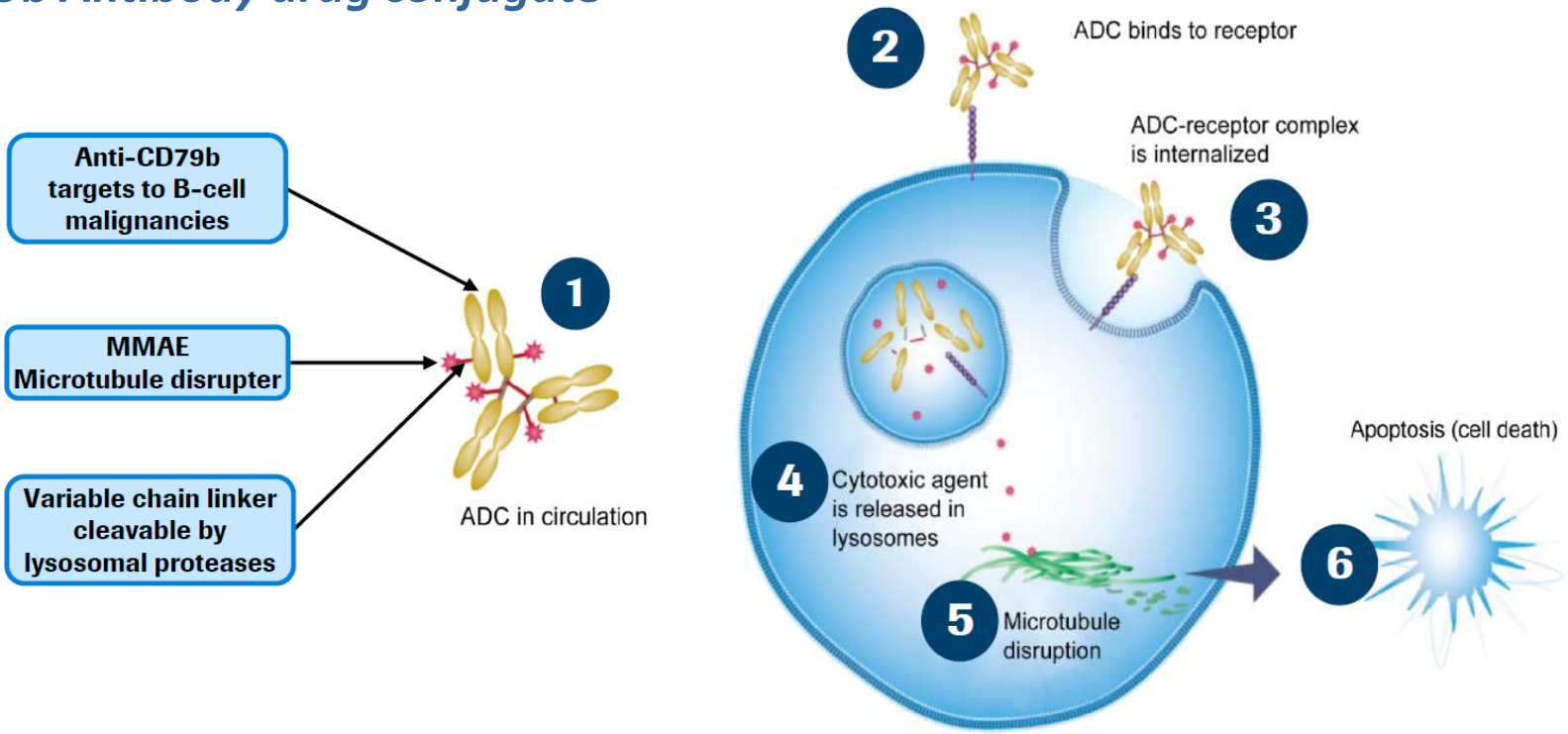
Indolente Lymphome
Follikuläres Lymphom (FL)

Wie sicher und effektiv ist eine Triple – Therapie, bestehend aus Obinutuzumab, Lenalidomid und Polatuzumab?

Indolente NHL

Polatuzumab Vedotin:

anti-CD79b Antibody drug conjugate



#126

POLATUZUMAB VEDOTIN PLUS OBINUTUZUMAB AND LENALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: PRIMARY ANALYSIS OF THE FULL EFFICACY POPULATION IN A PHASE IB/II TRIAL

Saturday, December 7, 2019: 10:45 AM
Hall E2, Level 2 (Orange County Convention Center)

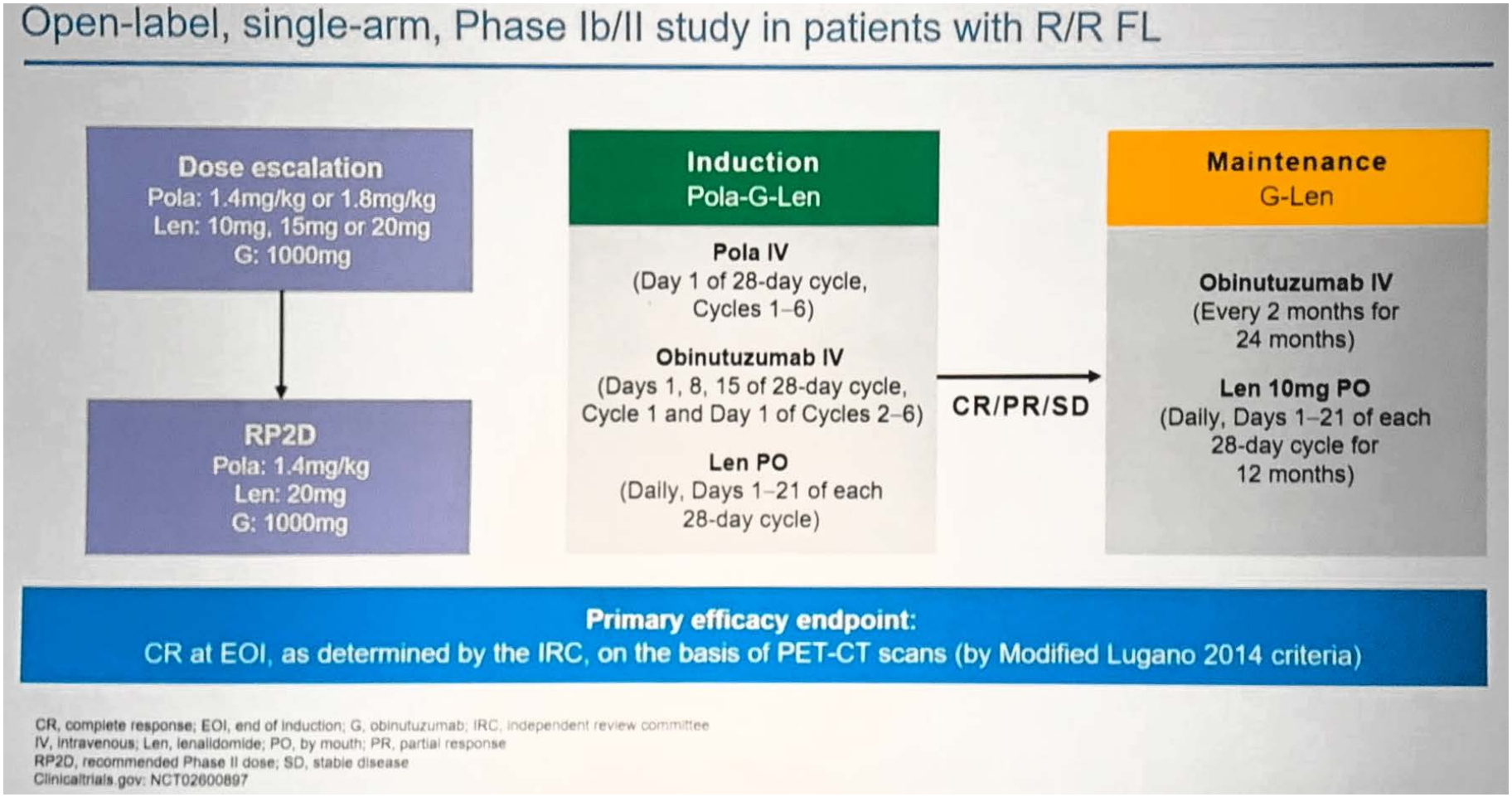
Catherine Diefenbach, MD1, *Brad S. Kahl, MD2, Lalita Banerjee, FRCPath3*, Andrew K McMillan, FRCP4, Fiona Miall, MD, FRCPath, MRCP, BMBS5*, Javier Briones, MD, PhD6*, Raul Cordoba, MD, PhD7, Jamie Hirata, PharmD8, YiMeng Chang, MSc9*, Lisa Musick, PharmD8* and Pau Abrisqueta, MD, PhD10**

[1]Perlmutter Cancer Center at NYU Langone Health, New York, NY

Hintergrund

- Polatuzumab-Vedotin (Pola) in Kombination mit Obinutuzumab (G)
  - Aktivität und Verträglichkeit in einer Phase-Ib/II-Studie bei Pts mit R/R follikulärem Lymphom
- Dublettkombination aus G plus Lenalidomid (Len): Günstige Aktivität und akzeptables Sicherheitsprofil
  - Phase-II-Studie an Patienten mit R/R FL
- Studienziel: Weitere Verbesserung des Antitumoransprechens bei R/R FL mit Pola-G-Len
- Präsentation der vollständigen Primäranalyse der Wirksamkeits- und Sicherheitsdaten aus einer Phase Ib/II-Studie von Pola-G-Len bei Patienten mit R/R FL

Studiendesign



CR, complete response; EOI, end of induction; G, obinutuzumab; IRC, independent review committee
IV, intravenous; Len, lenalidomide; PO, by mouth; PR, partial response
RP2D, recommended Phase II dose; SD, stable disease
Clinicaltrials.gov: NCT02600897

Studiendesign

Safety summary

Grade 3–4 AEs and AESIs

n (%)	*N*=56
Grade 3–4 AEs (≥2 patients)	**47 (84)**
Hematologic AEs	
Neutropenia	31 (55)
Thrombocytopenia	15 (27)
Anemia	8 (14)
Febrile neutropenia	6 (11)
Non-hematologic AEs	
Infections and infestations[1]	11 (20)
Hypokalemia	3 (5)
Diarrhea	2 (4)
Lipase increased	2 (4)
Laboratory tumor lysis syndrome	2 (4)
ALT increased	2 (4)
Syncope	2 (4)

- **Filgrastim (GCSF) use:**
  - 31 (55%) during induction
  - 20 (36%) during maintenance
- **Platelet transfusions:**
  - 1 (2%) during induction
  - 1 (2%) during maintenance

n (%)	*N*=56
AESIs	**6 (11)**
Neoplasms, benign, malignant, and unspecified	
Tumor flare	4 (7)
Myelodysplastic syndrome	1 (2)
Lung neoplasm malignant	1 (2)

AESI, adverse event of special interest; GCSF, granulocyte colony stimulating factor
Clinical cut-off date: 12 August 2019
[1]Presented as Systems Organ Class term – all other AEs are reported by 'preferred terms'

ASH 2019, Catherine Diefenbach *et al.*, 126: Polatuzumab Vedotin Plus Obinutuzumab and Lenalidomide in Patients With Relapsed/Refractory Follicular Lymphoma: [illegible]

Ergebnisse

Efficacy summary

Primary analysis efficacy-evaluable population (N=46)

	Modified Lugano 2014[1]		Lugano 2014	
EOI response, n (%)	INV	IRC	INV	IRC
Objective response	38 (83)	35 (76)	38 (83)	35 (76)
Complete response	28 (61)[2]	29 (63)[2]	34 (74)	33 (72)
Partial response	10 (22)	6 (13)	4 (9)	2 (4)
Stable disease	3 (7)	4 (9)	3 (7)	4 (9)
Disease progression	3 (7)	1 (2)	3 (7)	1 (2)
Missing/not evaluable/not available	2 (4)	6 (13)[3]	2 (4)	6 (13)[3]

INV, investigator assessed; IRC, independent review committee assessed

Clinical cut-off date: 12 Aug 2019

[1]Modified Lugano requires a negative bone marrow biopsy to confirm PET-CR and PET-PR must also meet CT-PR criteria

[2]CR downgraded to PR due to missing bone marrow biopsy in 6 patients by INV and 4 patients by IRC

[3]Three patients experienced early PD, scans were not sent to IRC and therefore were classified as missing

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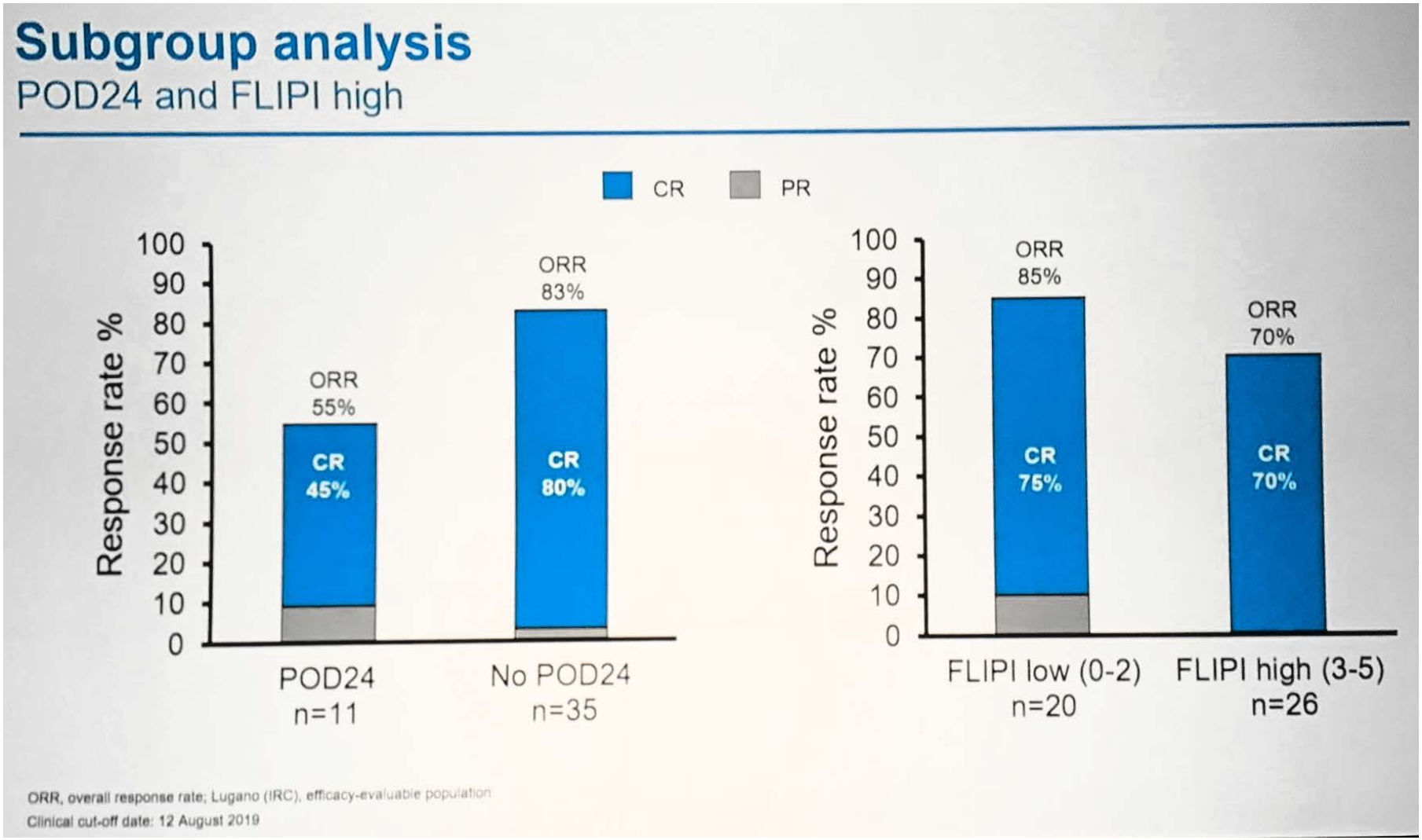
Ergebnisse


Subgroup analysis
POD24 and FLIPI high
CR
PR
Response rate %
100
90
80
70
60
50
40
30
20
10
0
ORR 55%
CR 45%
ORR 83%
CR 80%
POD24 n=11
No POD24 n=35
ORR 85%
CR 75%
ORR 70%
CR 70%
FLIPI low (0-2) n=20
FLIPI high (3-5) n=26
ORR, overall response rate; Lugano (IRC), efficacy-evaluable population
Clinical cut-off date: 12 August 2019

Schlussfolgerungen

- Diese Studie: Neuartige Triplettkombination Pola-G-Len zeigt ein Sicherheitsprofil, das mit den bekannten Profilen der einzelnen Arzneimittel übereinstimmt
- Bericht über die vollständige Wirksamkeit der Population:
  - Hohe CR-Raten bei EOI in einer stark vorbehandelten und refraktären Population, was im Vergleich zu derzeit verfügbaren R/R-FL-Therapien günstig ist
- Überzeugende Ergebnisse → Weitere Untersuchung dieser Triplett-Kombination in einer größeren Pt-Population
- Um das mediane PFS zu bestimmen, wird ein längerer Zeitraum der Nachsorge über die Erhaltungstherapie hinaus durchgeführt

ASH 2019, Catherine Diefenbach *et al.*, 126: Polatuzumab Vedotin Plus Obinutuzumab and Lenalidomide in Patients With Relapsed/Refractory Follicular Lymphoma: [illegible]

Kapitel 4

Indolente Lymphome
Morbus Waldenström

Sollte beim Morbus Waldenström einer Rituximab Erhaltungstherapie durchgeführt werden?

#343

TWO YEARS RITUXIMAB MAINTENANCE VS. OBSERVATION AFTER FIRST LINE TREATMENT WITH BENDAMUSTINE PLUS RITUXIMAB (B-R) IN PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA (MW): RESULTS OF A PROSPECTIVE, RANDOMIZED, MULTICENTER PHASE 3 STUDY (THE STIL NHL7-2008 MAINTAIN TRIAL)

Sunday, December 8, 2019: 7:30 AM
Tangerine 3 (WF3-4), Level 2 (Orange County Convention Center)

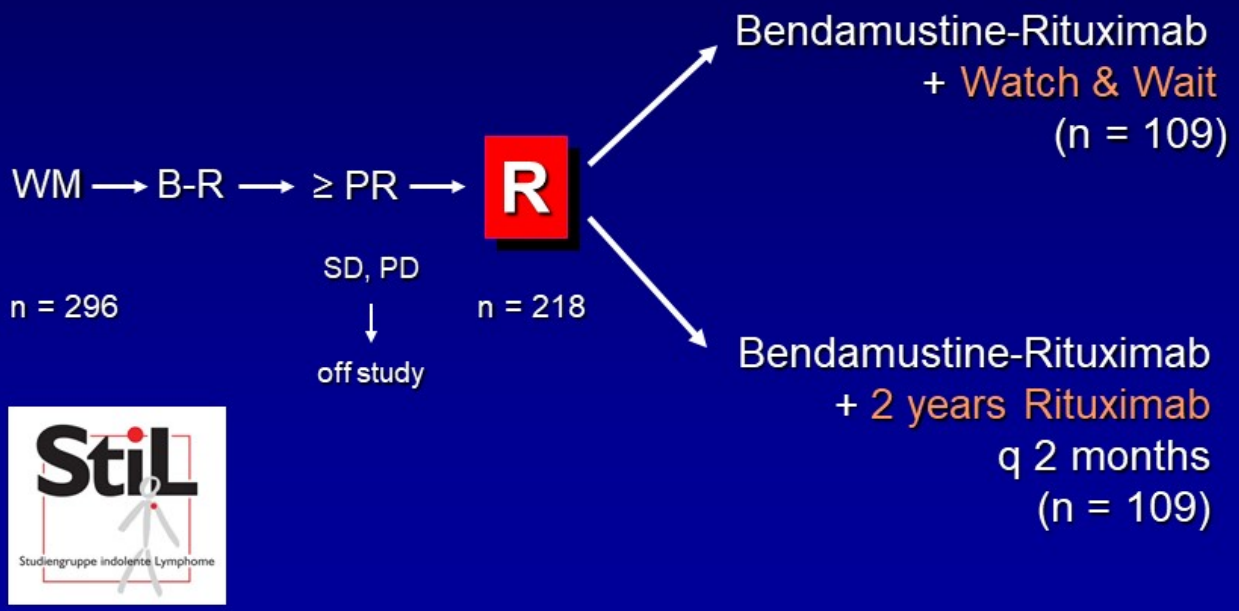
Mathias J Rummel, MD, PhD1*, *Christian Lerchenmüller, MD2*, Manfred Hensel, MD3*, Martin Goerner, MD4*, Christian Buske, MD, PhD5, Holger Schulz6*, Burkhard Schmidt, MD7*, Georgi Kojouharoff, MD8*, Elisabeth Lange, MD9*, Wolfgang Willenbacher, MD, PhD10, Jan Dürig11*, Erik Engel12*, Frank Kauff1*, Jürgen Barth1*, Alexander Christoph Burchardt, MD1*, Axel Hinke, PhD13*, Jasmin Wupperfeld1* and Richard Greil, MD14*

[1]Med. Clinic IV, Hematology, Justus Liebig University, Giessen, Germany

Indolente NHL

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

StiL NHL 7-2008 - MAINTAIN

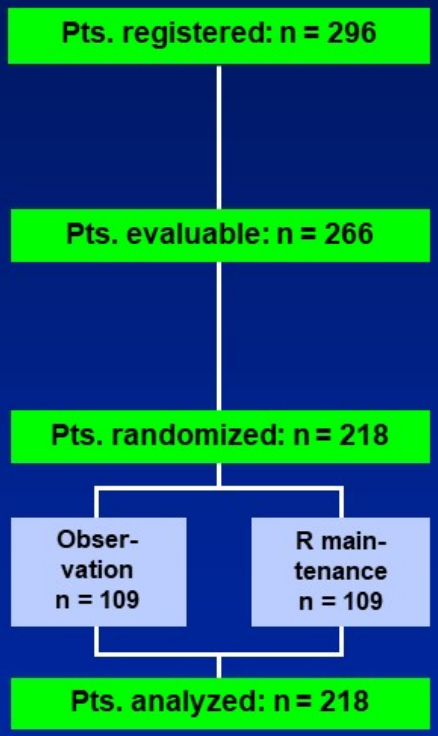


Inclusion criteria

- Patients with histological proven WM in need of treatment
- Previously untreated patients
- Histology not older than 6 months
- Stage III or IV
- Patients age 18 - 80 years
- ECOG 0-2
- Written informed consent of the patient

MJR

Patient disposition - Reasons for non-randomization



Patients not randomized	78 (26%)
Death	8
PD / SD	15
Transformation	5
Intolerance R / B	21
Withdrawn consent	14
Protocol violation	1
Neutropenia / Cytopenia	2
Infections	-
Toxicity	3
Other histology	4
Doctor's choice	1
Other reasons	4

MJR

Response rates following B-R induction

266 patients evaluable for response evaluation

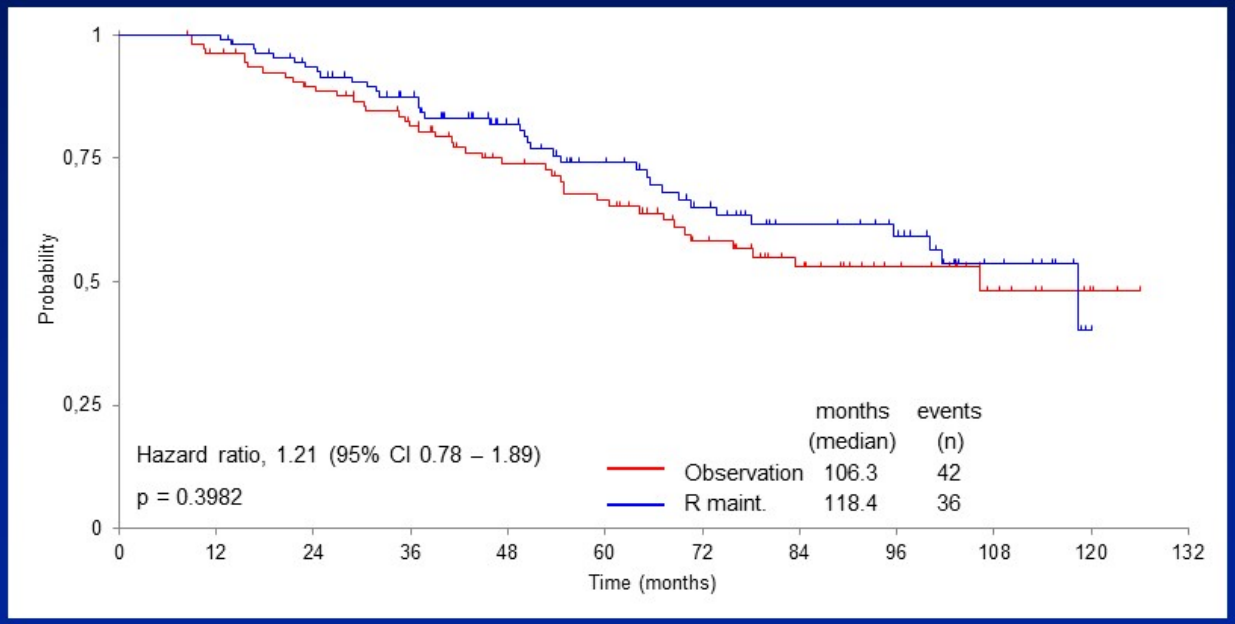
ORR	247	(93%)
MRR	235	(88%)
CR	3	(1%)
VGPR	65	(24%)
PR	167	(63%)
MR	12	(5%)
SD	3	(1%)
PD	11	(4%)
Early death *	5	(2%)

* Age of pts dying early: 65, 73, 74, 79, 79

MJR

Indolente NHL

Progression free survival (80 months median follow-up)

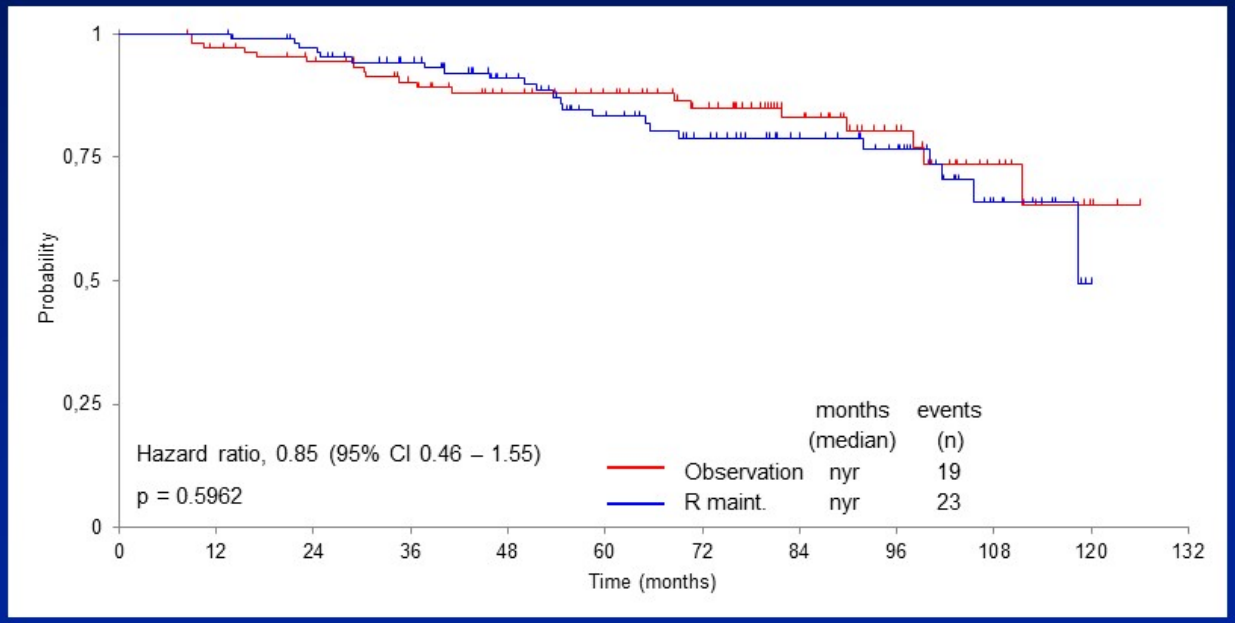


Pts at risk											
Observ.	109	102	92	79	62	54	39	27	18	9	3
R maint.	109	109	96	83	65	52	41	30	25	11	1

Indolente NHL

Overall survival

(80 months median follow-up)



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	1

Kapitel 5

Indolente Lymphome
Morbus Waldenström

Welche Ergebnisse lassen sich mit neuen chemotherapiefreien Ansätzen beim Morbus Waldenström erzielen?

#344

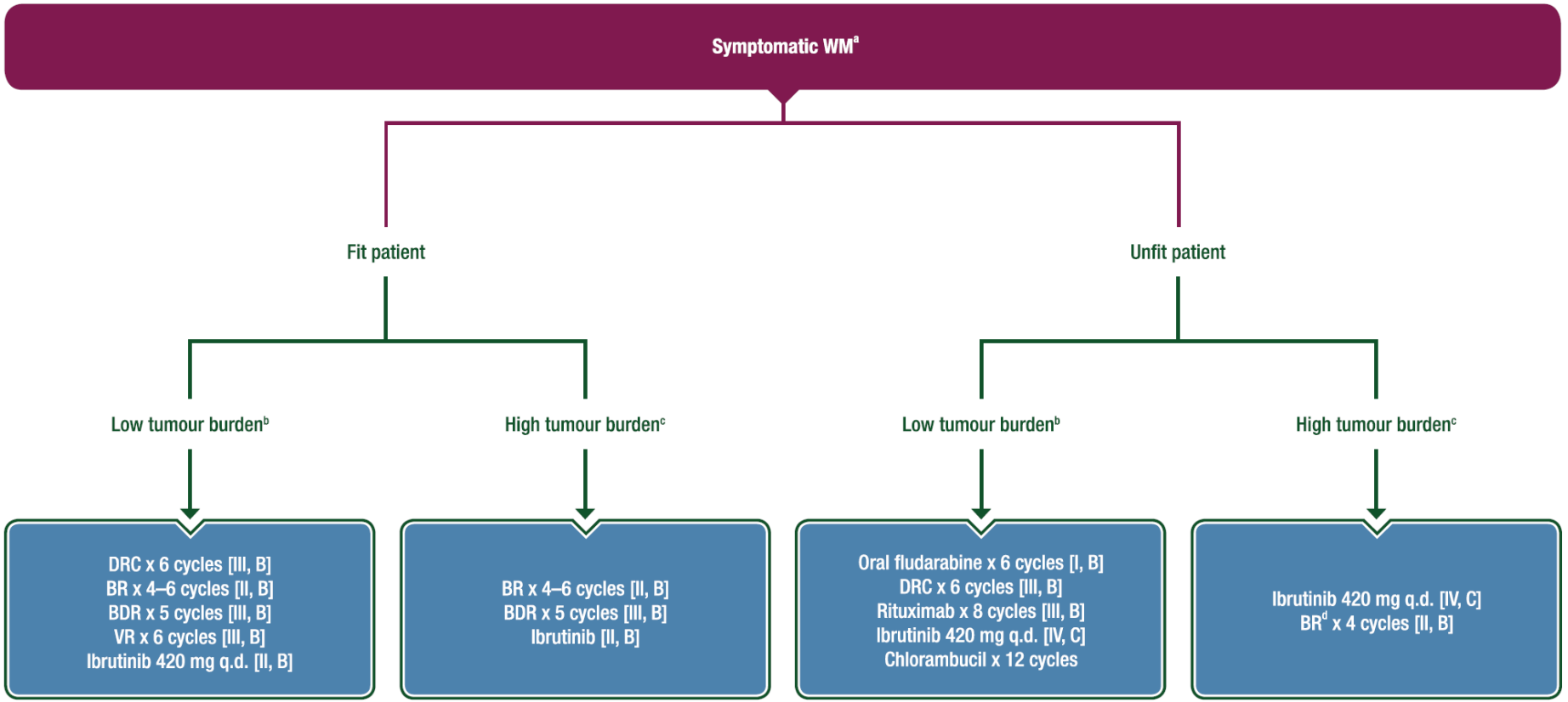
IXAZOMIB, RITUXIMAB AND DEXAMETHASONE (IRD) IN PATIENTS WITH RELAPSED OR PROGRESSIVE WALDENSTROM'S MACROBLOBULINEMIA: RESULTS OF THE PROSPECTIVE PHASE I/II HOVON 124/ECWM-R2 TRIAL

Sunday, December 8, 2019: 7:45 AM
Tangerine 3 (WF3-4), Level 2 (Orange County Convention Center)

Marie José Kersten, MD, PhD[1], *Monique C. Minnema*[2], *Josephine M. Vos, MD, PhD*[3,4*], *Kazem Nasserinejad*[5*], *Marcel Kap, BSc*[6*], *Eftathios Kastritis*[7*], *Maria Gavriatopoulou, MD*[8*], *Martine E.D. Chamuleau*[9], *Dries Deeren, MD, PhD*[10], *Lidwine Winnifred Tick, MD, PhD*[11], *Jeanette K. Doorduijn, MD, PhD*[12], *Fritz Offner, MD*[13], *Lara H Bohmer, MD*[14*], *Karima Amaador, MD*[3*], *Roberto D Liu, BSc*[3*], *Steven T Pals, MD, PhD*[15*] *and Meletios A. Dimopoulos, MD*[16]

[1]*Dept. of Hematology, Cancer Center, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands*

ESMO Guidelines Waldenström



Kastritis …. Buske 2018

Treatment schedule

Induction:
8 cycles q28 days

> SD

Maintenance:
2 years q3months

- Ixazomib citrate 4 mg d1,8,15
- Rituximab 1400 mg sc d1
  cycle 3-8 (1st dose iv)
- Dexamethasone 20 mg
  d1,8,15,22

- Rituximab 1400 mg sc d1

Eligibility

Main inclusion criteria

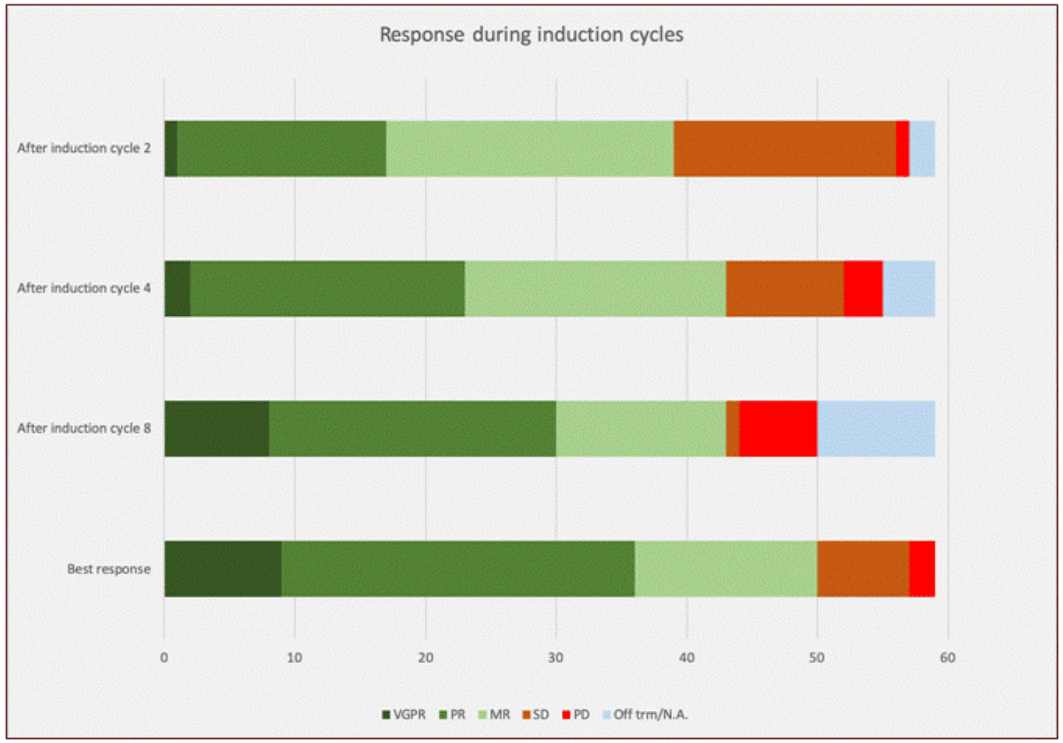
- Relapsed/progressed WM
- Need for treatment (consensus criteria)
- Measurable disease (IgM > 1 g/dl)
- Prior bortezomib and/or rituximab allowed, *unless refractory* (PD during treatment or < 6 months after last administration)
- Plt >80; ANC >1.0

Main exclusion criteria

- Amyloidosis
- Bing-Neel syndrome
- Known intolerance of rituximab and/or boron
- Other standard exclusion criteria

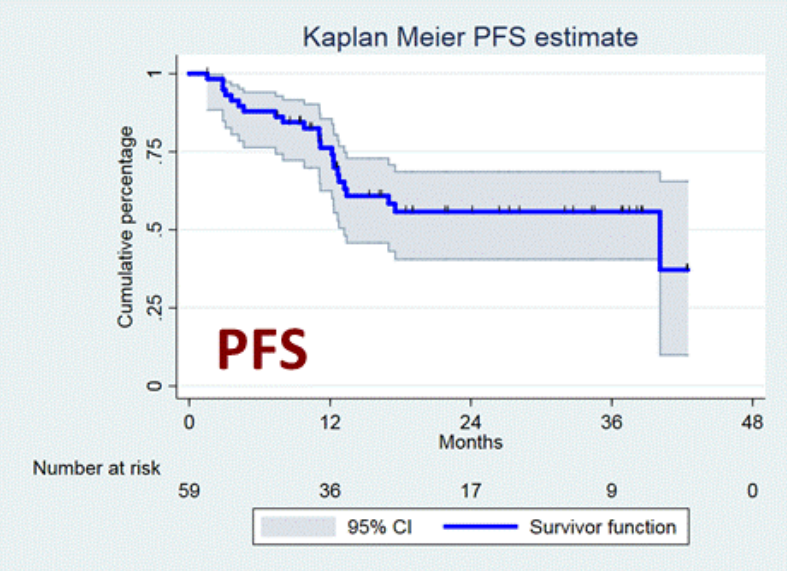
Response rates at c2, 4, 8 and best ORR

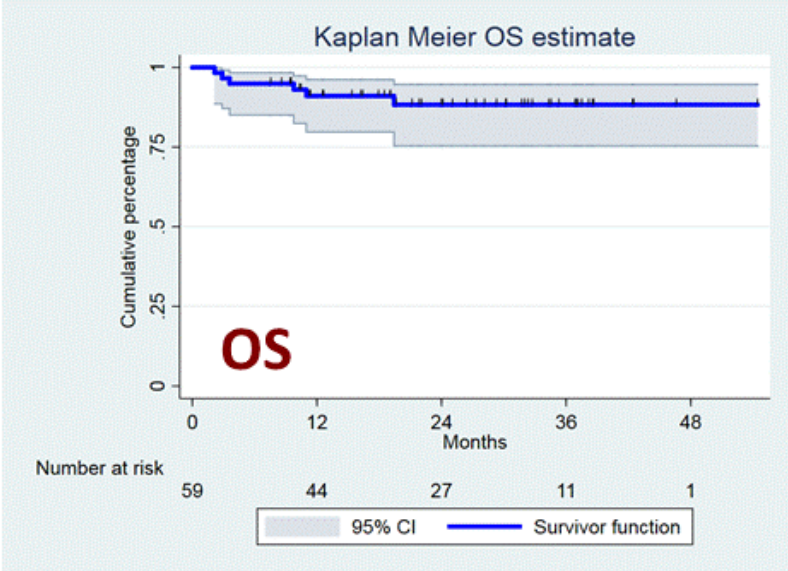
- Primary endpoint (ORR after c8 not <40%) was met:
  - ORR 71%; at least PR 51%
- Best response obtained during induction: ORR 85%
  - 15% VGPR, 46% PR, 24% MR



PFS and OS

median follow-up 24 months





At 24 months:

- **PFS 56%; DOR 60%; OS 88%**
- **Median PFS, DOR, OS not reached**

Conclusions

HOVON

IRD is feasible

- High ease of administration
- No IgM flares
- Using sc rituximab, none of the patients developed R hypersensitivity
- Using PROMs, no increase in symptom burden for PNP was seen

IRD is an active regimen

- Significant decrease in IgM and increase in Hb after cycle 2 (before start R)
- Significant increase global HR-QoL
- With a median follow-up of 24 months, median DOR and PFS have not been reached

Further improvement of results:

- Use as a backbone for combination treatment (e.g. with btk inhibitor, venetoclax, daratumumab)
- Ixazomib citrate consolidation/maintenance

#346

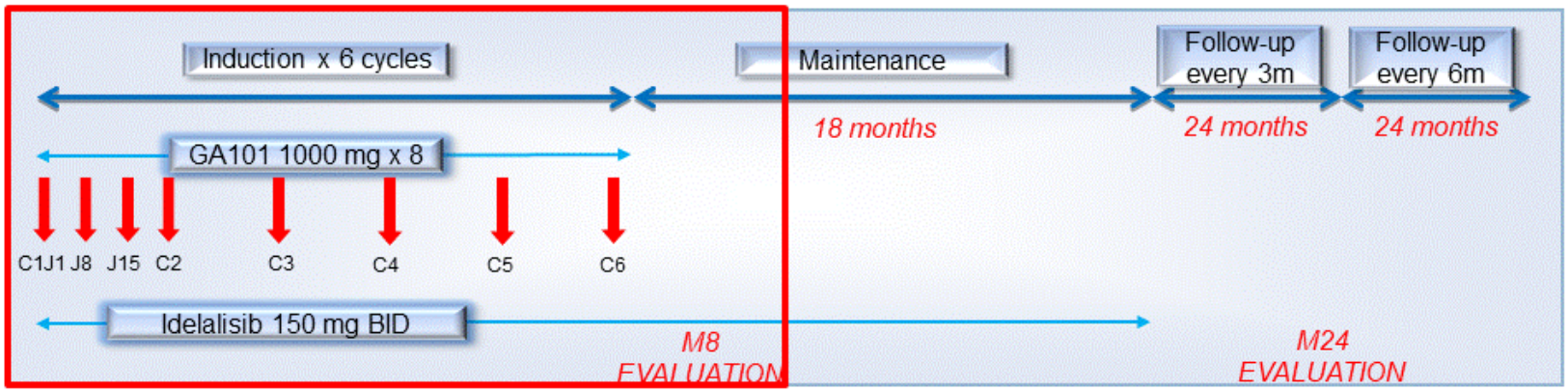
OPEN LABEL NON-RANDOMIZED PHASE II STUDY EXPLORING «CHEMO-FREE » TREATMENT ASSOCIATION WITH IDELALISIB + OBINUTUZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) WALDENSTROM'S MACROGLOBULINEMIA (MW), A FILO TRIAL: RESULTS OF THE INTERMEDIARY ANALYSIS OF THE INDUCTION PHASE

Sunday, December 8, 2019: 8:15 AM
Tangerine 3 (WF3-4), Level 2 (Orange County Convention Center)

Cecile Tomowiak, MD[1*], *Kristell Desseaux*[2*], *Stéphanie Poulain, MD, PhD*[3*], *Charles Herbaux, MD*[4*], *Aurore Perrot, MD, PhD*[5*], *Beatrice Mahe, MD*[6*], *Pierre Morel, MD*[7*], *Olivier Tournilhac*[8*], *Stephane Lepretre, MD*[9*], *Thérèse Aurran, MD*[10*], *Bruno Villemagne, MD*[11*], *Olivier Casasnovas, MD*[12*], *Delphine Nollet*[13*], *Brigitte Dreyfus, MD*[14*], *Sylvie Chevret, MD, PhD*[15*] *and Veronique Leblond, MD, PhD*[16]

[1]*Department of Oncology-Haematology and Cell Therapy, CHU, Poitiers, INSERM, Inserm CIC 1402, Poitiers, France, Poitiers, France*

Study design



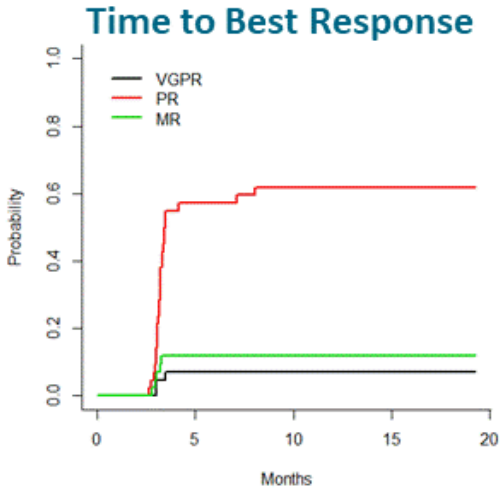
- Primary objective: PFS by investigator assessment in ITT
- Secondary objectives: response rate, OS, safety
- Results of early efficacy and safety, assessed after the induction phase
- DSMC planned meetings: 3 times (after the inclusion of 5 patients treated with 3 cycles, after 25 patients and at the end of the induction phase for the 50 patients)
- VZV and Pneumocystis prophylaxis, and CMV monitoring were mandatory for all patients

www.clinicaltrials.gov: NCT02962401

ASH 2019, REMODEL, Tomowiak *et al.*

Responses rate (n=49)

Best Responses	n (%)
ORR	34 (69)
CR	0
VGPR	3 (6)
PR	26 (53)
MR	5 (10)
Stable disease	6 (12)
Progressive disease	2 (4)



12-month rates
VGPR: 7%
PR: 62%
MR: 12%

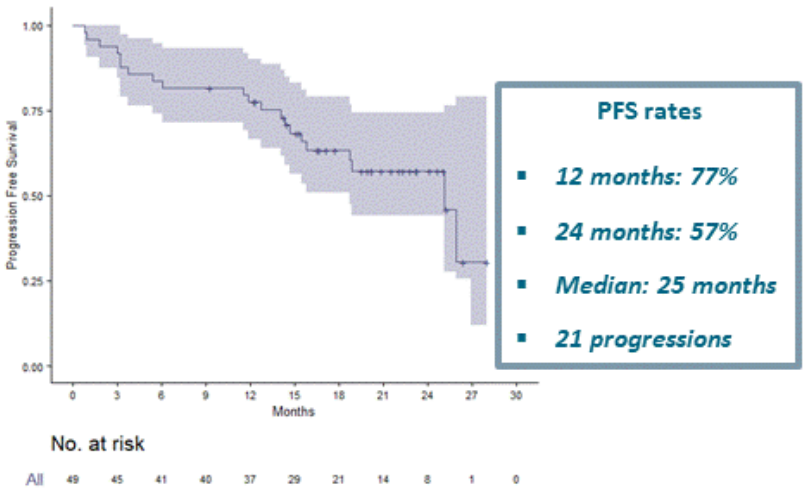
ORR: overall response rate, CR: complete response, VGPR: very good partial response, MR: minor response (according to Owen, B J Hematol 2012)

ASH 2019, REMODEL, Tomowiak *et al.*

Progression-Free and Overall Survival

Median follow-up 17 months

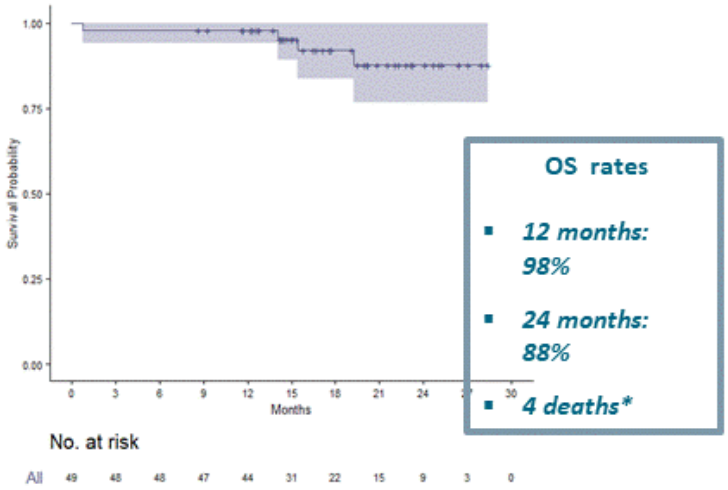
Progression–free survival



PFS rates

- *12 months: 77%*
- *24 months: 57%*
- *Median: 25 months*
- *21 progressions*

Overall survival



OS rates

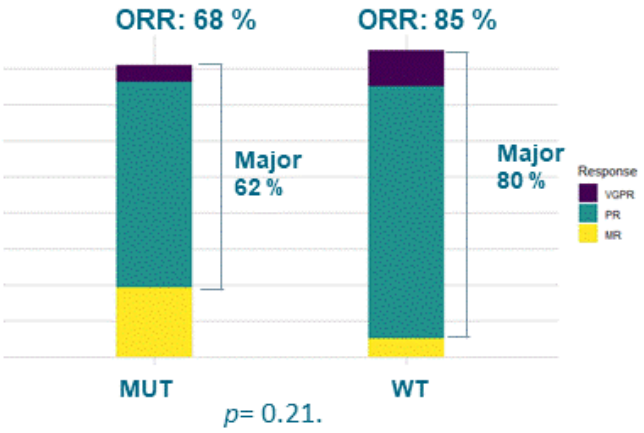
- *12 months: 98%*
- *24 months: 88%*
- *4 deaths**

**1 before starting treatment from unknown cause, 1 from progressive disease, 2 from infection 5 and 12 months after treatment discontinuation respectively*

ASH 2019, REMODEL, Tomowiak *et al.*

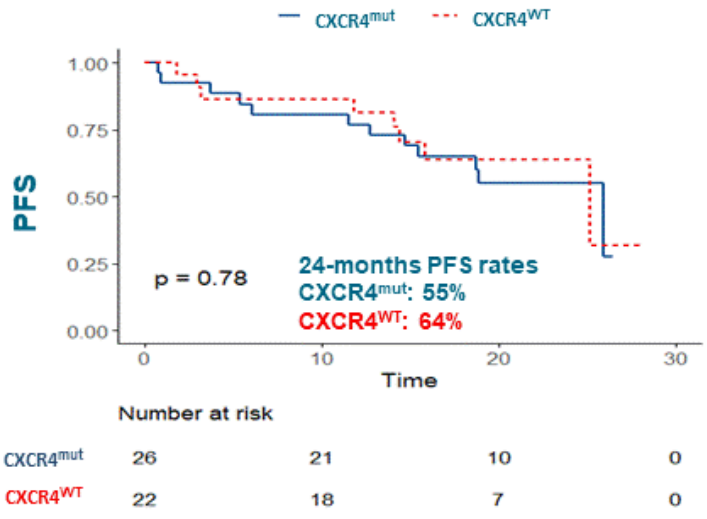
Response and PFS according to CXCR4 status

Response according to CXCR4^{mut}



CXCR4^{mut} (NGS + digital droplet PCR): 18 CXCX4^{S338X}, 8 CXCR4$^{frame\ shift}$
mut: mutation, WT: wild type

PFS according to CXCR4^{mut}



ASH 2019, REMODEL, Tomowiak *et al.*

Conclusions

- 1rst study evaluating combination with idelalisib + obinutuzumab in R/R WM with a chemo-free fixed-duration strategy
- 69% ORR and 25-month median PFS
- High risk genotype profile: 53% patients CXCR4mut

  68% ORR and 26-month median PFS
- No unexpected toxicity with obinutuzumab + idelalisib association but dose reduction in 43% of the patients and idelalisib discontinuation in 49% of the patients
- Specific attention to gastro-intestinal disorders and liver cytotoxicity

ASH 2019, REMODEL, Tomowiak *et al.*

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2019

Für den Inhalt verantwortlich:

Prof. Dr. med. Christian Buske

Ärztlicher Direktor – CCC Ulm, Institutes für Experimentelle Tumorforschung •

Universitätsklinikum Ulm

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