Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

63rd ASH Meeting 2021

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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Institut für Experimentelle Tumorforschung | Universitätsklinikum Ulm

Morbus Waldenström (WM) Marginalzonen-Lymphom (MZL)

Offenlegung potentieller Interessenskonflikte

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

Anstellungsverhältnis, Führungsposition	---
Beratungs-/ Gutachtertätigkeit	Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, MorphoSys, Regeneron
Besitz von Geschäftsanteilen, Aktien oder Fonds	----
Patent, Urheberrecht, Verkaufslizenz	----
Honorare	Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, MorphoSys, Regeneron
Finanzierung wissenschaftlicher Untersuchungen	Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, Amgen
Andere finanzielle Beziehungen	----
Immaterielle Interessenkonflikte	----

Kapitel 1

Prognostische Relevanz der MYD88 und CXCR4 Mutation bei asymptomatischen Morbus Waldenström?

MYD88 Mutation

Treon et al

- Whole Genome Seq. of 30 WM patients, validated by Sanger Seq.
- Sanger Seq. identified MYD88 $_{L265P}$ in 90% of patients (27/30 WM samples)
- 22/26 patients were heterozygous for MYD88 $_{L265P}$
- 9/9 patients with familial WM carried mutant MYD88 $_{L265P}$
- 2/21 patients with IgM-MGUS had MYD88 $_{L265P}$ expression

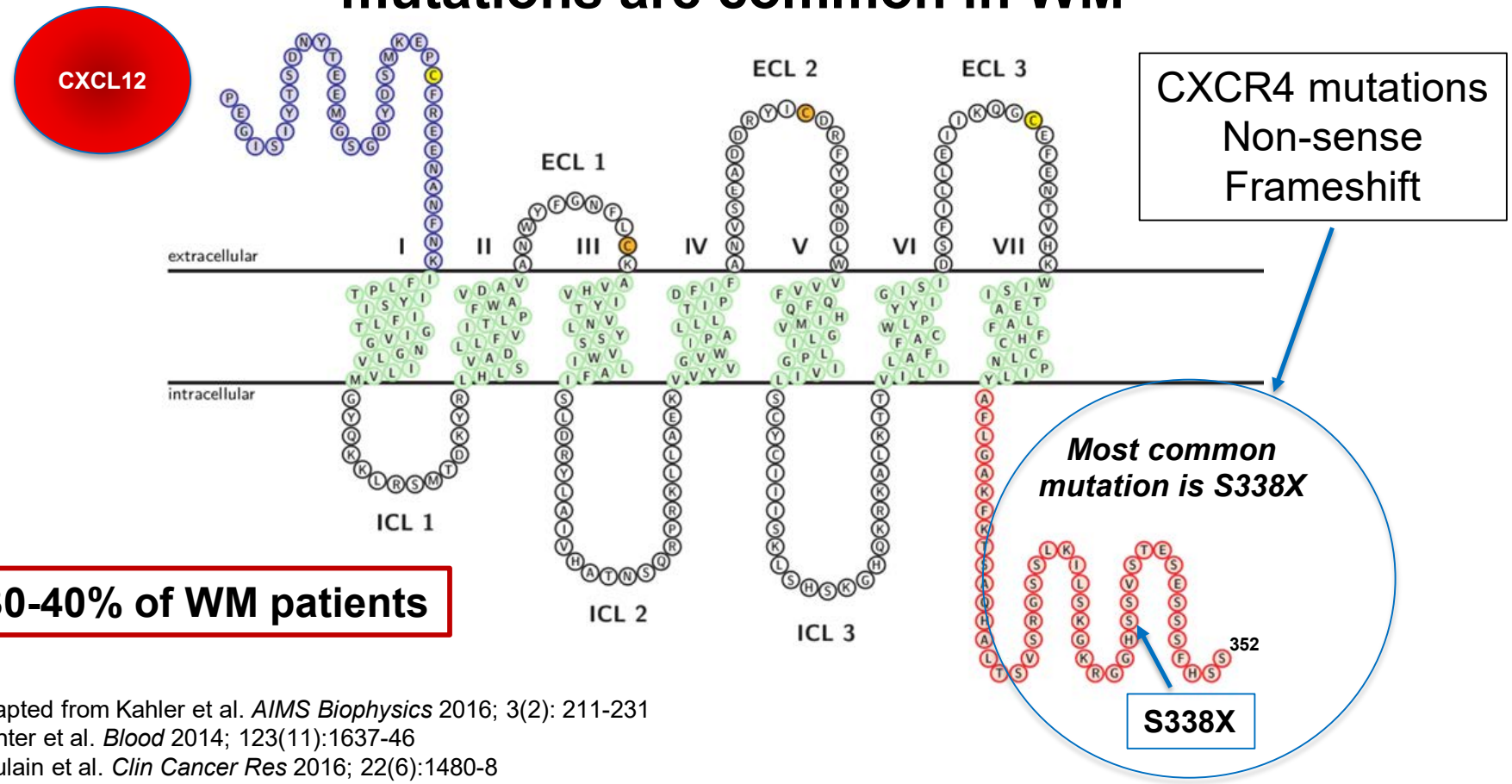
→ 94-95 % of all patients positive!

3-D structure of MY88 TIR domain

Base pair mismatch Leuc → Pro at position 265 in MYD88 coding region

Treon et al NEJM 2012; 367(9):826-33; Ngo et al Nature 2011; 470(7332):115-9

CXCR4 receptor C-terminal domain (WHIM-like) mutations are common in WM



30-40% of WM patients

Adapted from Kahler et al. *AIMS Biophysics* 2016; 3(2): 211-231
Hunter et al. *Blood* 2014; 123(11):1637-46
Poulain et al. *Clin Cancer Res* 2016; 22(6):1480-8

Prognostic impact of *MYD88* L265P mutation by droplet digital PCR in IgM MGUS and smoldering Waldenström macroglobulinemia

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CLÍNIC BARCELONA Hospital Universitari

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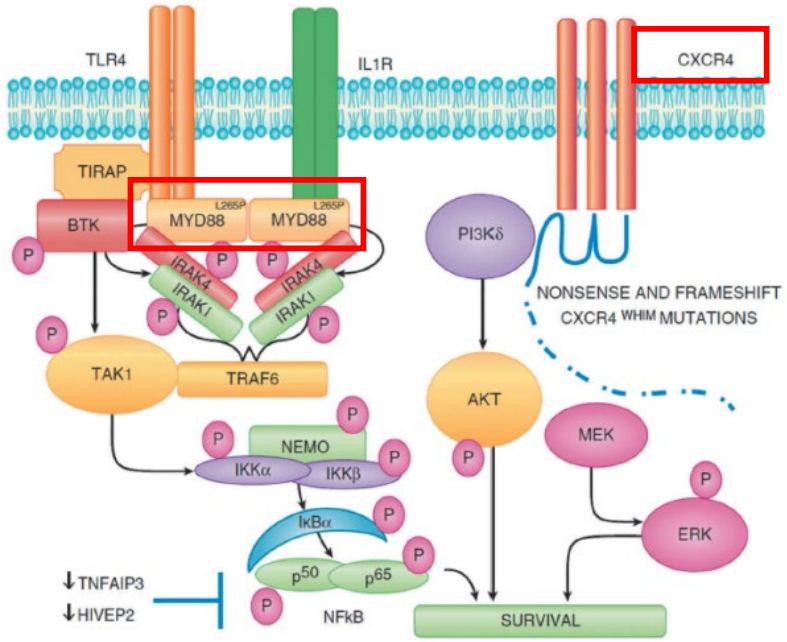
MYD88 and *CXCR4* mutations in asymptomatic IgM monoclonal gammopathies

Mutations in *MYD88* and *CXCR4* genes promote cell survival and lymphoma progression



Treon S.P., *et al*. Blood. 2014
Roccaro A. M., *et al*. Blood. 2014
Castillo J.J., *et al*. Exp Rev Hematol. 2018

Prognosis of the genomic status in IgM MGUS and smoldering Waldenström macroglobulinemia (SWM)

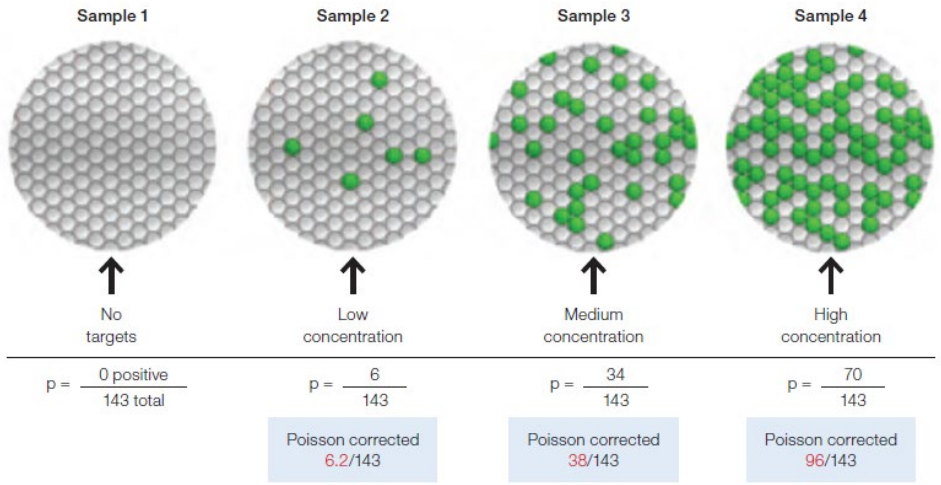
***MYD88* prevalence**	**PCR**	**Progression to symptomatic WM**
SWM 85%[1]	AS-PCR	Shorter PFS in *MYD88*^{wt}
IgM MGUS 54%[2]	AS-PCR	Shorter PFS in *MYD88*^{mut}
SWM 79%[3] SWM 17% (*CXCR4*^{mut})	AS-PCR Sanger	Trend to shorter PFS in *MYD88*^{wt} and *CXCR4*^{wt}

Bustoros M., *et al*. J Clin Oncol. 2019[1]
Varettoni M., *et al*. Br J Haematol. 2019[2]
Zanwar S., *et al*. Br J Haematol. 2021[3]

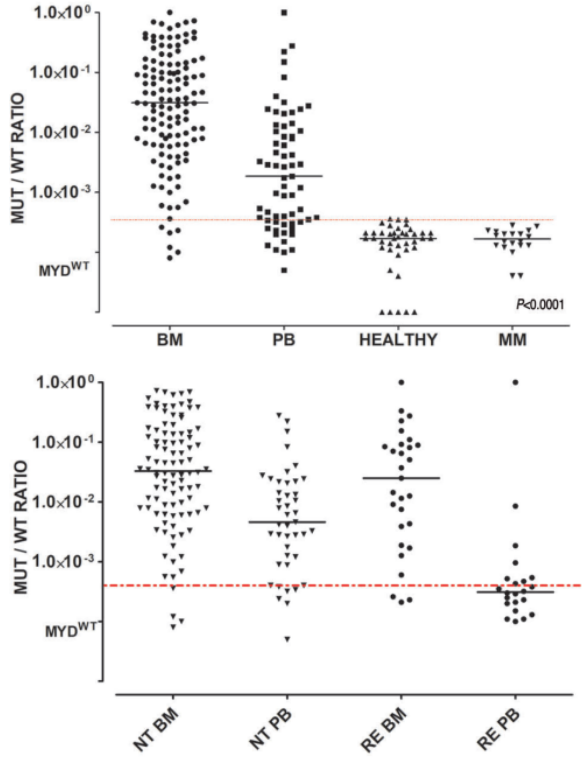
MYD88 L265P by droplet digital PCR (ddPCR)

Allele-specific PCR has been used routinely to assess *MYD88* mutation.

ddPCR is more precise and able to perform an absolute quantification.

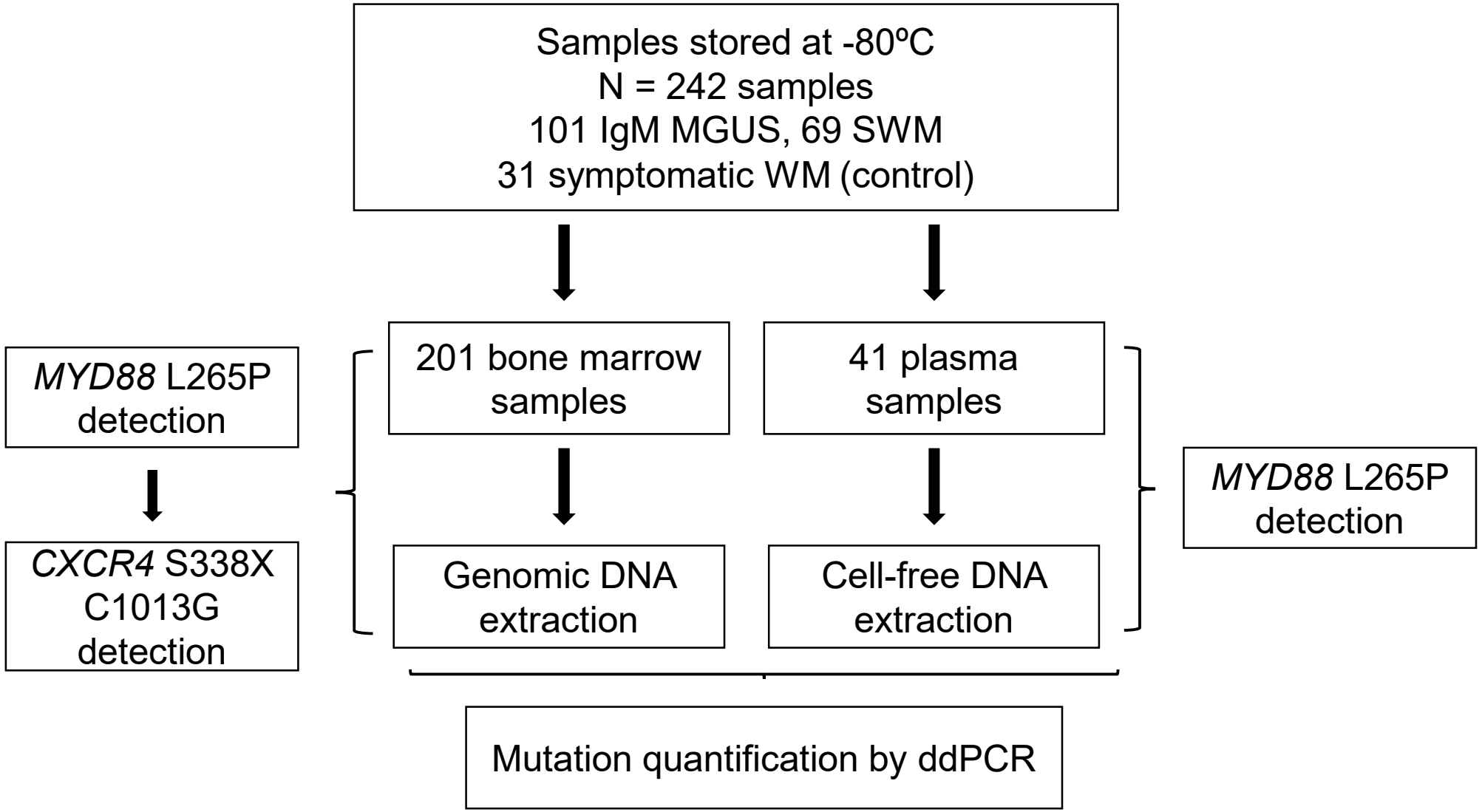


Benson B.J., *et al*. Anal Chem. 2011

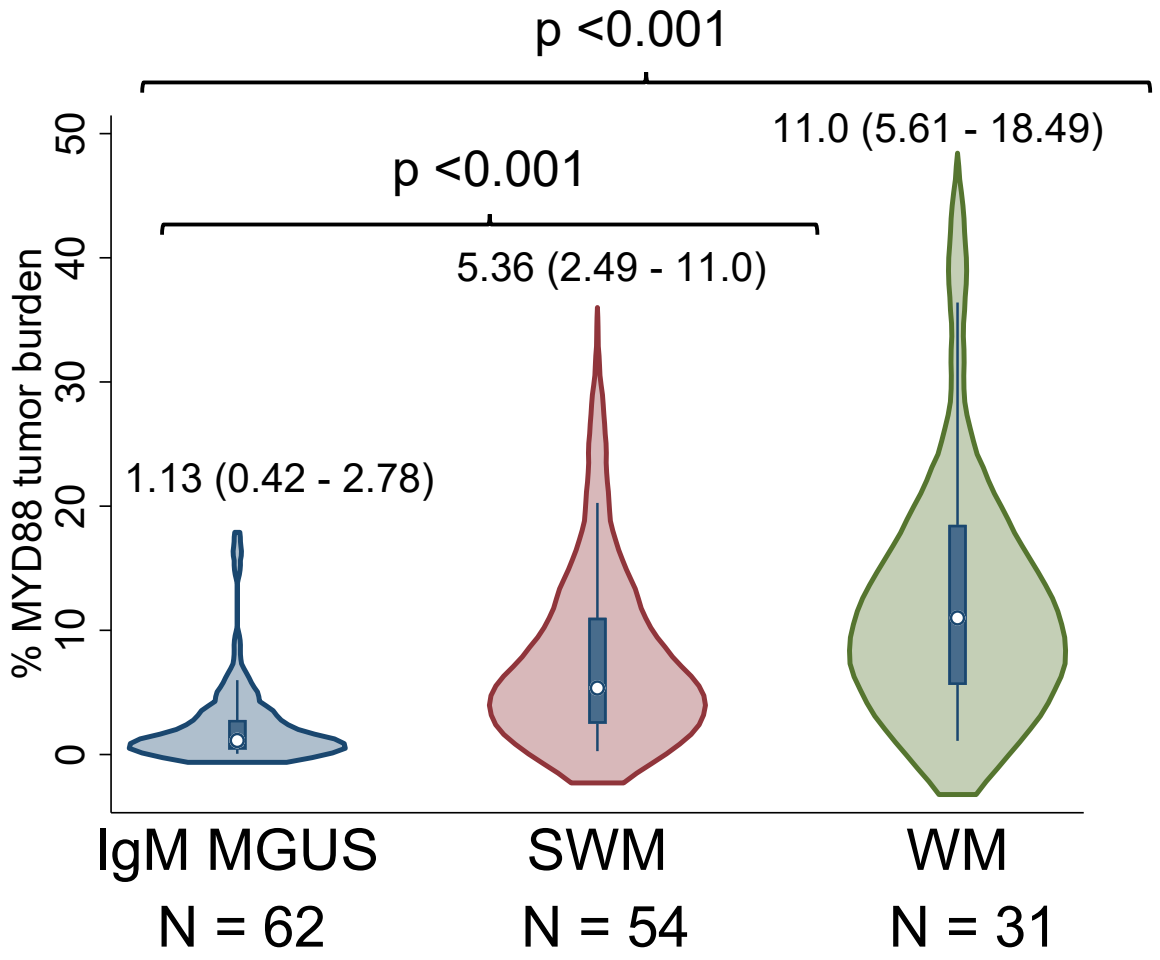


Drandi D., *et al*. Haematologica. 2018

Methods


Samples stored at -80ºC
N = 242 samples
101 IgM MGUS, 69 SWM
31 symptomatic WM (control)
201 bone marrow samples
41 plasma samples
MYD88 L265P detection
CXCR4 S338X C1013G detection
Genomic DNA extraction
Cell-free DNA extraction
MYD88 L265P detection
Mutation quantification by ddPCR

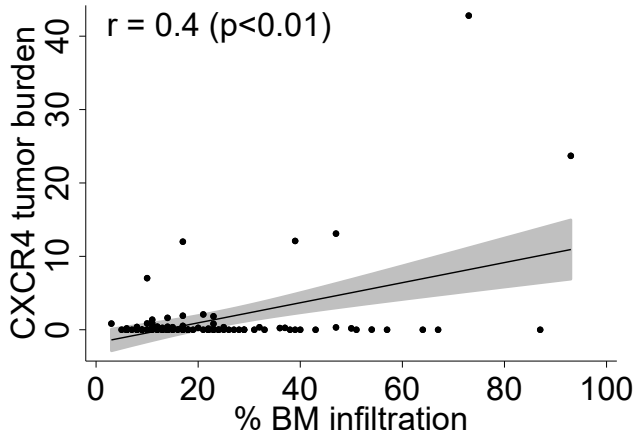
MYD88 L265P tumor burden by ddPCR was higher in successive disease stages

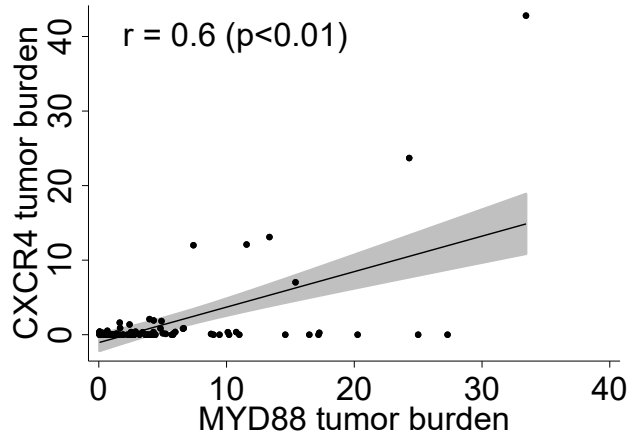


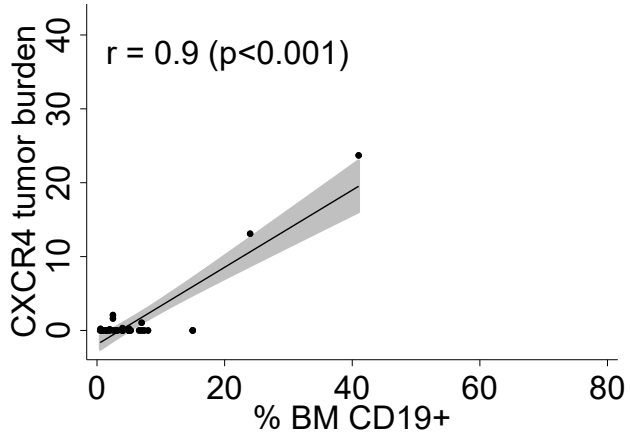
MGUS: Monoclonal gammopathy of undetermined significance
SWM: Smoldering Waldenström macroglobulinemia
WM: Symptomatic Waldenström macroglobulinemia

ddPCR was able to detect *CXCR4* C1013G in *MYD88*+ IgM MGUS and SWM

	***CXCR4* C1013G**
IgM MGUS	19/54 (**35%**)
SWM	18/42 (**43%**)



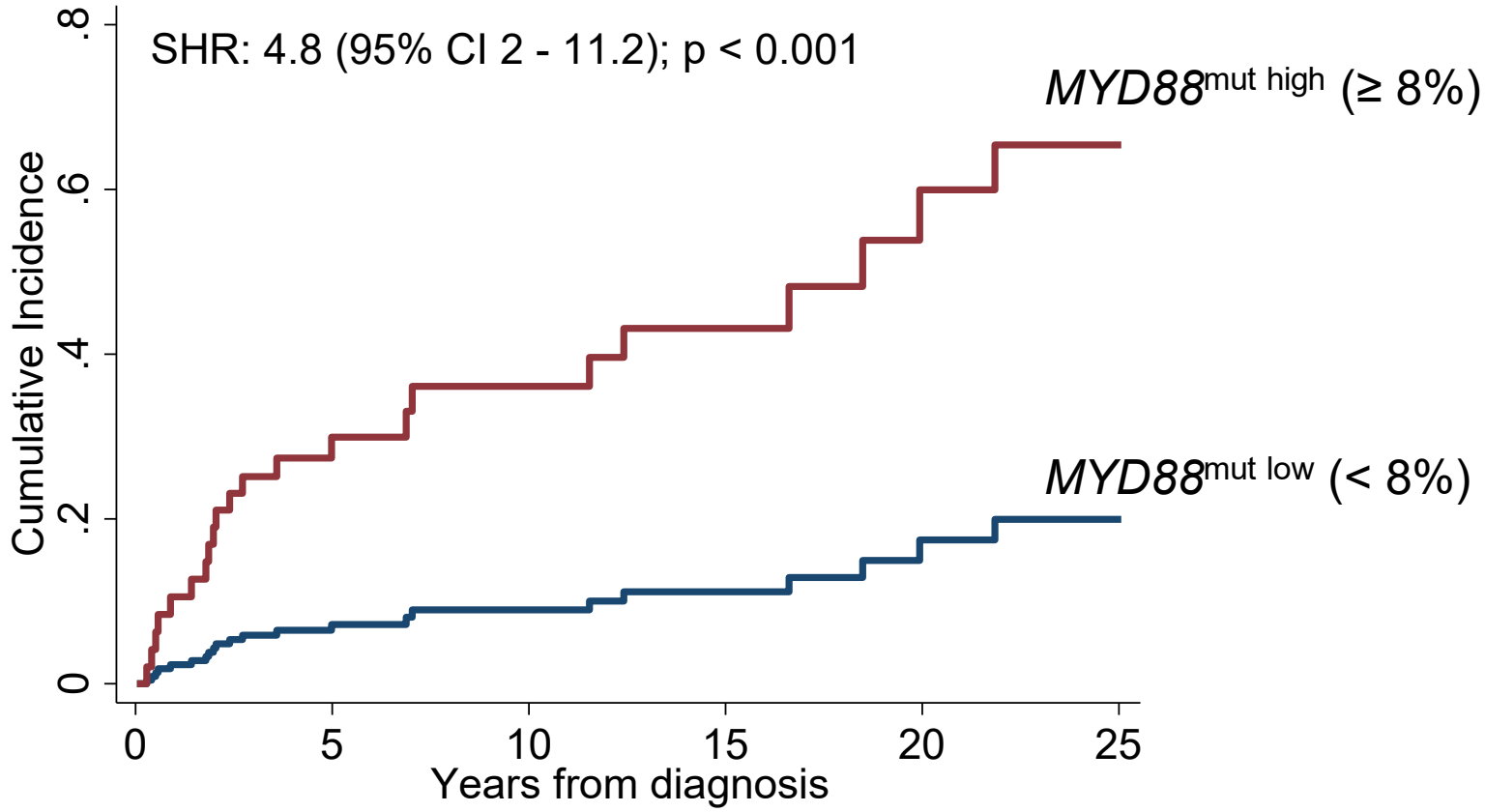




MGUS: Monoclonal gammopathy of undetermined significance
SWM: Smoldering Waldenström macroglobulinemia

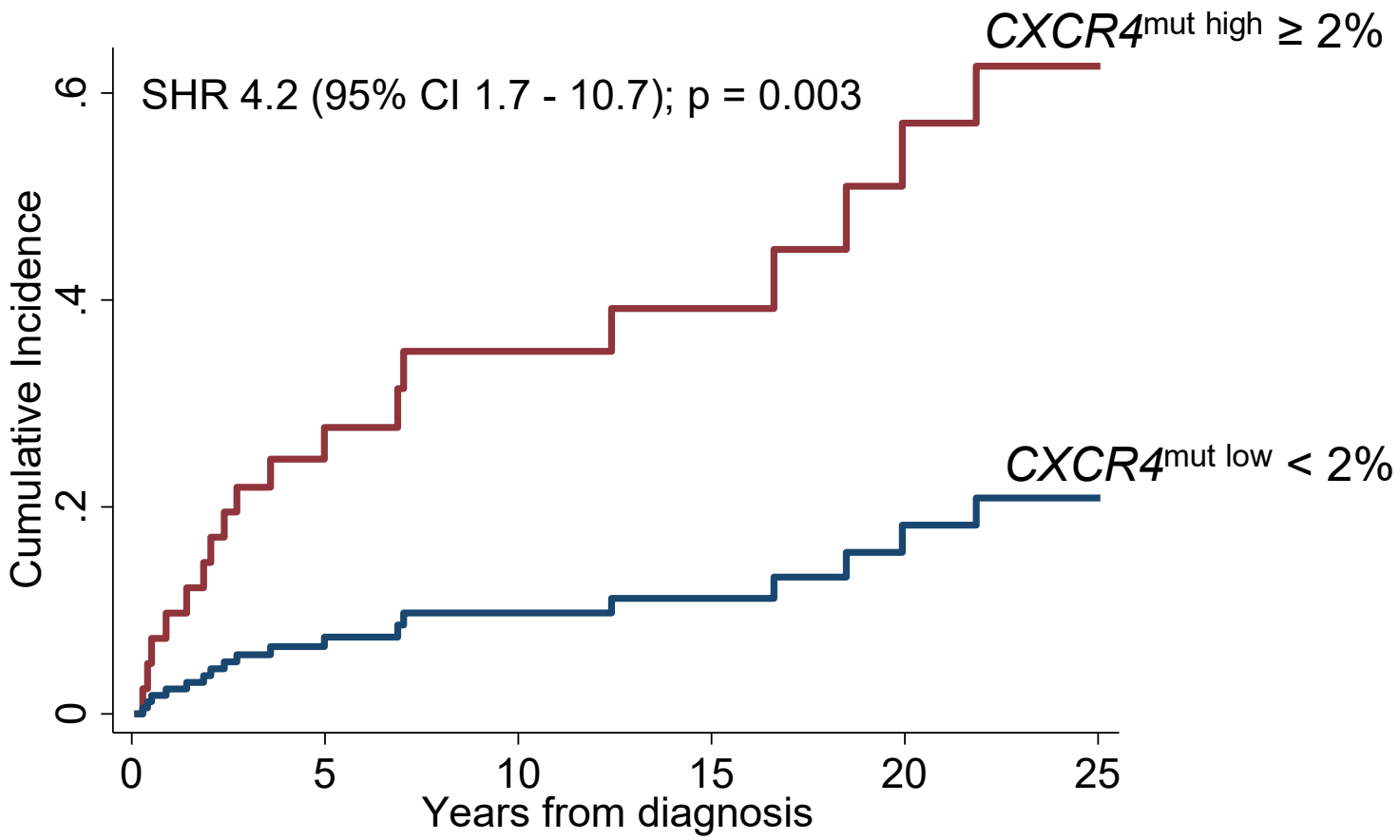
Risk of progression was higher in both IgM MGUS and SWM patients with ≥ 8% *MYD88* tumor burden

MYD88$^{mut\ high}$ defined as ≥ 8% tumor burden



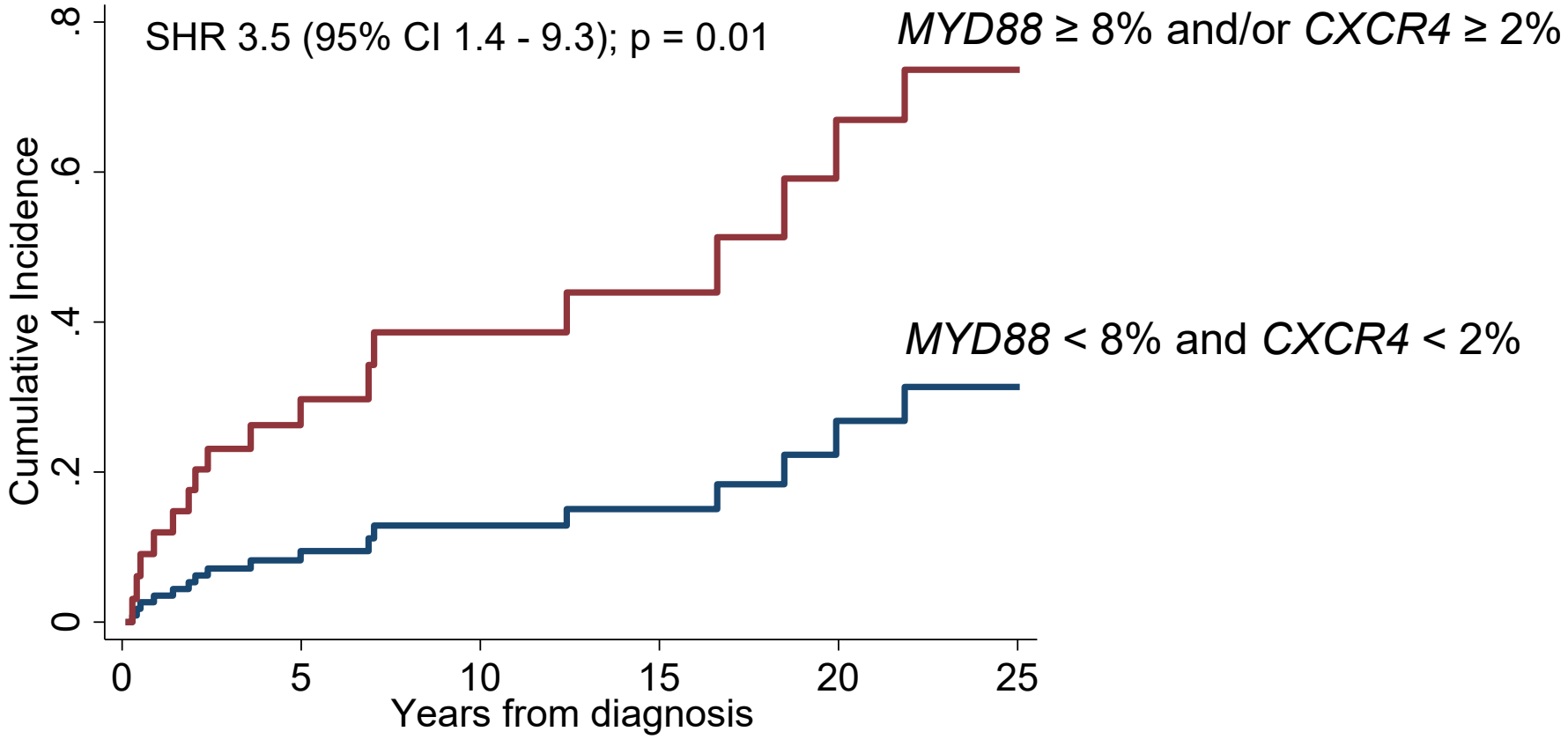
Risk of progression to symptomatic WM was higher in both IgM MGUS and SWM patients with ≥ 2% *CXCR4* tumor burden

CXCR4$^{mut\ high}$ defined as ≥ 2% tumor burden



MYD88 and *CXCR4* tumor burden by ddPCR defined risk categories in IgM MGUS and SWM

The genomic landscape of IgM MGUS and SWM



Kapitel 2

Morbus Waldenström: Bedeutung von CXCR4 Antagonisten?

Responses to ibrutinib are impacted by *MYD88* (L265P and non-L265P) and *CXCR4* mutations

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

2 patients subsequently found to have other *MYD88* mutations not picked up by AS-PCR

Treon et al., N Engl J Med. 2015; 372(15):1430-40; NEJM 2015; Letter, August 6, 2015

WM: what can we achieve (and what not) with ibrutinib?

Ibrutinib is among the most efficient single chemo-free agents in WM

but.....

Genotype determines clinical activity

#1362, Steven P. Treon et al.

Preliminary Clinical Response Data From a Phase 1b Study of Mavorixafor in Combination With Ibrutinib in Patients With Waldenström's Macroglobulinemia With *MYD88* and *CXCR4* Mutations

Steven P. Treon et al., Abstract #1362, ASH 2021.

Mavorixafor: a First-in-Class CXCR4 Antagonist

First-in-class CXCR4 antagonist

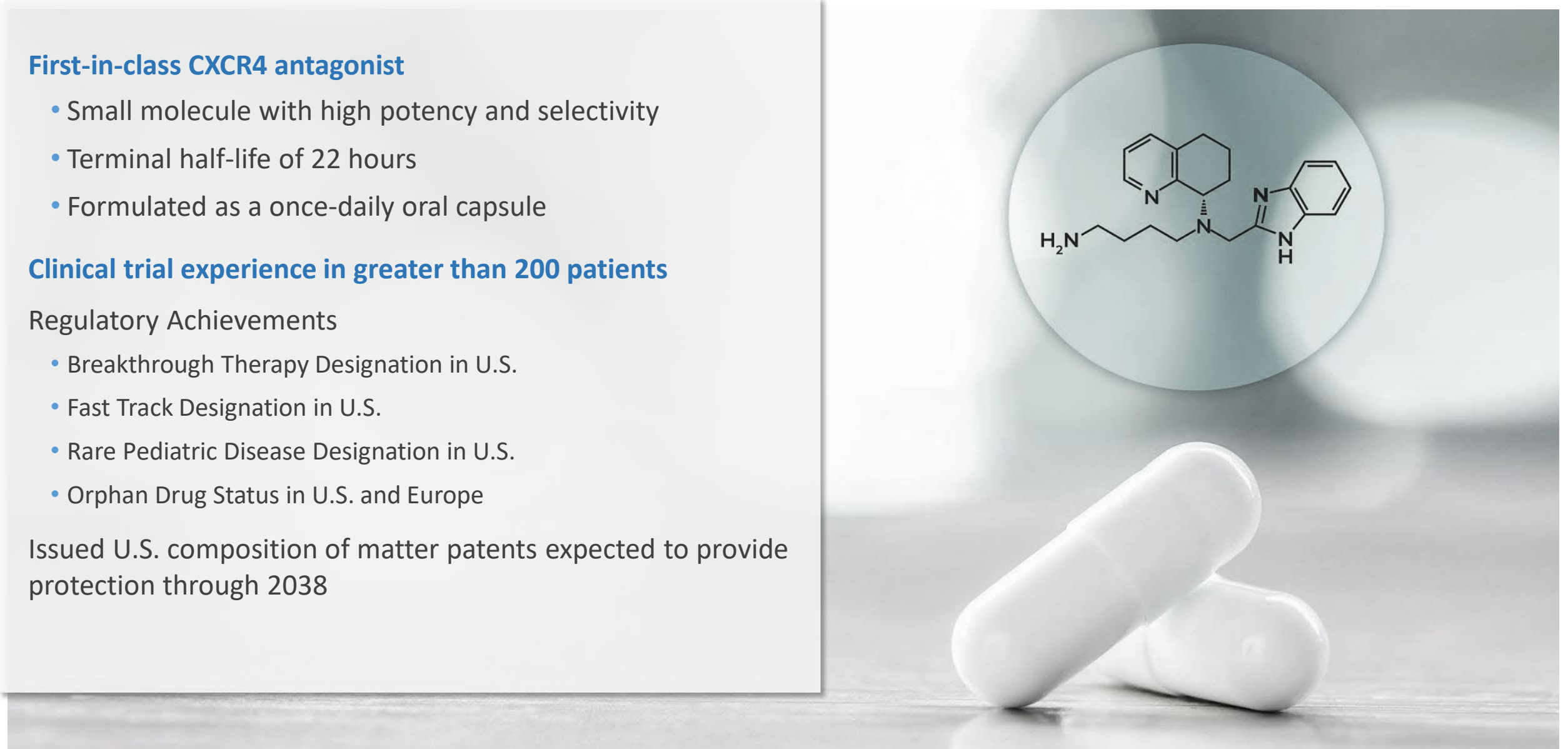
- Small molecule with high potency and selectivity
- Terminal half-life of 22 hours
- Formulated as a once-daily oral capsule

Clinical trial experience in greater than 200 patients

Regulatory Achievements

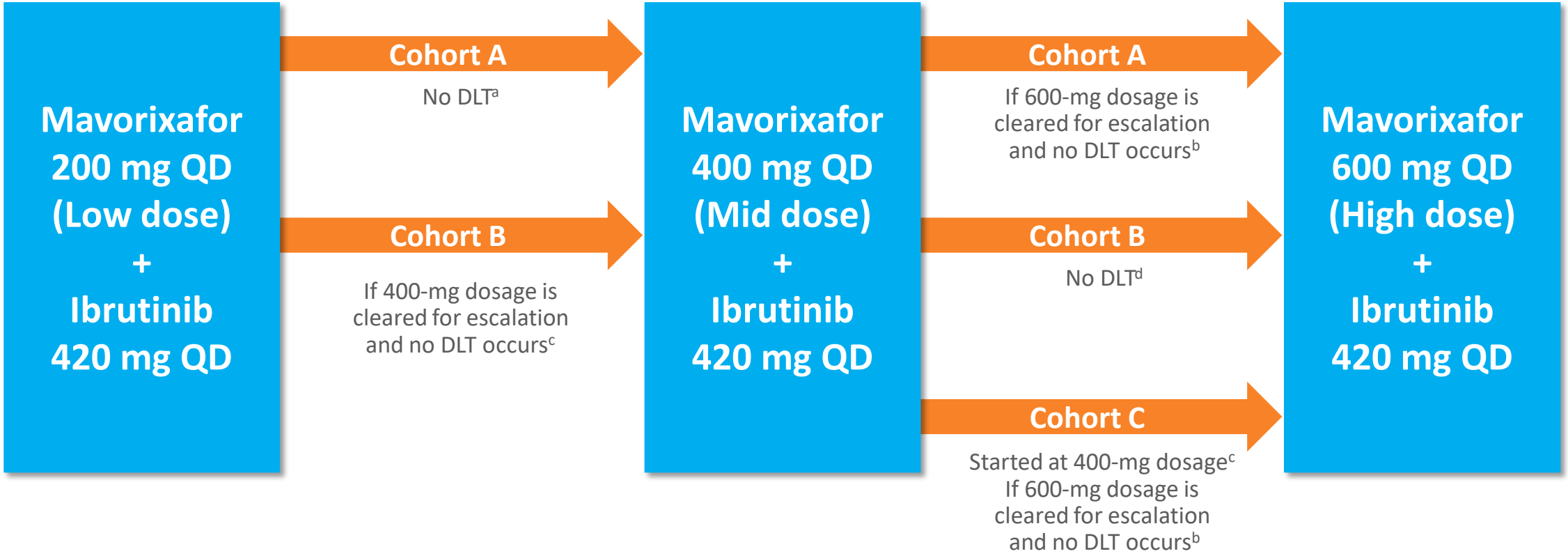
- Breakthrough Therapy Designation in U.S.
- Fast Track Designation in U.S.
- Rare Pediatric Disease Designation in U.S.
- Orphan Drug Status in U.S. and Europe

Issued U.S. composition of matter patents expected to provide protection through 2038



Studiendesign (NCT04274738)

Each treatment cycle is 28 days

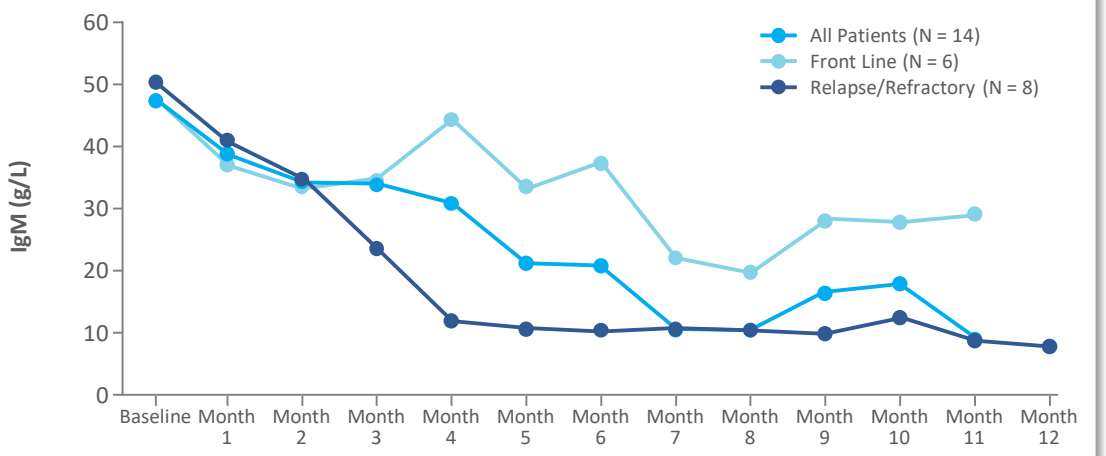


[a] If DLT occurs, patient is withdrawn from study.
[b] If dose escalation not cleared, patient remains at current dose level. If dose escalation is cleared but DLT occurs, patient stays in the study after dose de-escalation.
[c] If dose escalation is not cleared, patient remains at current dose level. If dose escalation is cleared but DLT occurs, patient is withdrawn.
[d] If DLT occurs, patient stays in the study after dose de-escalation.
Cohort A will continue to receive 400 mg until 600 mg is deemed tolerable by Cohort B. Once 600 mg is deemed tolerable, all enrolled patient doses may escalate to 600 mg, and Cohort C will start at 400 mg and their doses will escalate to 600 mg.

Steven P. Treon et al., Abstract #1362, ASH 2021.

Ergebnisse

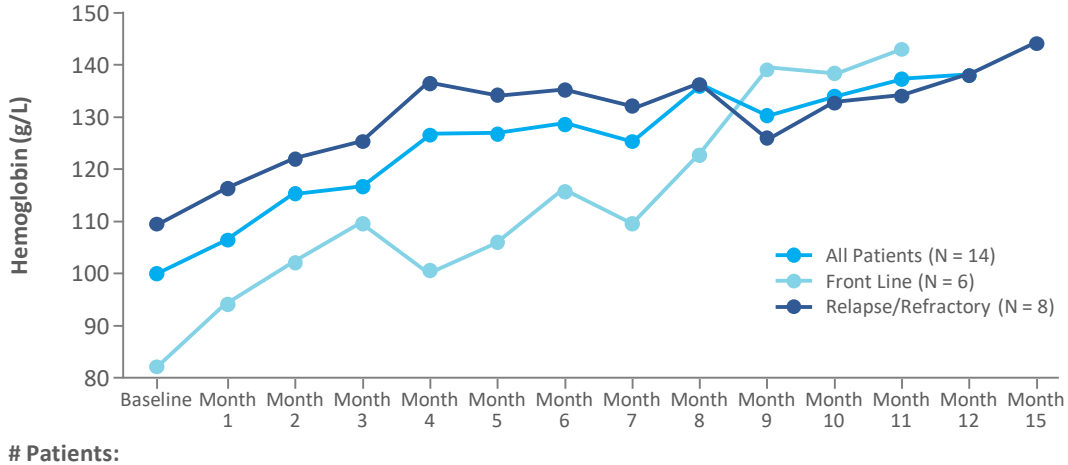
Median Serum IgM Levels[a,b]



 # Patients:

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
All	14	13	12	11	9	8	8	7	7	6	6	4	3
Front Line	6	5	5	5	4	3	3	2	2	1	1	1	0
Relapse/ Refractory	8	8	7	6	5	5	5	5	5	5	5	3	3

Median Change From Baseline in Hgb[a,b]



 # Patients:

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 15
All	14	13	12	12	10	8	8	7	7	6	6	5	3	0
Front Line	6	5	5	5	4	3	3	2	2	1	1	1	0	0
Relapse/ Refractory	8	8	7	7	6	5	5	5	5	5	5	4	3	1

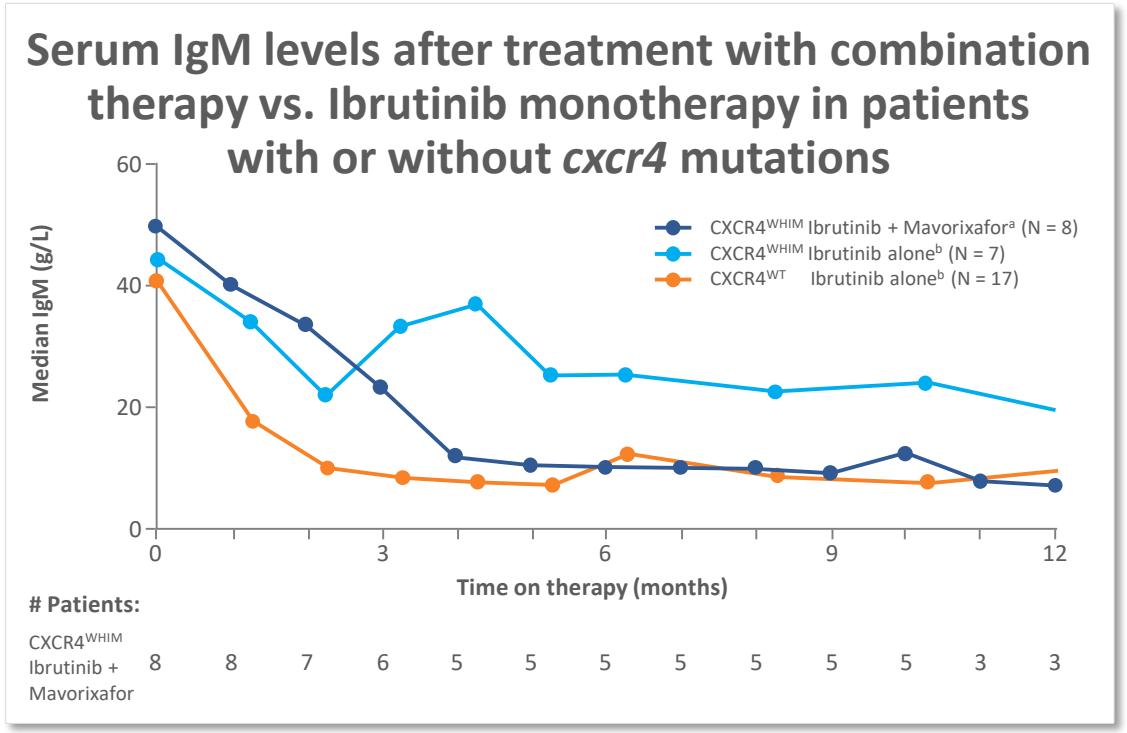
[a] Interim early data analysis performed with data cutoff at Oct 12, 2021.
[b] Missing data imputed using last observation carried forward.

[a] Data cut as of October 12, 2021.
[b] For 1 participant receiving frontline therapy, study treatment was temporarily withheld due to an AE the week prior to Month 4 IgM sample collection; the subject subsequently restarted on a reduced dose and then discontinued from the study at Month 6. Another participant discontinued study treatment after Month 2.

Serum IgM levels decreased and Hgb increased over time during dose escalation

Steven P. Treon et al., Abstract #1362, ASH 2021.

Ergebnisse



Clinical Response Rates			
Response Category	**Overall (n = 10)**	**Frontline (n = 3)**	**Relapse/ Refractory (n = 7)**
ORR, n (%)	10 (100)	3 (100)	7 (100)
Major response (CR+VGPR+PR), n (%)	4 (40)	1 (33)	3 (43)
VGPR, n (%)	1 (10)	0 (0)	1 (14)
PR, n (%)	3 (30)	1 (33)	2 (29)
MR, n (%)	6 (60)	2 (67)	4 (57)

[a] Previously treated patients on study

[b] This study included adults with WM requiring treatment refractory to their last rituximab-containing therapy treated with ibrutinib 420mg[13]

Steven P. Treon et al., Abstract #1362, ASH 2021.

Conclusions

- Overall, mavorixafor in combination with ibrutinib (420 mg) was tolerated with manageable safety profile in patients with WM with MYD88 and CXCR4^{WHIM} mutations, with cohorts completing the low (200-mg) and mid (400-mg) QD levels; dose escalation at the highest (600-mg) QD level continues
- Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies, suggesting no drug-drug interactions
- ORR was 100% in all evaluable patients, with 40% achieving major response, including 10% VGPR attainment as of data cut off Oct 12, 2021, with additional patients continuing to show decreases in IgM
- Combination of mavorixafor with ibrutinib led to rapid, clinically meaningful, and durable decrease in IgM levels and increase in Hgb levels
- Greater decreases in serum IgM levels were seen after treatment with combination therapy (ibrutinib and mavorixafor) compared to decreases seen with ibrutinib monotherapy in a previous study
- Emerging data from this ongoing study inform on the safety, tolerability, and efficacy of combining ibrutinib with mavorixafor to improve responses inpatients with WM with MYD88 and CXCR4^{WHIM} mutations

Steven P. Treon et al., Abstract #1362, ASH 2021.

Kapitel 3

COVID-19 Impfung bei Patienten mit Morbus Waldenström?

Efficacy of Vaccine BNT162b2 (Pfizer-BioNTech) in People with Waldenström's Macroglobulinemia and Follicular Lymphoma in Australia

A Prospective Observational Study

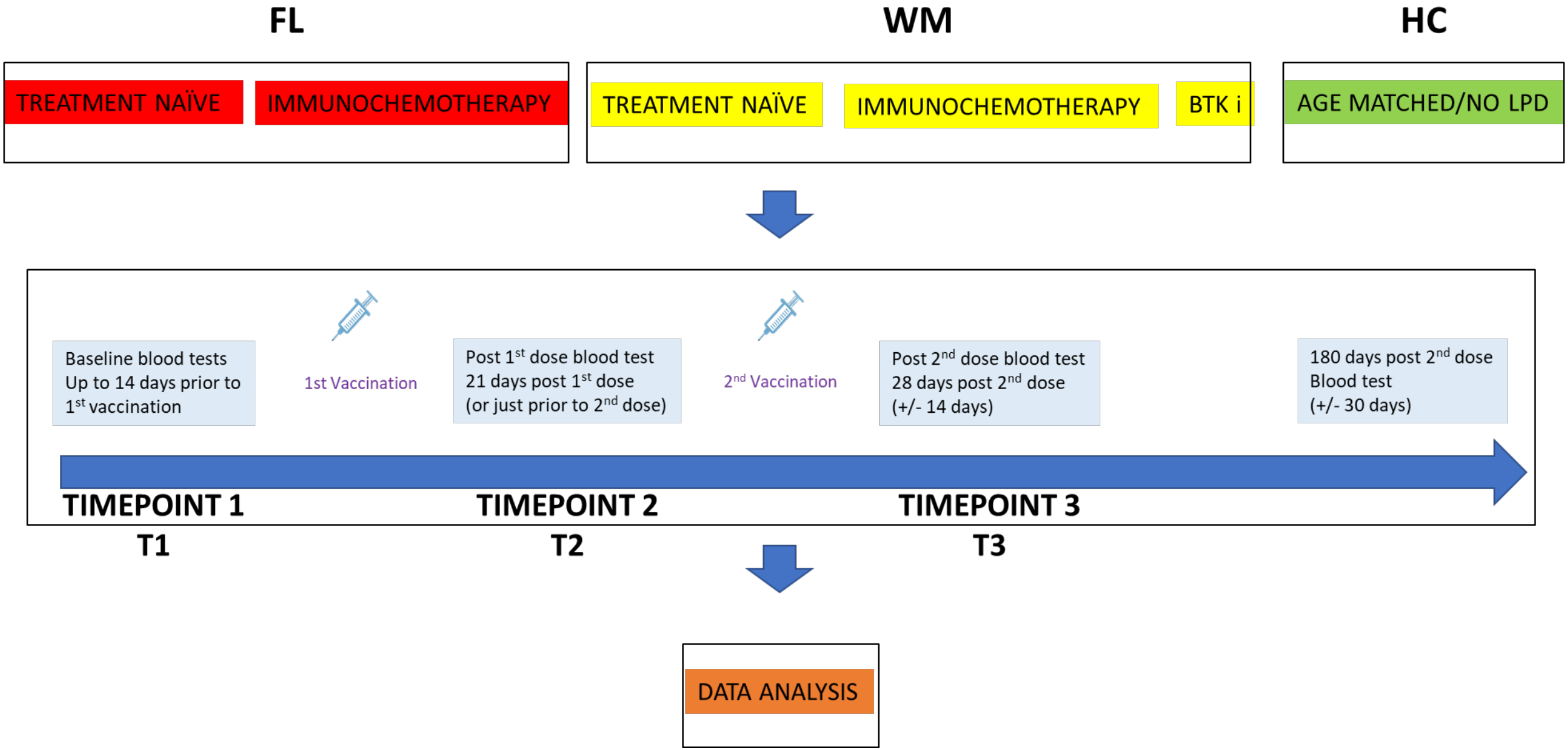
Brendan Beaton[1,2], Sarah C Sasson[3,4], Katherine Rankin[1], Juliette Raedemaeker[1], Alexander Wong[1], Priyanka Hastak[3], Andrew Warden[5], Alberto Ospina Stella[3], Anupriya Aggarwal[3], Ian D Caterson[6], Chansavath Phetsouphanh[3], Stuart Turville[3], Anthony D Kelleher[3], Fabienne Brilot[7] and Judith Trotman[1,2]

1. Haematology Department, Concord Repatriation General Hospital, Sydney, Australia;
2. Concord Clinical School, the Faculty of Medicine and Health, The University of Sydney, Sydney, Australia;
3. The Kirby Institute, The University of New South Wales, Sydney, Australia;
4. Immunology Department, Westmead Hospital, Sydney, Australia;
5. WMozzies Australian Patient Support Group for Waldenstrom's Macroglobulinemia, Sydney, Australia;
6. COVID Vaccination Hub, Sydney Local Health District, Sydney, Australia;
7. School of Medical Sciences, The University of Sydney, Sydney, Australia.

Overview

- General Aims
  - Assess humoral and cellular responses to BNT162b2 COVID-19 vaccination in patients with Follicular Lymphoma and Waldenström's Macroglobulinaemia compared to treatment naïve and healthy controls without the confounding impact of endemic infection
- Study Design
  - Prospective Observational Study
- Participants
  - FL and WM: Treatment naïve, Immunochemotherapy (ICT) & BTKi treated
  - Age-matched Healthy Controls
  - ~ 10 per cohort (all with humoral assessment; ~50% with cellular response assessment due to logistical and budget considerations)
- Primary Endpoints
  - Anti-Spike IgG level
  - Neutralizing antibody activity
  - Antigen specific T-cell responses (CD4 & CD8) incl. comprehensive subset analysis

Study Schema



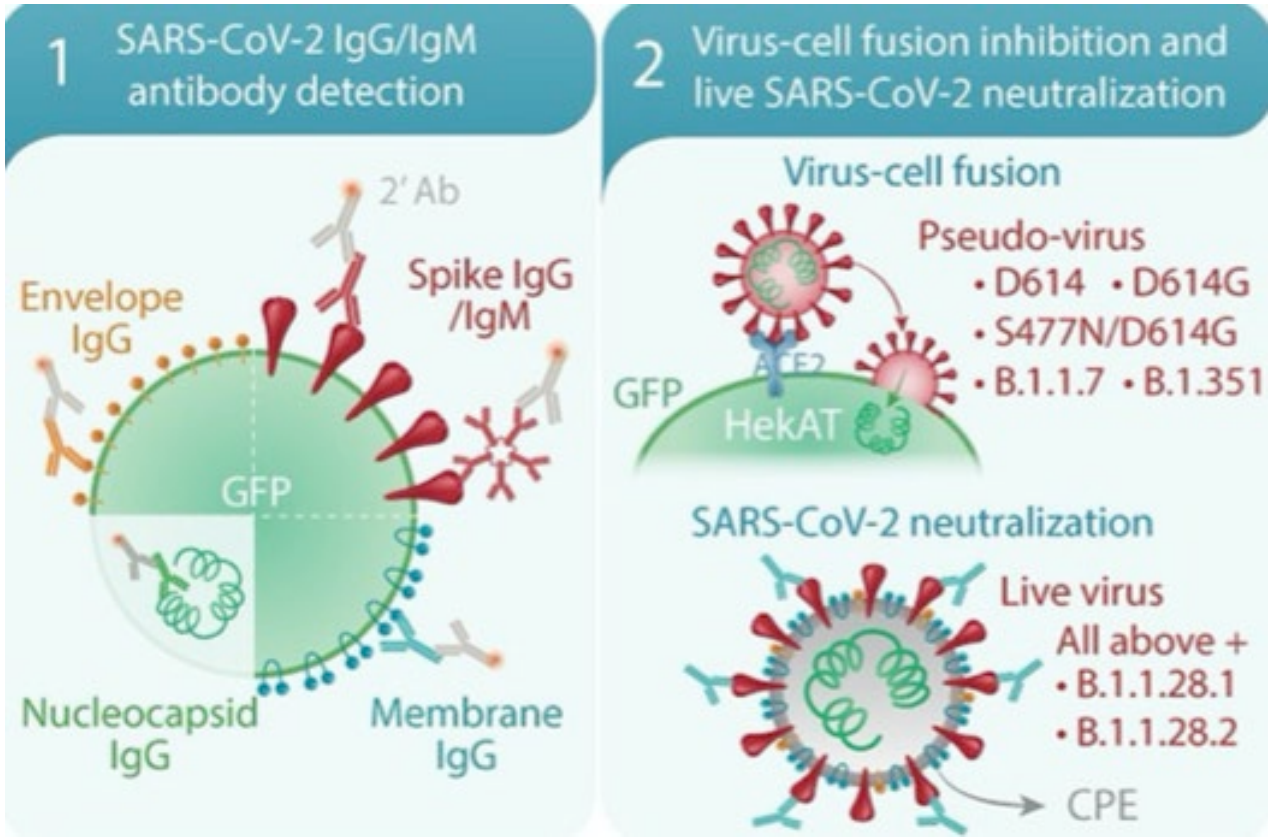
Humoral Tests Performed

1. Anti-SARS-CoV-2 Spike IgG

- Spike protein expressed on HEK293 cell line
- Patient serum diluted 1:20
- Added to **LIVE CELLS**
- Addition of anti-human IgG
- Analyzed on BD LSRII Flow cytometer

2. Live virus neutralization assay

- Titrated dilutions of patient serum mixed with media containing Wuhan clade & Delta strain
- Added to freshly trypsanized SARS-CoV-2 permissive cell lines (VERO & HEK)
- Imaged to assess for cell death
- % neutralization at each titration determined

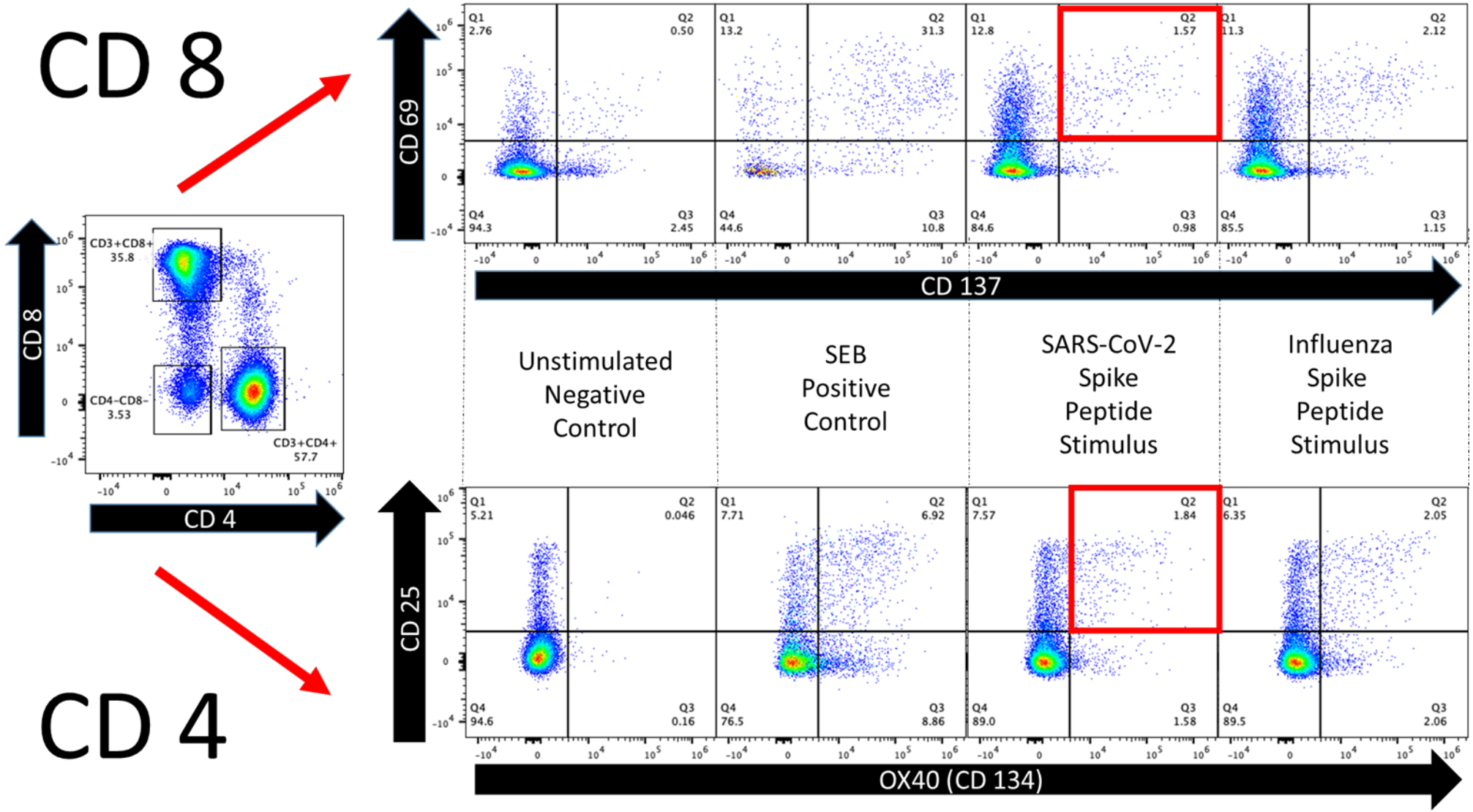


Tea F, et al. Plos Medicine. July 2021.

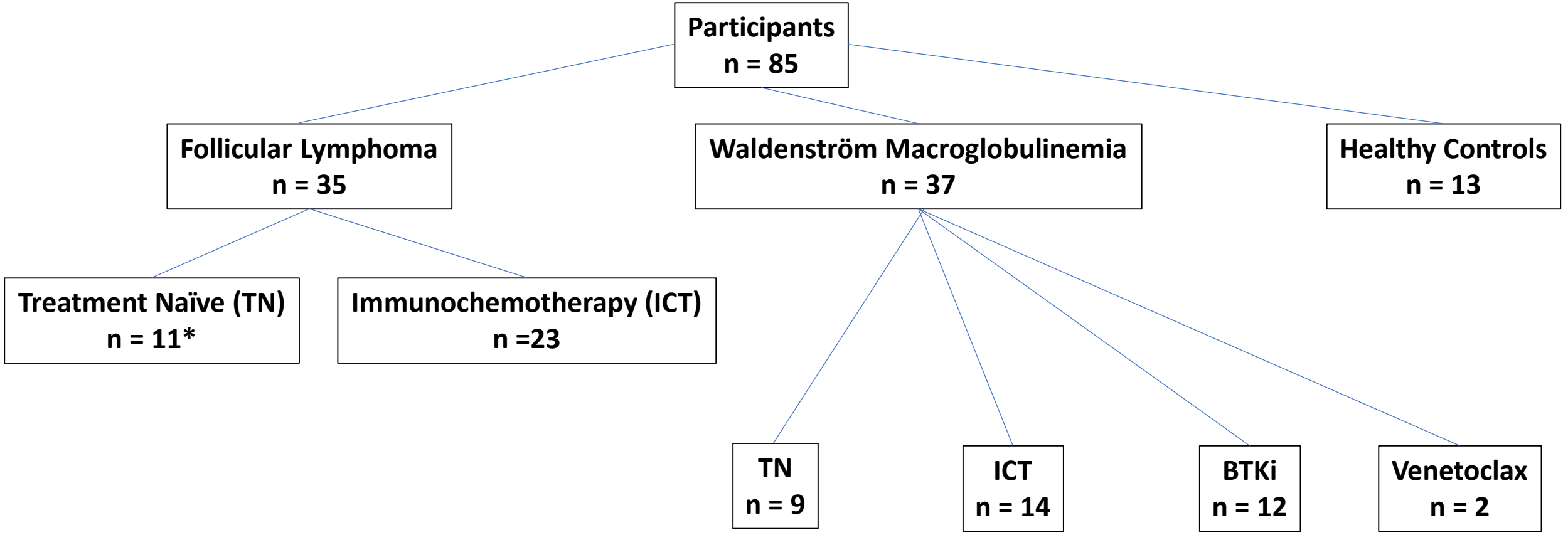
T Cell Functional Assessment

Reactive CD 8
= % CD69 + CD137
Co-expression with
Stimulus

Reactive CD 4
= % CD25 + CD134
Co-expression with
Stimulus



Results: Study population



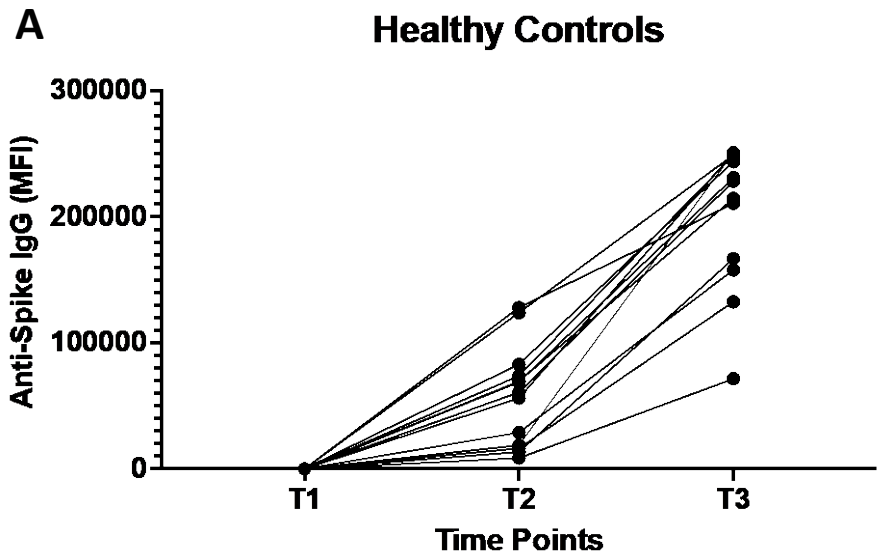
*1 death following first vaccination (unrelated)

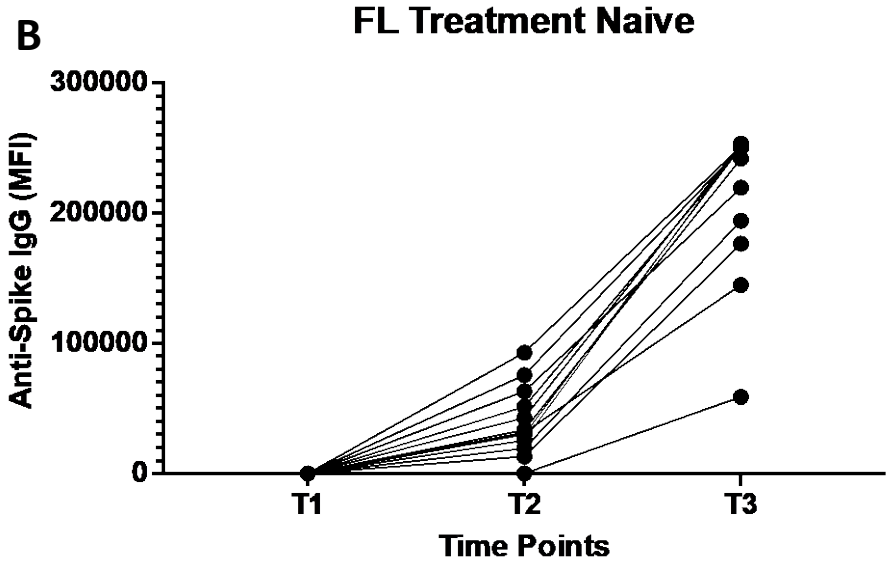
Patient Characteristics

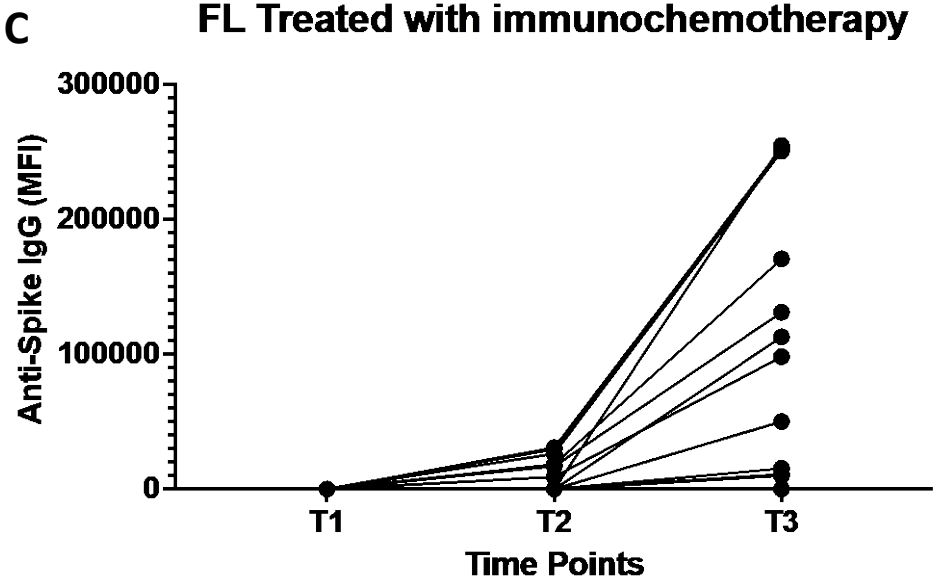
	FL n= 34	WM N= 37
Age in years, median (IQR)	65 (54-71)	71 (63-74)
Gender, male n (%)	16 (47)	19 (51.3)
Treatment status		
Treatment Naïve, n (%)	11 (32.3)	9 (24.3)
AntiCD20 monoclonal + other, n (%)	23 (65.7)	14 (37.8)
Rituximab-chemotherapy +/- maint., n (%)	19 (55.9)	11 (29.7)
Obintuzumab-chemotherapy +/- maint., n (%)	4 (11.8)	/
Completed treatment with AntiCD20 < 6mo, n (%)	10 (29.4)	0 (0)
Median time from therapy, months (IQR)	15.5 (7.5-30.5)	22 (12-39)
Bruton tyrosine kinase inhibitors n (%)	2 (6)	12 (32.4)
Median time on BTKi, months (IQR)	56.5 (20-93)	64.5 (46-75)
Other – Venetoclax, n (%)	/	2 (5)
Median previous lines, n (IQR)	1 (1-2)	2 (1-4)
Median baseline IgG g/L, (IQR)	/	8.11 (3.93-18.5)
IVIg supplementation, n (%)	1 (3)	7 (18.9)
Lymphocyte count, n $x10^9$/L (IQR)	1.4 (0.78-1.73)	1.4 (0.93-1.7)

Healthy Controls:
Median age 72 years
(IQR 57-74)
Male 5/13 (39.5%)

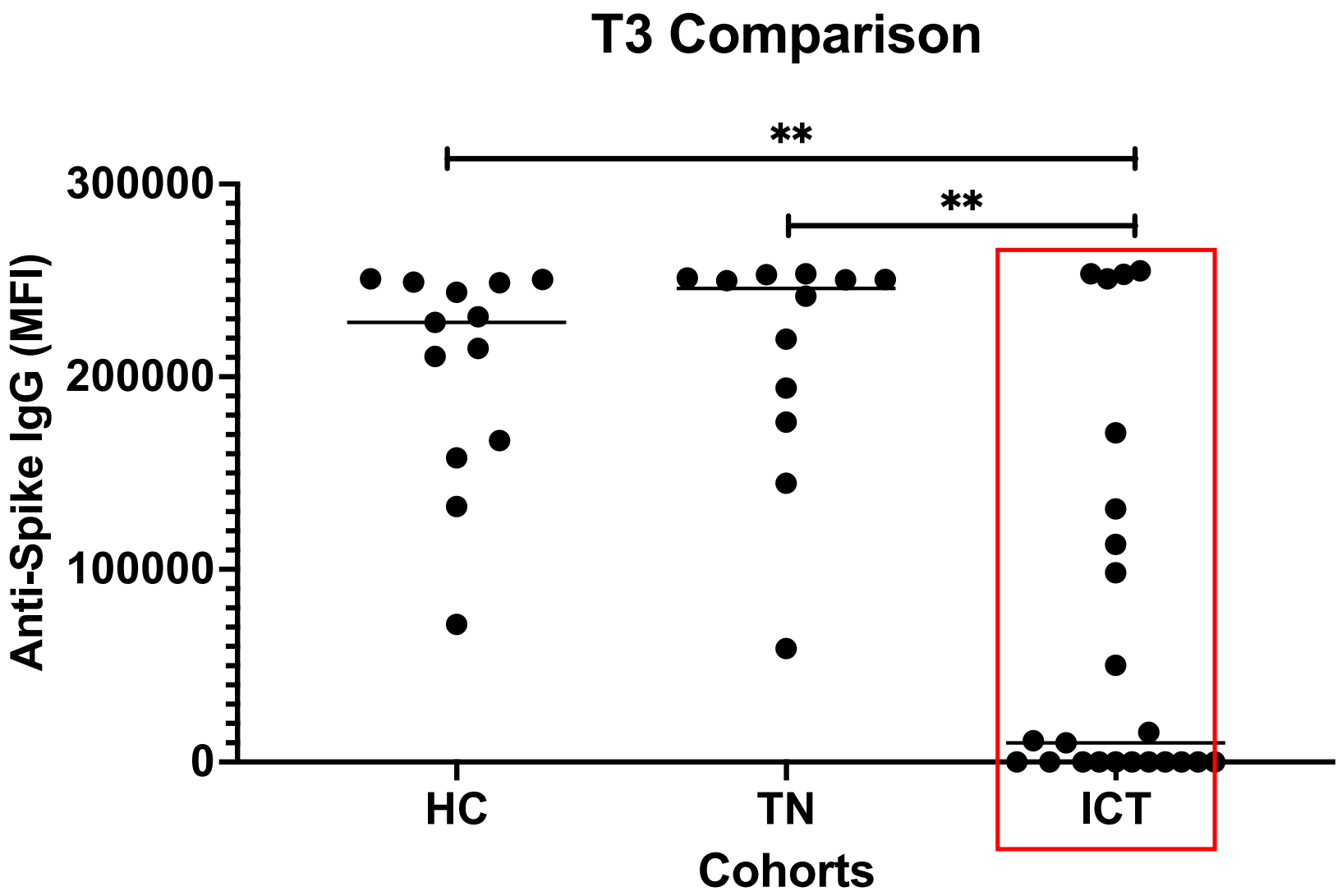
Follicular lymphoma population: SARS-CoV-2 Anti-Spike IgG







Follicular lymphoma population: SARS-CoV-2 Anti-Spike IgG



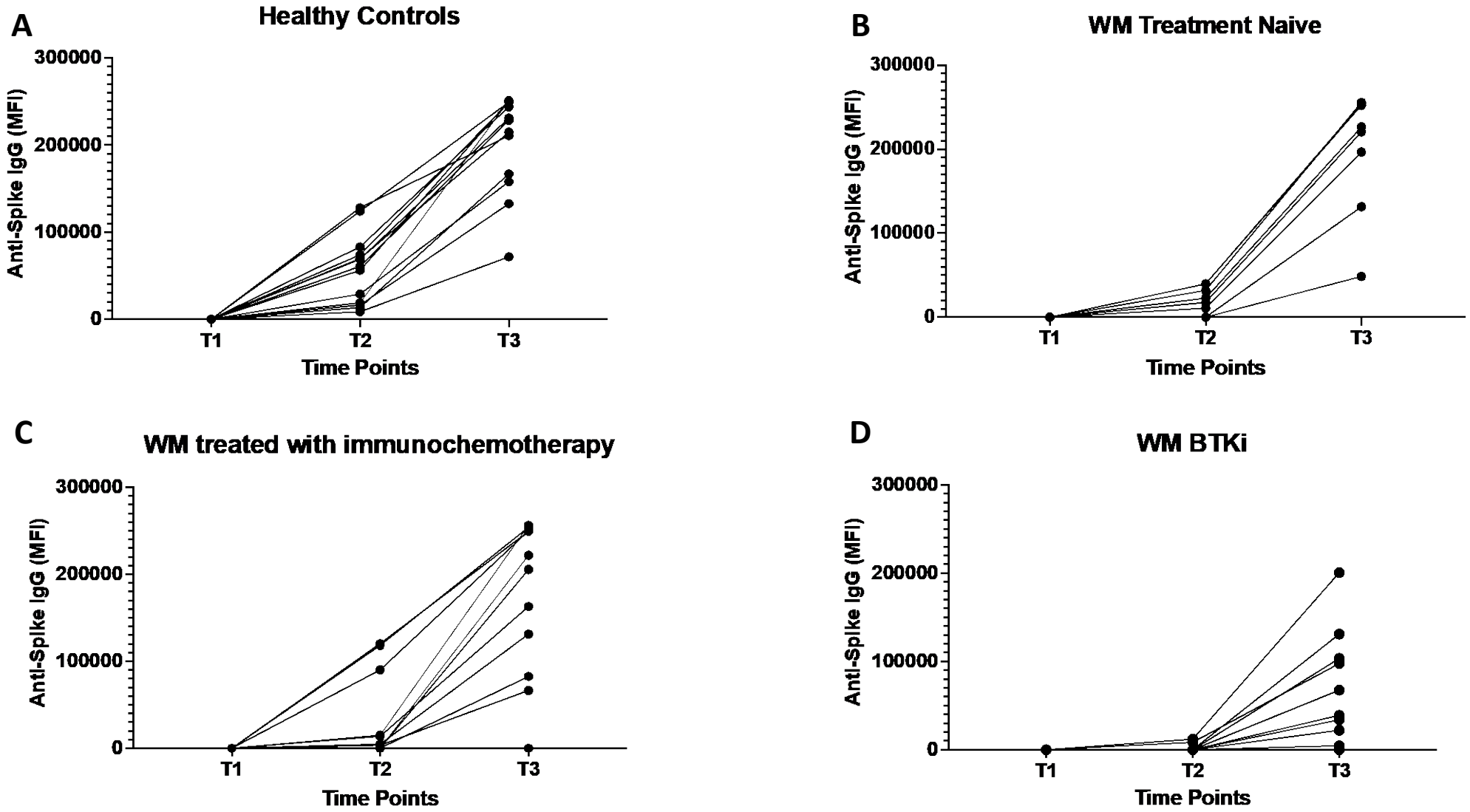
Significantly lower Anti-Spike IgG in the ICT treated cohort

Cohort	Median MFI	IQR	p
HC	228,255	162,383-249,019	
TN	245,898	180,876-251,062	0.41
ICT	9,977	0-131,350	0.002

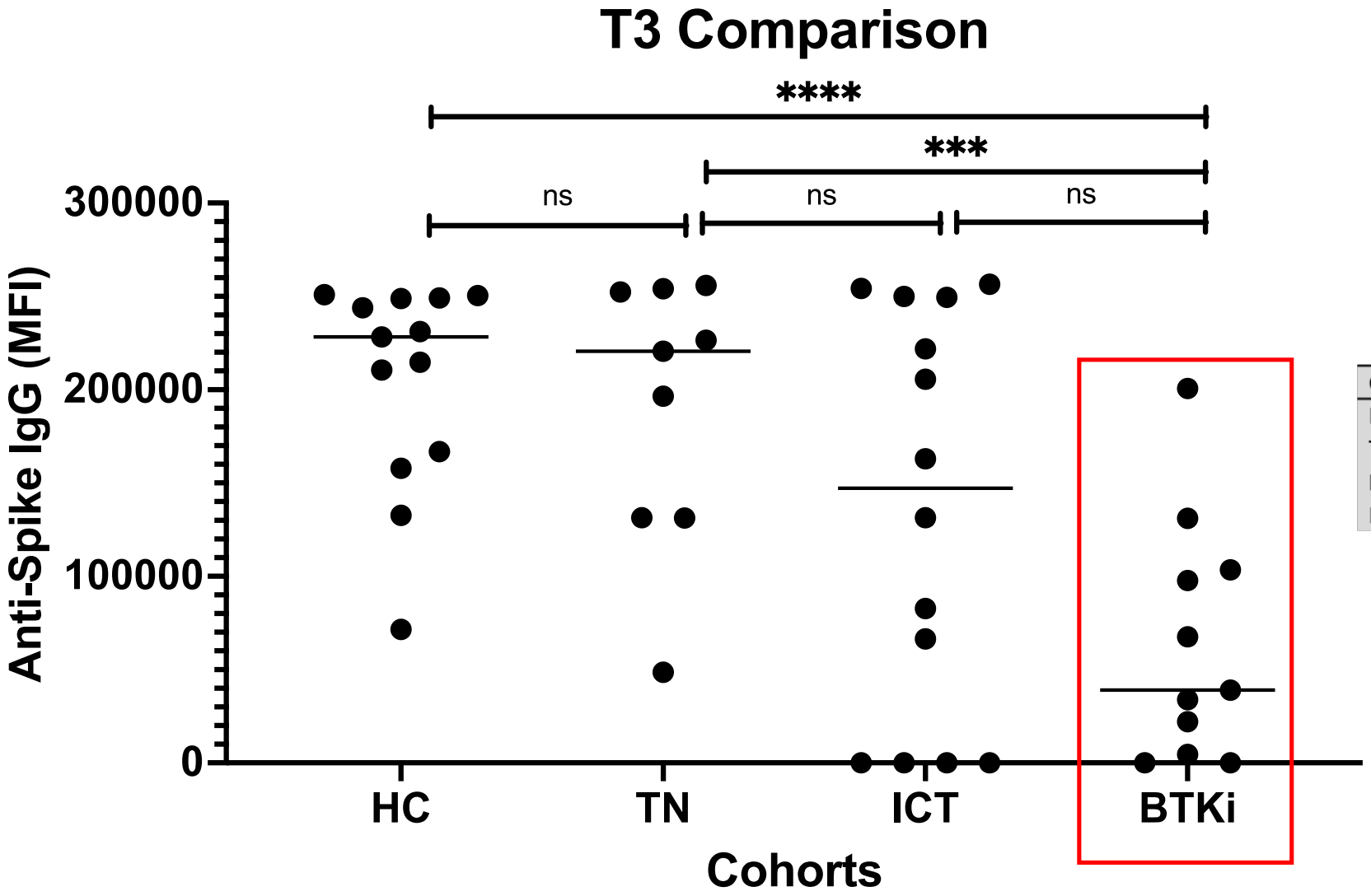
No patients receiving obinutuzumab (n=4) had a response up to 21 months following maintenance

* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001

Waldenström's Macroglobulinemia population: SARS-CoV-2 Anti-Spike IgG



Waldenström's Macroglobulinemia population: SARS-CoV-2 Anti-Spike IgG

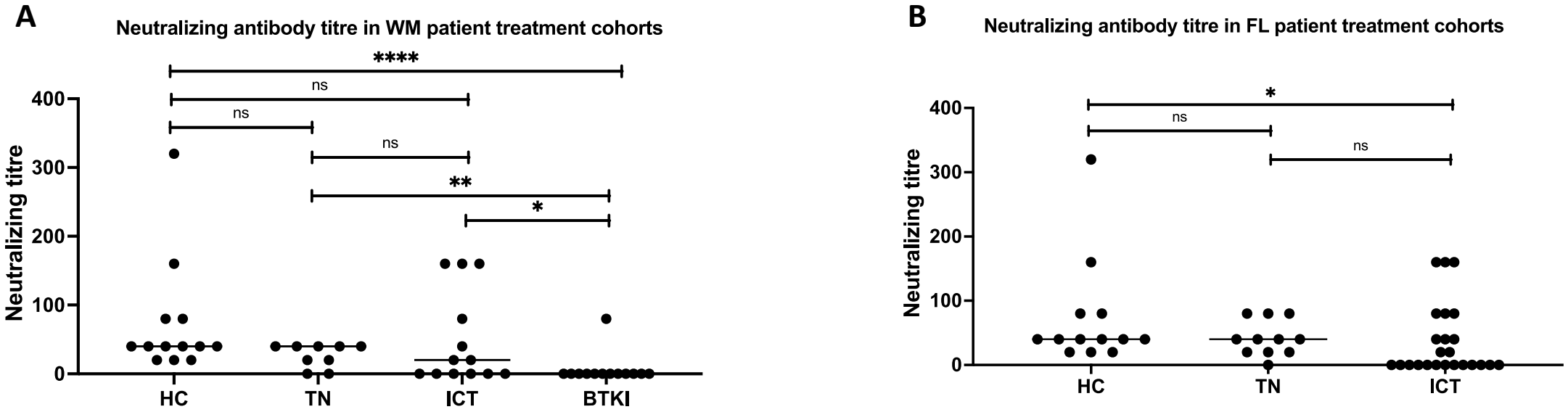


Significantly lower Anti-Spike IgG in the BTKi treated cohort

Cohort	Median MFI	IQR	p
HC	228,255	162,383-249,019	
TN	220,645	131,374-253,237	0.95
ICT	147,197	0-249,655	0.18
BTKi	39,093	4,486-103,484	0.0008

* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001

Live virus Neutralization: Delta variant in HEK cell line at T3



Neutralizing activity for all cohorts in HEK & VERO cell cultures were comparable

Trend toward lower Delta neutralizing activity – esp. apparent in BTKi

Legend
HC: Healthy Controls
TN: Treatment naïve
ICT: Immunochemotherapy
BTKi: Bruton's Tyrosine Kinase inhibitor

* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001

B cell, CD4 & CD8 Proportions

- FL treatment naive patients
  - have reduced CD8 cell overall
- WM patients treated with BTKi
  - have markedly reduced B cells and a relatively reversed CD4:CD8 ratio
- WM patients treated with ICT
  - have reduced CD8 cells overall

Legend
HC: Healthy Control
WB: WM BTKI treated
WN: WM Treatment naive
WT: WM ICT treated
FN: FL Treatment naive
FT: FL ICT treated

B

Cohort	B cell %	IQR	p
HC (n=10)	3.08	2.37-5.90	
WB (n=9)	0.11	0.055-1.31	0.0003
WN (n=4)	1.42	1.07-2.39	0.23
WT (n=5)	2.74	0.955-4.46	0.55
FN (n=5)	3.51	2.56-4.35	0.13
FT (n=12)	2.26	1.28-4.64	0.22

CD4

	CD4 %	IQR	p
HC (n=10)	69.9	56.4-81.6	
WB (n=9)	46.9	45.8-57.7	0.006
WN (n=4)	59.5	47.6-82.1	0.54
WT (n=5)	81.9	64.7-87.1	0.1
FN (n=5)	81.1	77.7-85.6	0.08
FT (n=12)	55.5	47.1-66.5	0.05

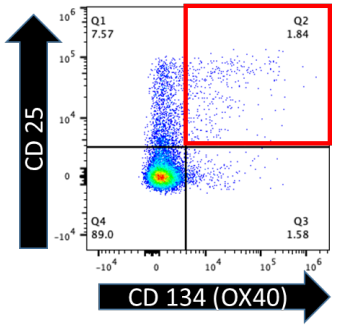
CD8

	CD8 %	IQR	p
HC (n=10)	22.7	10.9-36.7	
WB (n=9)	45.4	31.85-47.5	0.004
WN (n=4)	30.7	12.8-46.1	0.61
WT (n=5)	6.79	4.28-10.6	0.01
FN (n=5)	5.01	3.35-7.73	0.004
FT (n=12)	31.1	22.5-41.3	0.2

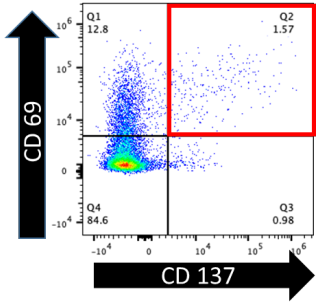
Functional CD4 & CD8 Assessment COVID Spike Peptides T3

- All cohorts, despite treatment type or proportion of CD 4 or CD8 measured, mount reactivity against SARS-CoV-2 Spike peptides

CD 4 Reacting to COVID Spike Peptides



CD 8 Reacting to COVID Spike Peptides



	CD25/OX40 % of CD4	IQR	p
HC (n=10)	0.75	0.48-0.91	
WB (n=9)	0.15	0.11-0.90	0.19
WN (n=4)	0.4	0.15-0.95	0.37
WT (n=5)	0.36	0.025-0.98	0.13
FN (n=5)	0.75	0.48-0.91	0.31
FT (n=12)	0.62	0.28-0.81	0.54
	CD69/CD137 % of CD8	**IQR**	**p**
HC (n=10)	0.81	0.52-0.94	
WB (n=9)	1.1	0.57-1.4	0.28
WN (n=4)	0.47	0.27-0.86	0.39
WT (n=5)	0.14	0-1.4	0.09
FN (n=5)	0.36	0.23-0.87	0.33
FT (n=12)	0.46	0.29-1.37	0.2

Legend
HC: Healthy Control
WB: WM BTKI treated
WN: WM Treatment naive
WT: WM ICT treated
FN: FL Treatment naive
FT: FL ICT treated

* PBMCs from T1 showed no reactivity to SARS-CoV-2 Spike Peptides

Summary

- Treatment naïve FL & WM patients can be reassured their humoral responses to the BNT162b2 COVID vaccine are comparable to age-matched healthy controls
- Anti-Spike IgG levels correlate with live virus neutralizing activity
- Time from treatment and lymphocyte count correlate with anti-spike IgG levels in FL pts treated with immunochemotherapy
- WM patients on BTK inhibitors had markedly reduced anti-Spike IgG level and no Delta neutralization activity
- **Despite poor humoral response as a result of therapy, cellular (CD4 & CD8) response is maintained across all cohorts supporting the value of vaccination in all**

Kapitel 4

Marginalzonenlymphom: PI3K Inhibitoren?

CHRONOS-3: Study Design

Copanlisib in Combination With Rituximab in Patients With Relapsed iNHL

- Patients with relapsed iNHL[a]
- Patients who had a progression-free and treatment-free interval ≥12 months after completion of the last rituximab-containing regimen
- OR patients who are unwilling/unfit or for whom chemotherapy is contraindicated[b]

N=458

Randomized 2:1

Rituximab + copanlisib

Rituximab 375 mg/m^2 weekly

Copanlisib 60 mg weekly until PD

Rituximab + placebo

Rituximab 375 mg/m^2 weekly

Primary endpoint:
PFS by central review

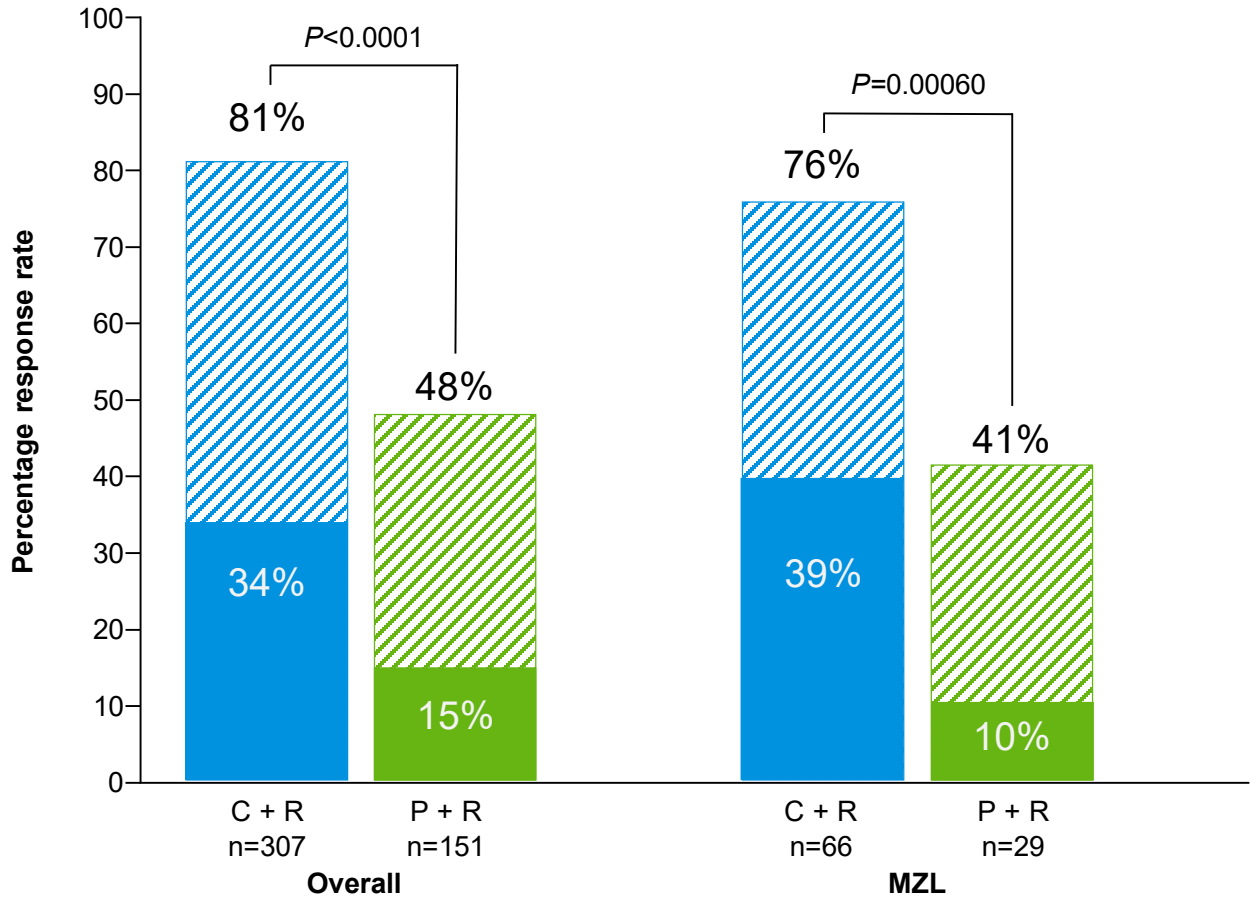
Secondary endpoints:
TTP, ORR, CR, DoR, OS, safety

Exploratory end points:

PK, biomarkers, QoL

[a]Patients who have received ≥1 rituximab-containing therapies. [b]Contraindicated by reason of age, comorbidities and/or residual toxicity.
CR, complete response; **DoR**, duration of response; **iNHL**, indolent non-Hodgkin's lymphoma; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **QoL**, quality of life; **TTP**, time to progression.
ClinicalTrials.gov. NCT02367040. Accessed March 30, 2021. https://clinicaltrials.gov/ct2/show/NCT02367040.

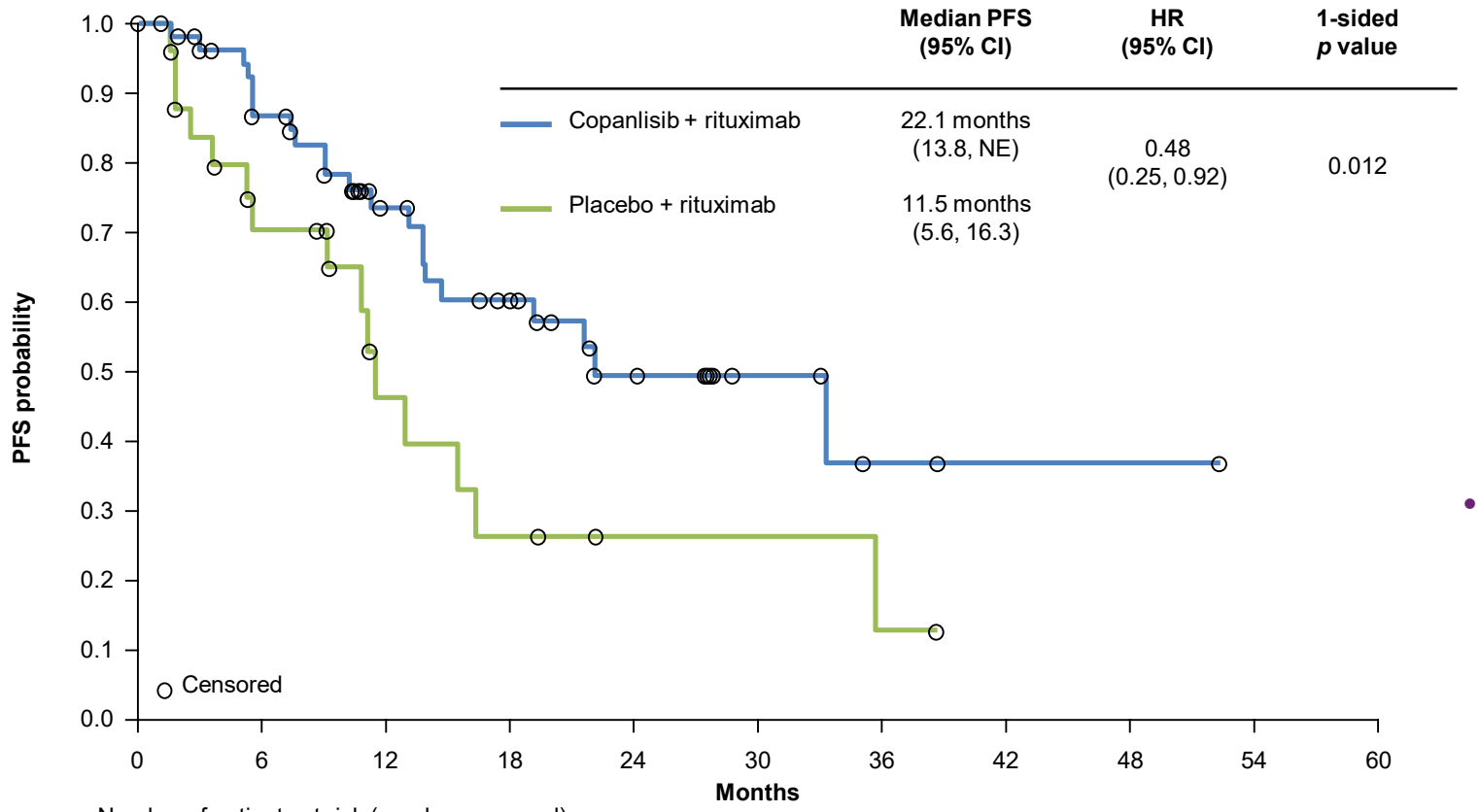
Objective Response Rate (Independent Review)



C, copanlisib; **MZL**, marginal zone lymphoma; **P**, placebo; **R**, rituximab.

Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001.

PFS in Patients With MZL



- Median follow-up of 19.2 months

MZL, marginal zone lymphoma; NE, not estimable.

Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001.

Efficacy and Safety of Parsaclisib in Patients With Relapsed or Refractory Marginal Zone Lymphoma: Primary Analysis From a Phase 2 Study (CITADEL-204)

VIDEO

Tycel Phillips,[1] Abraham Avigdor,[2,3] Ronit Gurion,[4] Caterina Patti,[5] Paolo Corradini,[6] Monica Tani,[7] Amitkumar Mehta,[8] Izidore S. Lossos,[9] Pier Luigi Zinzani,[10] Catherine Thieblemont,[11] Wojciech Jurczak,[12] Fred Zheng,[13] Erica Rappold,[13] Wanying Zhao,[13] Peter Johnson[14]

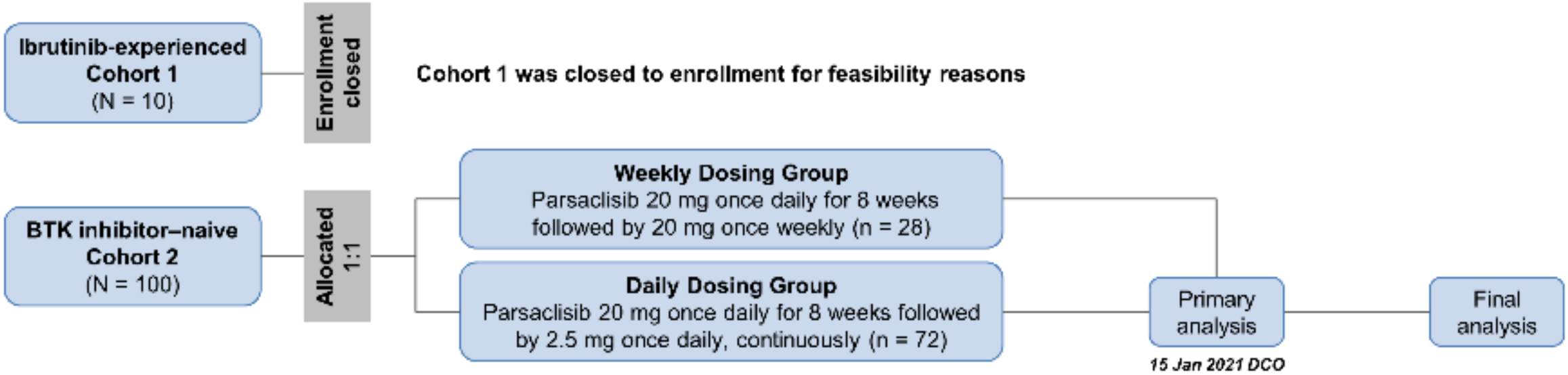
[1]Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA; [2]Institute of Hematology, Sheba Medical Center, Ramat Gan, Israel; [3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Institute of Hematology, Rabin Medical Center & Tel Aviv University, Tel Aviv, Israel; [5]Division of Oncohematology, Azienda Villa Sofia-Cervello, Palermo, Italy; [6]University of Milano Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [7]Azienda Unità Sanitaria Locale della Romagna, Ospedale di Ravenna, Ravenna, Italy; [8]University of Alabama School of Medicine, Birmingham, AL, USA; [9]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [10]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [11]APHP, Hôpital Saint-Louis, Hémato-oncologie, DMU DHI, Université de Paris, Paris, France; [12]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [13]Incyte Corporation, Wilmington, DE, USA; [14]Cancer Research UK Centre, Southampton General Hospital, Southampton, UK

Presented at the 63rd ASH Annual Meeting & Exposition • Atlanta, GA, USA • December 11–14, 2021 (Abstract #44)

CITADEL-204 Study Design

Key inclusion criteria

- ≥18 years of age and histologically confirmed R/R MZL (nodal, extranodal, and splenic)
- Received ≥1 prior systemic therapy, including ≥1 anti-CD20 antibody (as monotherapy or chemoimmunotherapy combination)
- ECOG performance status ≤2
- No prior BTK (BTKi-naive cohort) or PI3K inhibitor (both cohorts)
- No recent HSCT (allogeneic ≤6 months, autologous ≤3 months)



- Following an interim analysis, enrollment continued in the Daily Dosing Group and was closed in the Weekly Dosing Group
- Parsaclisib daily dosing (20 mg daily for 8 weeks followed by 2.5 mg daily) is the recommended dose
- Data are presented for the Daily Dosing Group and for All Treated Patients, which includes patients that switched from 20-mg once-weekly to 2.5-mg once-daily dosing

DCO, data cutoff; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant.

Study Endpoints and Assessments

Primary endpoint

- ORR

Secondary endpoints

- CRR
- DOR
- PFS
- OS
- Best percentage change in disease burden from baseline
- Safety and tolerability of parsaclisib

Assessments

- Response assessed by CT/MRI using the Lugano criteria[1]
- Radiology-based endpoints determined by IRC
- Adverse events assessed using CTCAE v4.03

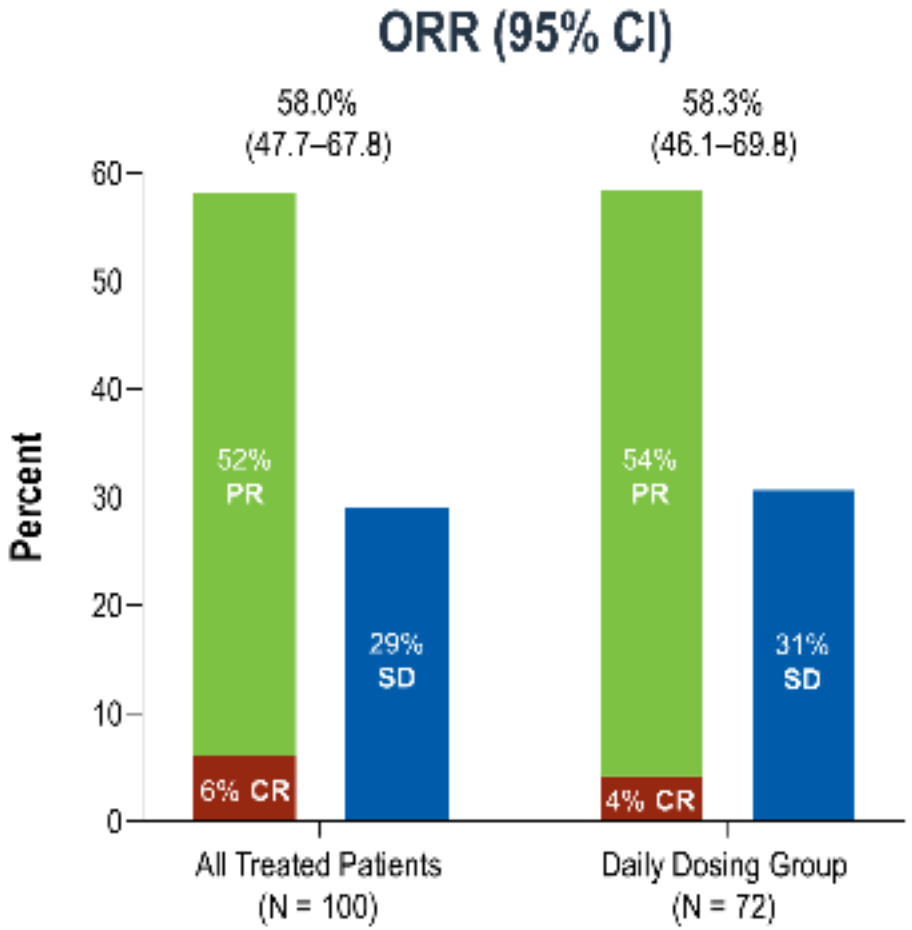
CRR, complete response rate; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; IRC, independent review committee; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

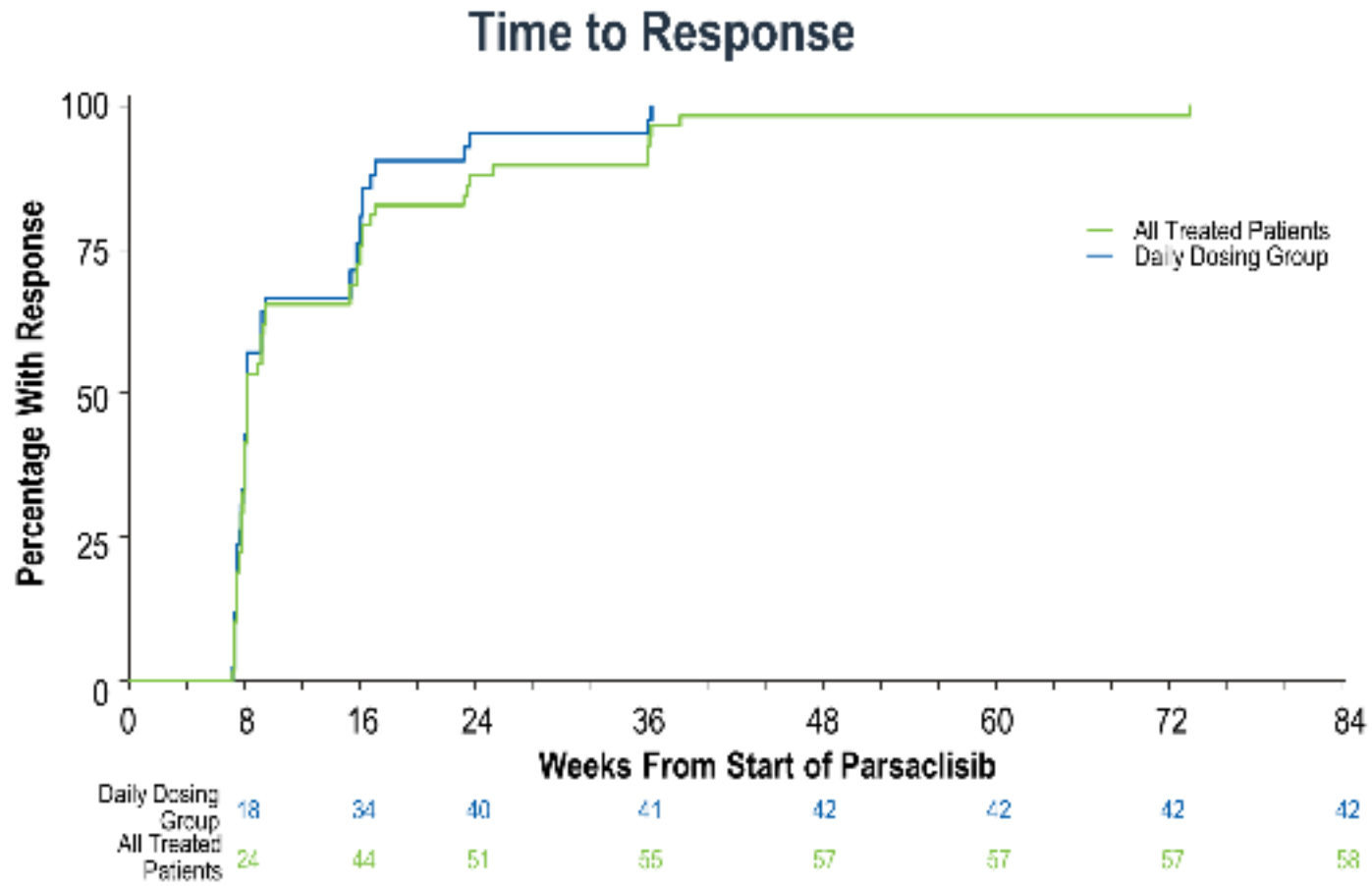
1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059–3068.

Baseline Characteristics

Characteristic	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Age, median (range), years	71.0 (35–95)	72.0 (35–95)
≥65 years, %	72	72
Male, %	53	57
Time since MZL diagnosis, median (range), years	4.6 (0.1–20.1)	4.4 (0.1–19.8)
MZL subtypes, %		
Nodal	31	35
Extranodal	34	32
Splenic	35	33
ECOG performance status ≤1, %	95	96
Prior therapies		
Median (range) number of prior systemic therapy regimens	2 (1–8)	2 (1–5)
Anti-CD20 monoclonal antibodies, %	100	100
Chemotherapy, %	72	74
Surgery/surgical procedures, %	19	15
Radiation, %	11	10
Prior HSCT, %	4	4
Relapse or refractory to most recent systemic therapy, %		
Relapsed	46	46
Refractory	49	49
Unknown	5	6

Objective Responses by IRC





- ORR by investigator assessment: 72.0% in All Treated Patients, 69.4% in Daily Dosing Group
- 65.5% of all responders had their first response occur at the first disease assessment (8 weeks)

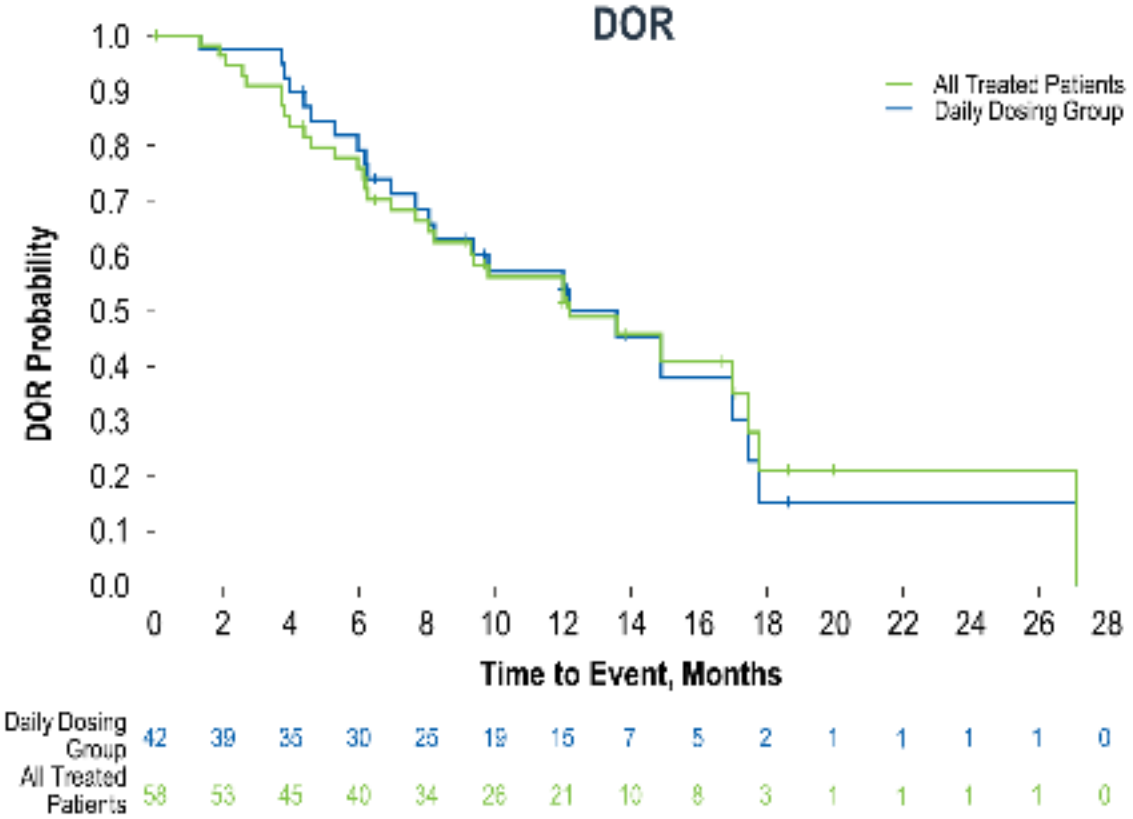
CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

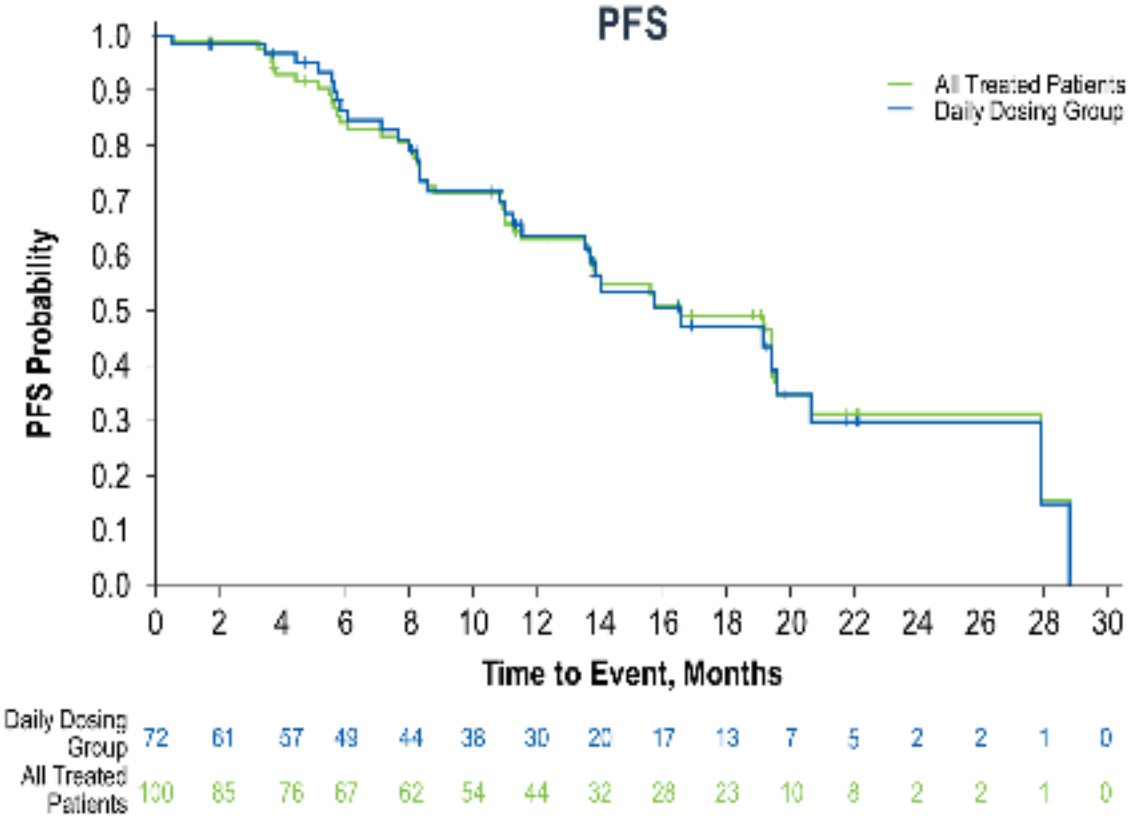
Objective Response Rate by Subtype and Prior Response by IRC

	All Treated Patients (N = 100)				
	Nodal MZL (N = 31)	Extranodal MZL (N = 34)	Splenic MZL (N = 35)	Refractory to Prior Therapy† (N = 49)	Relapsed on Prior Therapy† (N = 46)
Objective response rate, % 95% CI	51.6 33.1–69.8	55.9 37.9–72.8	65.7 47.8–80.9	55.1 40.2–69.3	65.2 49.8–78.6
Best objective response, n (%)					
Complete response	2 (6.5)	3 (8.8)	1 (2.9)	2 (4.1)	4 (8.7)
Partial response	14 (45.2)	16 (47.1)	22 (62.9)	25 (51.0)	26 (56.5)
Stable disease	10 (32.3)	11 (32.4)	8 (22.9)	17 (34.7)	9 (19.6)
Progressive disease	1 (3.2)	1 (2.9)	0	1 (2.0)	1 (2.2)
Not evaluable/Not assessed*	4 (12.9)	3 (8.8)	4 (11.4)	4 (8.2)	6 (13.0)

*Patients with "Not assessed" had no postbaseline response data available by data cutoff.
†Five patients had unknown refractory/relapse status to the most recent prior therapy.

DOR and PFS by IRC





	All Treated Patients (58 Responders)	Daily Dosing Group (42 Responders)
Median DOR (95% CI), months	12.2 (8.1–17.5)	12.2 (8.1–17.5)

	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Median PFS (95% CI), months	16.5 (13.5–19.6)	16.5 (11.5–20.6)

TEAEs Occurring in >10% of All Treated Patients

Event, %*	All Treated Patients (N = 100)		Daily Dosing Group (N = 72)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	96	63	97	72
Diarrhea	47	12	53	15
Cough	23	1	26	1
Rash	18	2	18	3
Anemia	15	6	17	8
Nausea	15	0	17	0
Pruritus	15	0	14	0
Pyrexia	15	1	15	1

Event, %	All Treated Patients (N = 100)		Daily Dosing Group (N = 72)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	14	1	15	1
Constipation	13	0	15	0
Decreased appetite	13	0	15	0
Headache	13	0	14	0
Neutropenia	13	9	14	11
Upper respiratory tract infection	13	2	18	3
Abdominal pain	12	3	15	4
Arthralgia	12	2	11	3

*Pneumonia was reported as a grade ≥3 TEAE in 9% and 10% of patients among All Treated Patients and in the Daily Dosing Group; colitis was reported as a grade ≥3 TEAE in 7% and 10% of patients among All Treated Patients and in the Daily Dosing Group, respectively.
TEAE, treatment-emergent adverse event.

Dose Modifications and High-Grade Diarrhea/Colitis Events

Dose Modifications Due to TEAEs (Any Grade)

Modification, %	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Interruption	56	60
Reduction	16	17
Discontinuation	29	37.5

In the Daily Dosing Group:

- Most frequently occurring TEAEs leading to dose interruption were diarrhea (15%) and neutropenia (6%)
- Most frequently occurring TEAEs leading to dose reduction were diarrhea (7%), and colitis and maculopapular rash (3% each)
- Most common TEAEs leading to treatment discontinuation were diarrhea (12.5%) and colitis (7%)

Time to High-Grade Onset and Improvement of Diarrhea or Colitis Events

Time to Onset or Improvement*	All Treated Patients (N = 100)	Daily Dosing Group (N = 72)
Diarrhea		
Number of patients with grade ≥3 events, %	12	15
Onset of grade ≥3 events, median (range), months	5.6 (0.6–15.1)	5.1 (0.6–15.1)
Improvement to grade ≤2, median (95% CI), days	11.0 (3.0–24.0)	12.0 (3.0–24.0)
Colitis		
Number of patients with grade ≥3 events, %	7	10
Onset of grade ≥3 events, median (range), months	5.6 (1.0–15.4)	5.6 (1.0–15.4)
Improvement to grade ≤2, median (95% CI), days	21.0 (3.0–33.0)	21.0 (3.0–33.0)

*Analyses were for the longest duration of grade ≥3 events using Kaplan-Meier method, and the longest grade ≥3 events that improved in these patients.

Summary

VIDEO

- BTK-naive patients with R/R MZL demonstrated rapid and durable clinical response after treatment with parsaclisib, a potent, highly selective, next-generation PI3Kδ inhibitor
  - 58.3% ORR, 12.2 months DOR, and 16.5 months PFS were observed in the Daily Dosing Group, the recommended dose for parsaclisib
  - Comparable ORRs were observed in patients with nodal, extranodal, and splenic MZL
- Parsaclisib had a manageable safety profile and was generally well tolerated

➢ Results of parsaclisib treatment in patients with follicular lymphoma (CITADEL-203; Abstract #813) and mantle cell lymphoma (CITADEL-205; Abstract #382) are also presented at this meeting

Zusammenfassung | Take-Home-Messages

- MYD88 und CXCR4 Mutationslast beeinflusst das Progressionsrisko zu einem symptomatischen WM
- CXCR4 Antagonisten beim Morbus Waldenström: konzeptionell ein hochattraktives Konzept mit bislang allerdings präliminären klinischen Daten
- Die zelluläre Antwort T-Zellantwort auf ie BNT162b2 COVID-19 Impfung erscheint beim Morbus Waldenström und beim FL intakt
- Der PI3K Inhibitor Parsaclisib zeigt eine hohe Aktivität beim MZL, allerdings sind Nebenwirkungen zu beachten

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2021

Für den Inhalt verantwortlich:

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Universitätsklinikum Ulm

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Lymphom Kompetenz KOMPAKT

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