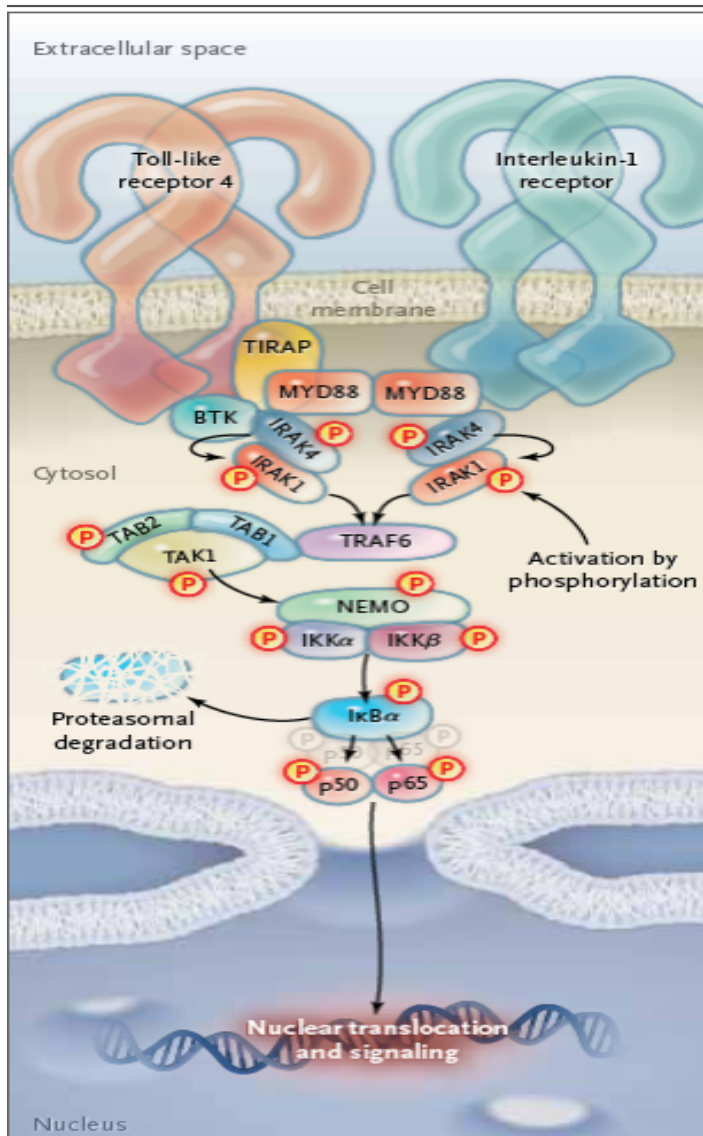


MYD88 (L265P) mutation in Waldenstrom's Macroglobulinemia



- ❖ Induces NFκB signaling via IRAK and BTK pathways
- ❖ Overexpression of MYD88 promotes survival of WM cells
- ❖ Inhibition of MYD88 signaling leads to WM LPC apoptosis

A new era for Waldenstrom macroglobulinemia: MYD88 L265P

Steven P. Treon and Zachary R. Hunter

- » Diagnostic tool (WM vs other B cell LPD)
- » Prognostic marker in IgM-MGUS
- » Response assessment after therapy
- » Novel therapeutic target

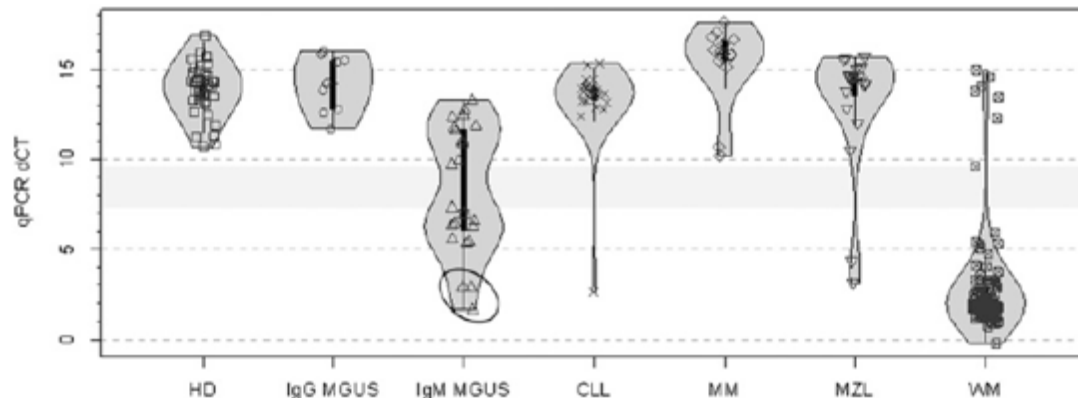
MYD88 (L265P) mutation in patients with WM and IgM-MGUS

Reference	Method	Tissue	WM		IgM-MGUS	
			n. pts	MYD88 L265P	n. pts	MYD88 L265P
Treon et al, 2012	WGS/Sanger	BM CD19+	30/24	91%	21	10%
Landgren et al, 2012	Sanger	BM	-	-	9	56%
Xu et al, 2013	AS-PCR	BM CD19+	104	93%	24	54%
Varettoni et al, 2013	AS-PCR	BM	58	100%	77	47%
Gachard et al, 2013	PCR	BM	31	67%	-	-
Jiménez et al, 2013	AS-PCR	BM/LN	117	86%	31	87%
Poulain et al, 2013	PCR	BM CD19+	67	79%	-	-
Ansell et al, 2013	WGS/Sanger/ AS-PCR	NA	39	97%	-	-

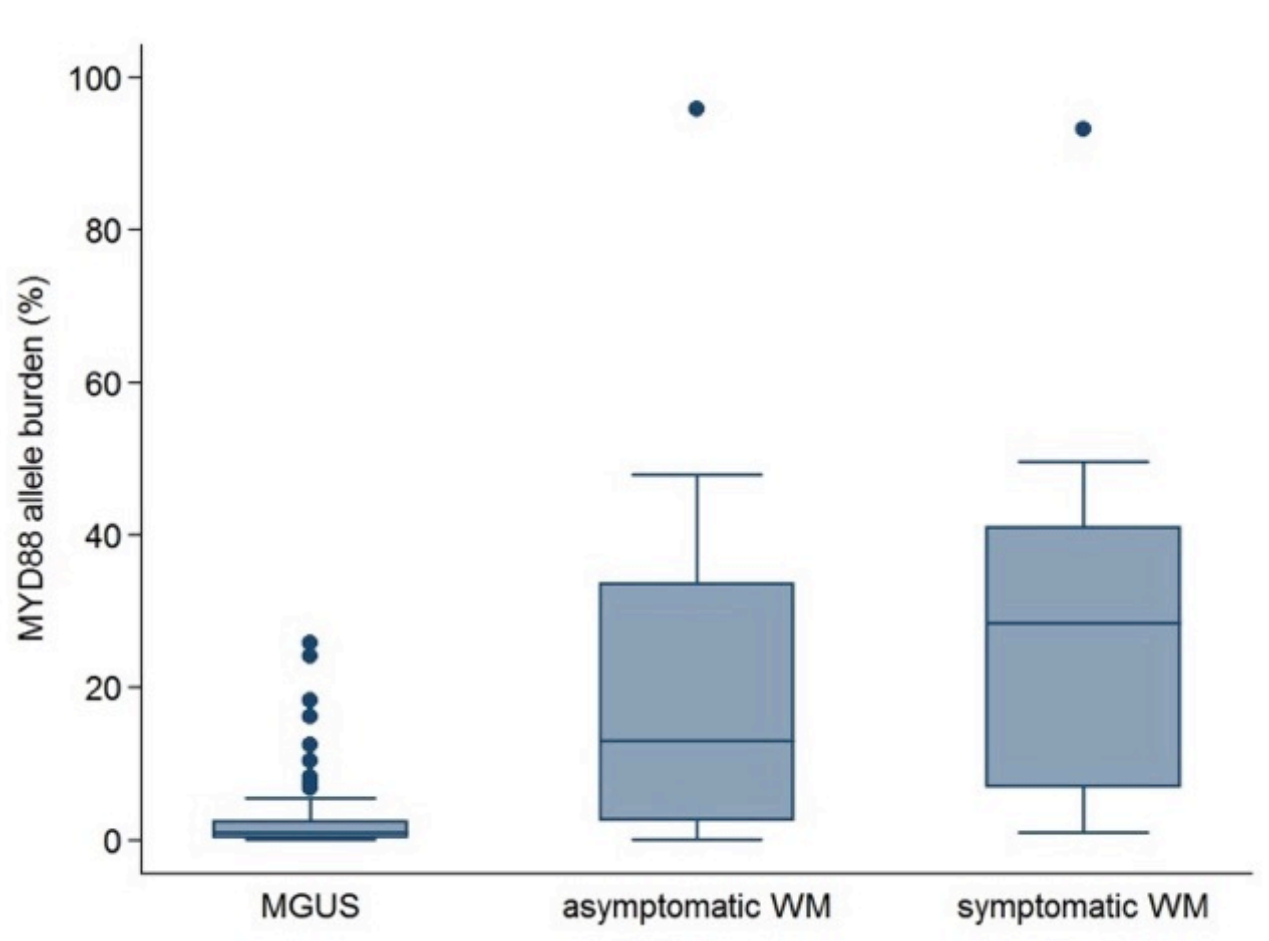
MYD88 L265P-MUT

- Marker highly characteristic of **WM and IgM-MGUS** and post-GC LPDs
- Few studies ipotesize its use as tool for diagnostic and response assessment

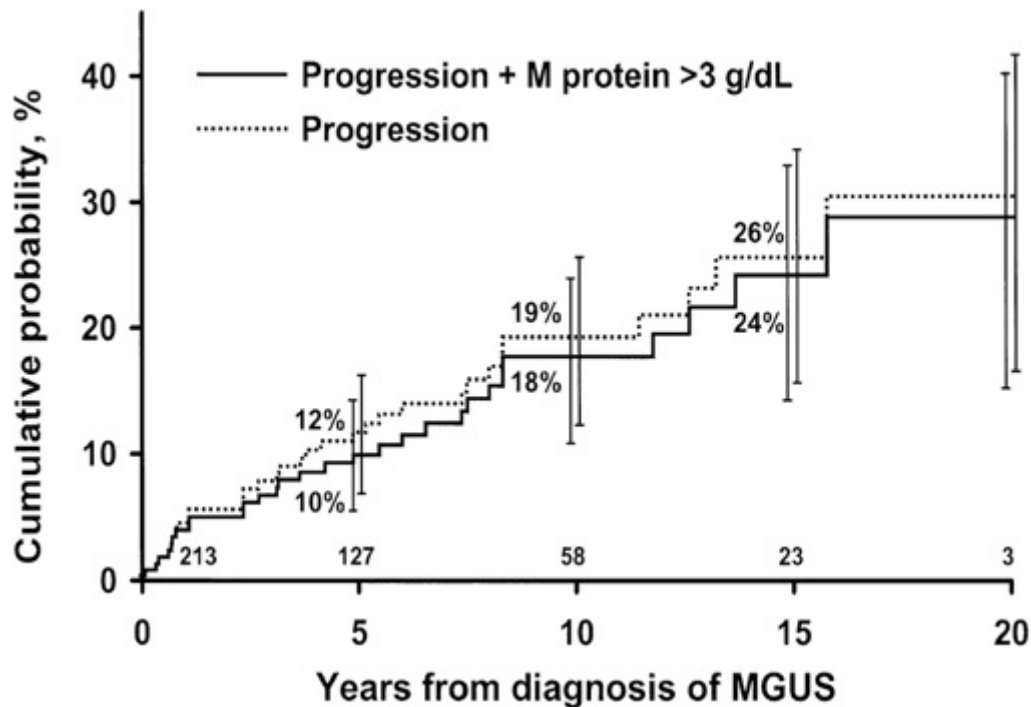
Disease categories	Mutation frequency by (AS-PCR)
WM	79–100%
IgM-MGUS	50–80%
non-GC DLBCL	19%
MZL, MALT	<10%
CLL, FL	<5%
MM, HCL, MCL IgA/IgG MGUS	0%
HEALTHY	0%



MYD88 allele burden in IgM-MGUS, asymptomatic and symptomatic WM by RT-qPCR

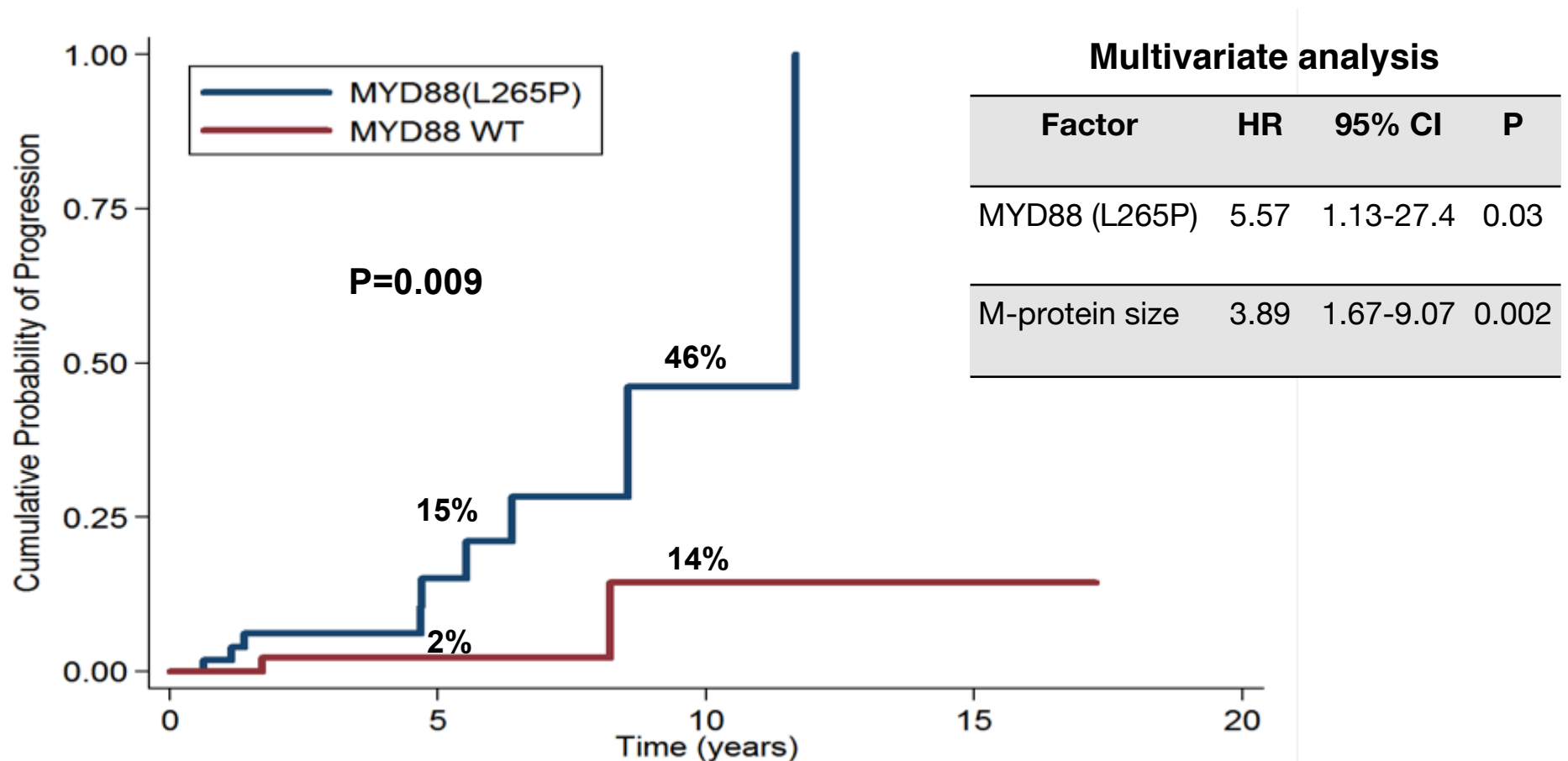


Probability of progression in patients with IgM-MGUS



M protein concentration	Risk of progression
0.5 g/dl	14%
1.5 g/dl	26%
2.0 g/dl	34%
2.5 g/dl	41%

Probability of progression in patients with IgM-MGUS according to the MYD88 mutational status



Multivariate analysis

Factor	HR	95% CI	P
MYD88 (L265P)	5.57	1.13-27.4	0.03
M-protein size	3.89	1.67-9.07	0.002



Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia

Steven P. Treon, Yang Cao, Lian Xu, Guang Yang, Xia Liu and Zachary R. Hunter

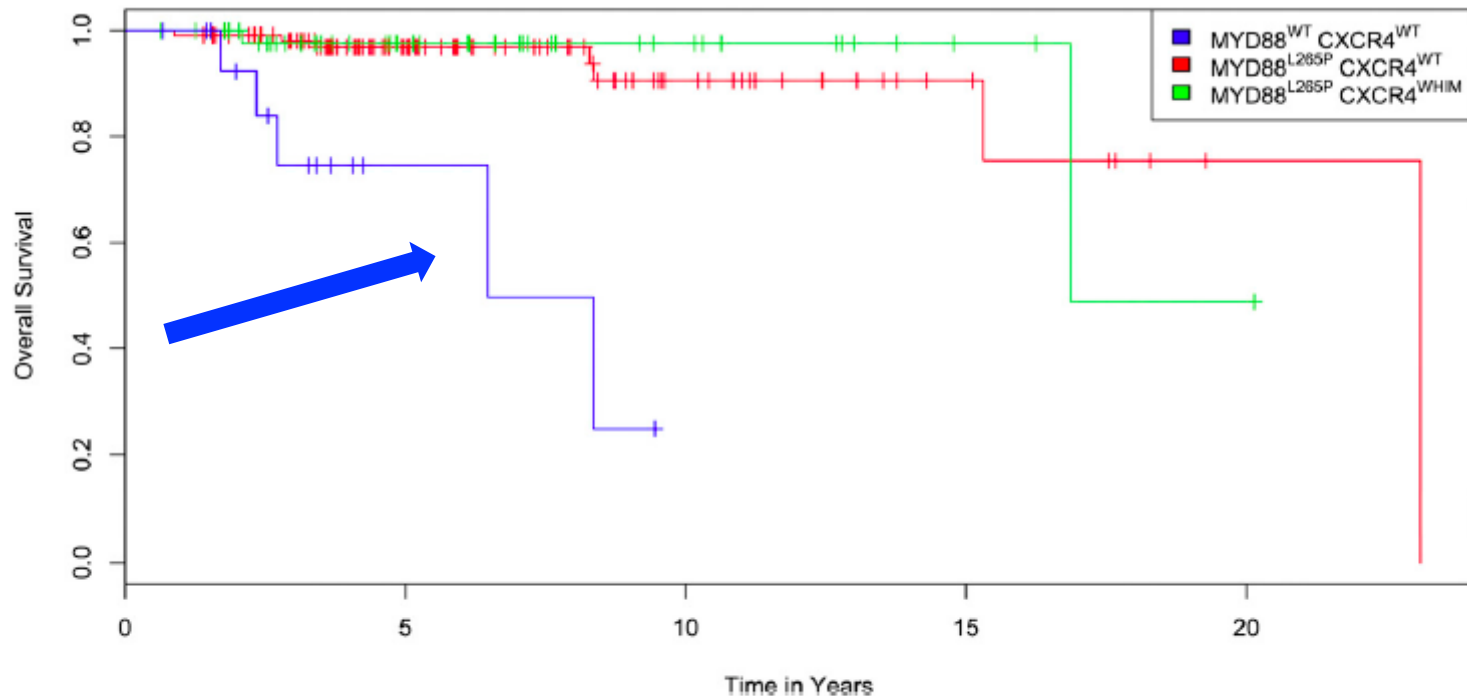


Figure 2. Kaplan-Meier plot for overall survival of 175 WM patients from time of diagnosis stratified by MYD88 and CXCR4 mutation status. Differences in survival curves based on CXCR4 and MYD88 mutation status were significant ($P < .0001$), as was the analysis based on MYD88 status alone ($P < .0001$) by Fleming-Harrington log-rank analysis.

MYD88^{L265P}: a novel marker for MRD

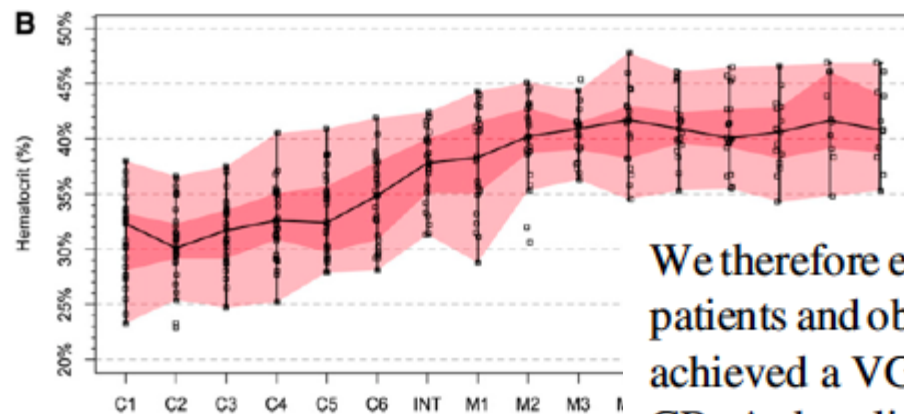
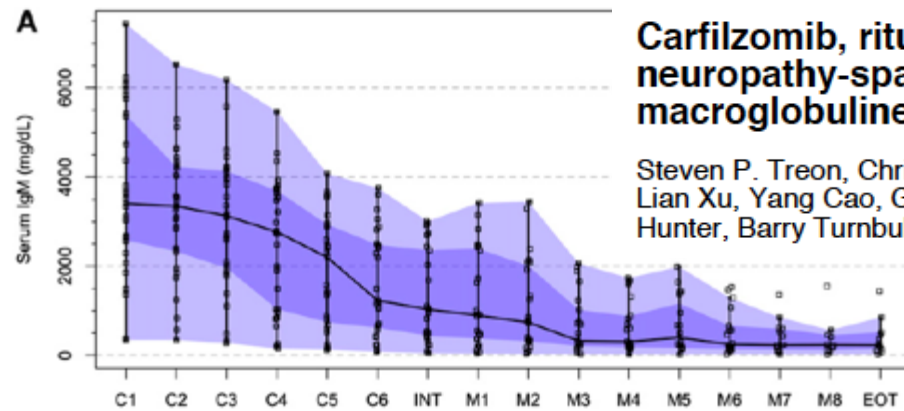


blood

2014 124: 503-510
doi:10.1182/blood-2014-03-566273 originally published
online May 23, 2014

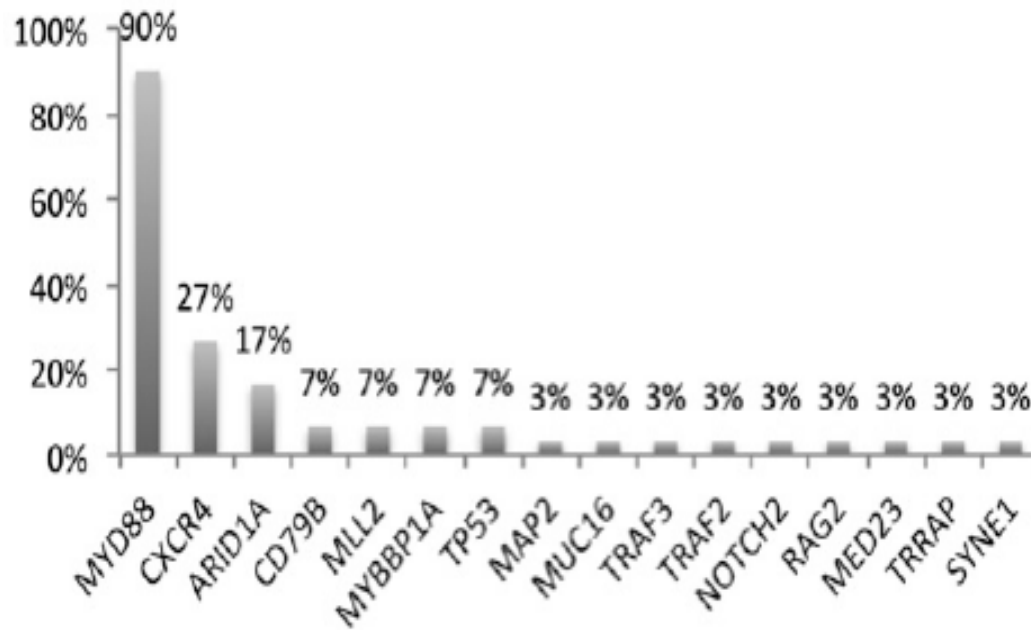
Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia

Steven P. Treon, Christina K. Tripsas, Kirsten Meid, Sandra Kanan, Patricia Sheehy, Stacey Chuma, Lian Xu, Yang Cao, Guang Yang, Xia Liu, Christopher J. Patterson, Diane Warren, Zachary R. Hunter, Barry Turnbull, Irene M. Ghobrial and Jorge J. Castillo



We therefore examined CaRD as a frontline treatment option for WM patients and observed an ORR of 87.1%. Importantly, 36% of patients achieved a VGPR/CR, including 1 patient who attained a molecular CR. At baseline, this patient had strongly detectable MYD88^{L265P}-positive BM and PB disease with Δ CTs of 1.8 and 3.8, respectively, using a highly sensitive allele-specific-PCR assay.^{24,25} Following

Beyond MYD88 and CXCR4: the genomic landscape of WM



Hunter et al, Blood 2014; 123: 1637-1745

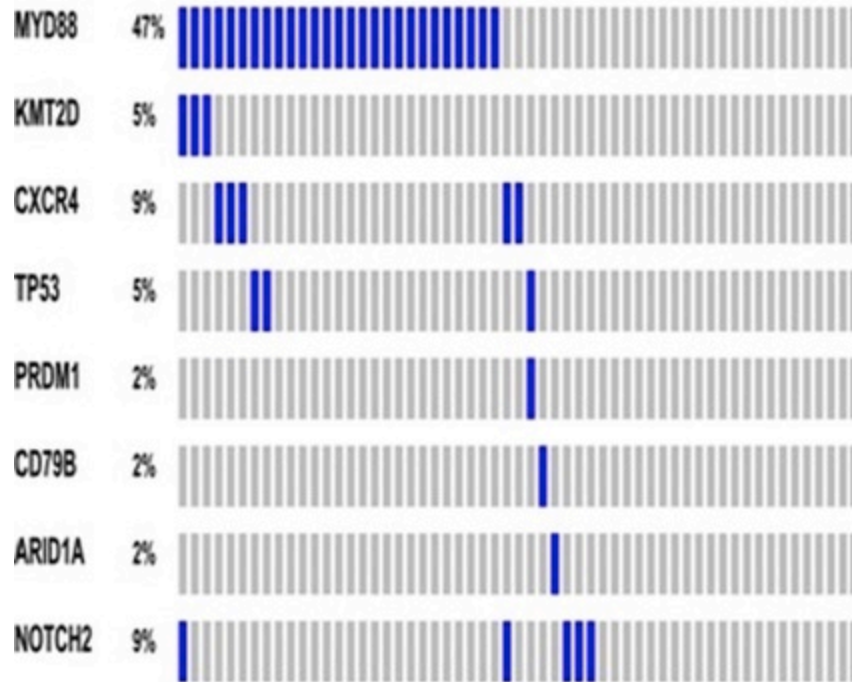
TP53 alterations are associated with

- inferior OS
- shorter time to treatment
- shorter TTP after therapy

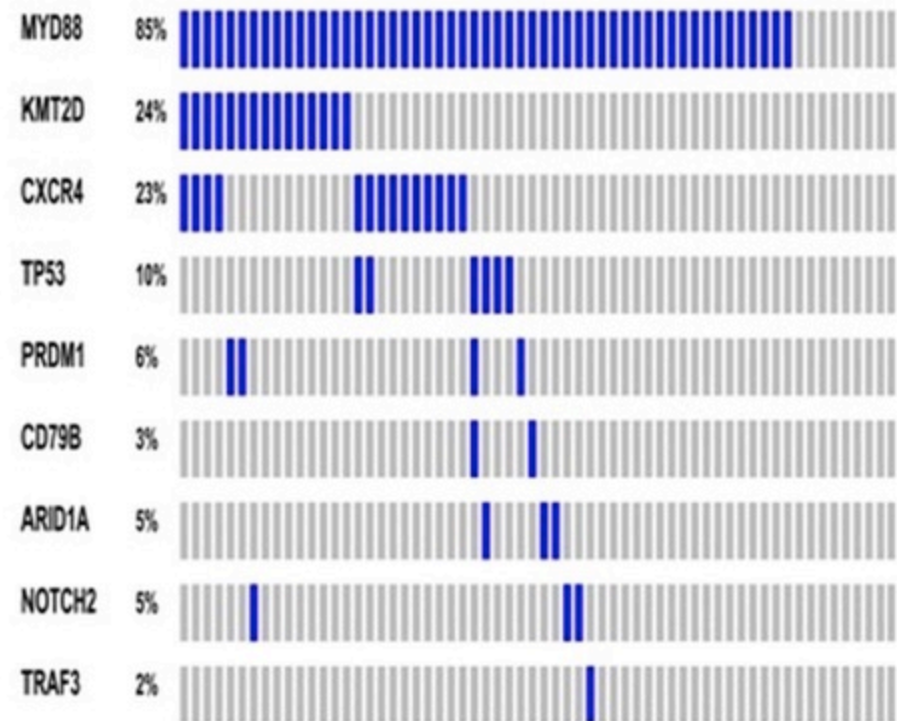
Poulain et al, Clin Cancer Research 2017

Pattern of somatic mutations in WM and IgM-MGUS patients

IgM MGUS (n=57)



WM (n=62)



MYD88 mutations other than L265P:

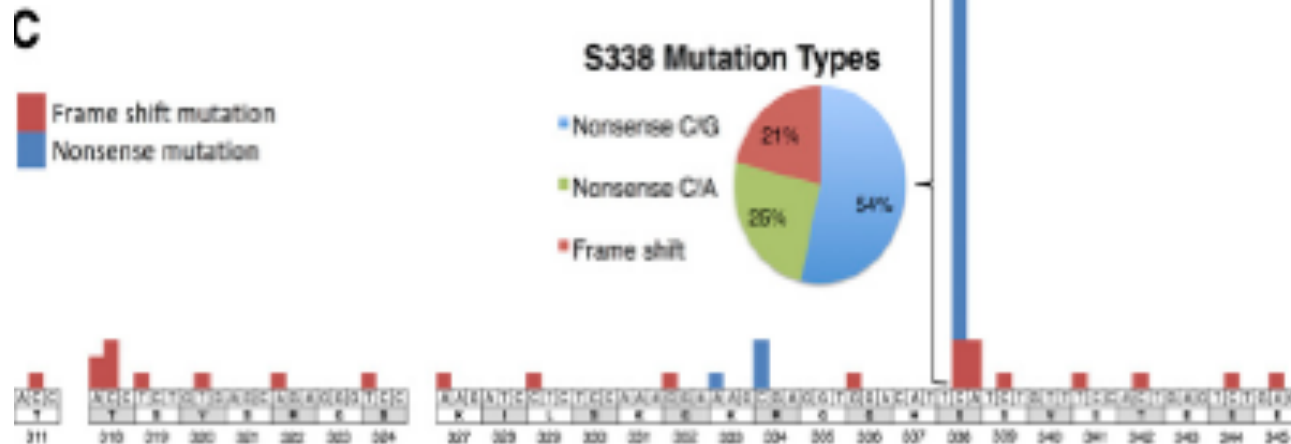
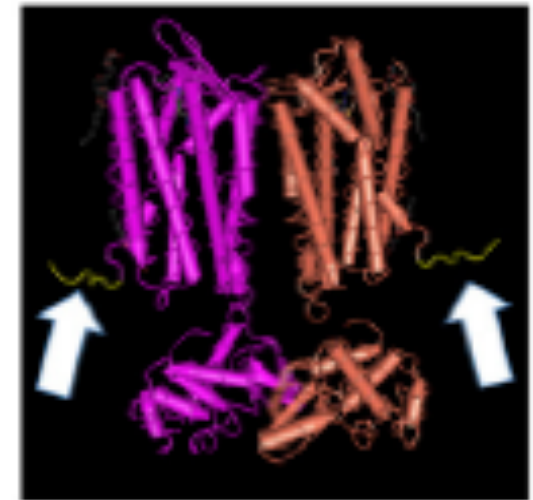
V217F (n=2)

S219C (n=1)

M232T (n=1)

CXCR4 WHIM-like mutations in WM

- ❖ WM is the first cancer with reported CXCR4 somatic mutations
- ❖ Over 30 nonsense (NS) or frameshift (FS) C-tail mutations
- ❖ CXCR4 (S338X) mutation represent ~ 50% of all mutations
- ❖ Similar to germline mutations typical of WHIM syndrome



CXCR4 mutations in WM and IgM-MGUS

Reference	Method	WM		IgM-MGUS	
		n. pts	% of CXCR4 mutated pts	n. pts	% of CXCR4 mutated pts
Treon et al, 2014	WGS/Sanger	177	29%	-	-
Roccaro et al, 2014*	AS-PCR for S338X (C1013G)	131	28%	40	20%
Schmidt et al, 2015*	Sanger	47	36%	-	-
Xu et al, 2016*	Sanger/AS-PCR for S338X (C1013G and C1013A)	102 untreated 62 treated	43% 34%	12	17%
Poulain et al, 2016	Sanger/NGS	98	25%	-	-

* These studies included also MZL patients with a prevalence of CXCR4 mutations of 5-7%
No CXCR4 mutations were found in CLL, MM, IgA and IgG MGUS, HCL and healthy subjects

Treon et al, Blood 2014; Roccaro et al, Blood 2014; Schmidt et al, Br J Haematol 2015; Xu et al, Br J Haematol 2016; Poulain et al, CCR 2016

CXCR4 → C-X-C chemokine receptor type 4



blood

2014 123: 4120-4131

doi:10.1182/blood-2014-03-564583 originally published
online April 7, 2014

C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma

Aldo M. Roccaro, Antonio Sacco, Cristina Jimenez, Patricia Maiso, Michele Moschetta, Yuji Mishima, Yosra Aljawai, Ilyas Sahin, Michelle Kuhne, Pina Cardarelli, Lewis Cohen, Jesus F. San Miguel, Ramon Garcia-Sanz and Irene M. Ghobrial

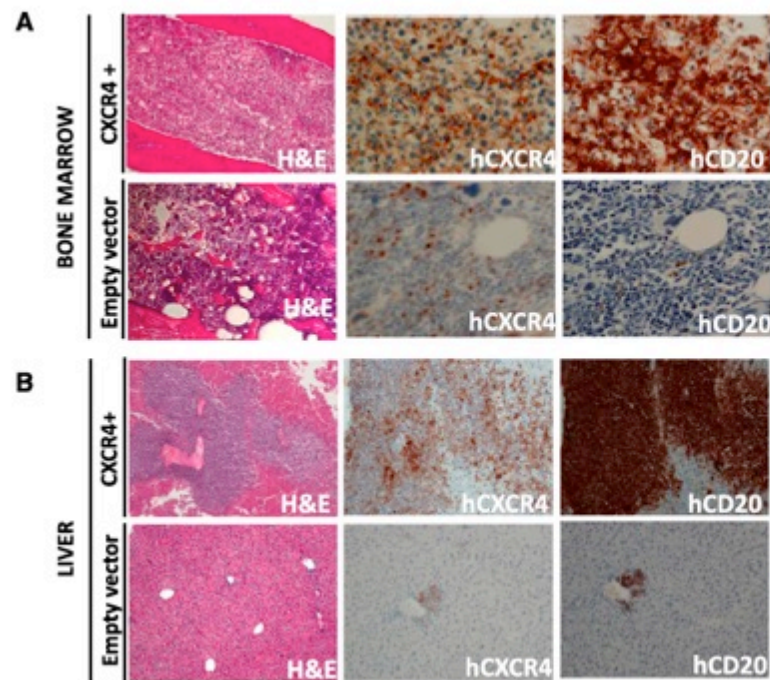
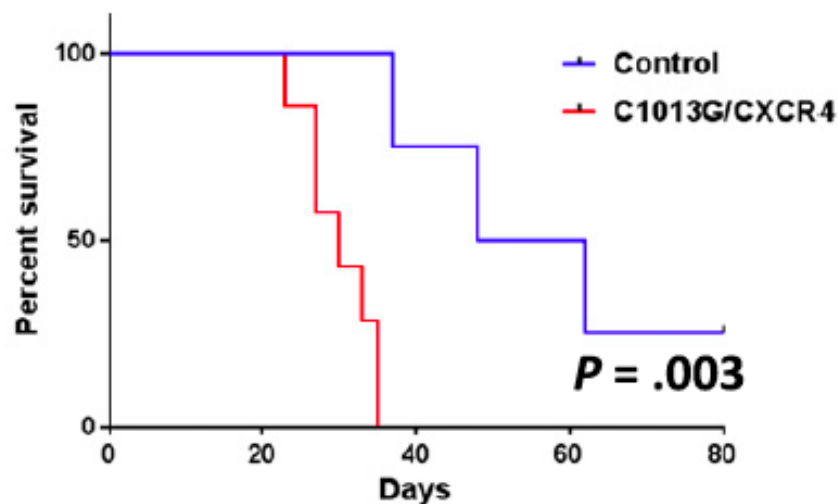


Figure 2. Overexpression of CXCR4 in WM cells leads to increased disease dissemination in vivo and enhanced adhesion properties and growth in vitro. CXCR4 overexpressing cells (CXCR4⁺) presented with a more aggressive ability to disseminate to BM (A), liver (B), and kidneys (C) compared with the related empty vector-infected cells (Hematoxylin Eosin ×10; Ab staining ×20 and ×10, magnifications). Quantification of human CD20 and CXCR4 staining is shown in supplemental Figure 1.

were detected in BM, liver, and kidneys (magnifications). increased survival in vector cell-injected and 62. Pindica overexpression primary BM-ME contrast with C in which reduced cell proliferation and standard deviation. NS, not significant.



Clinical significance of CXCR4 mutations in WM

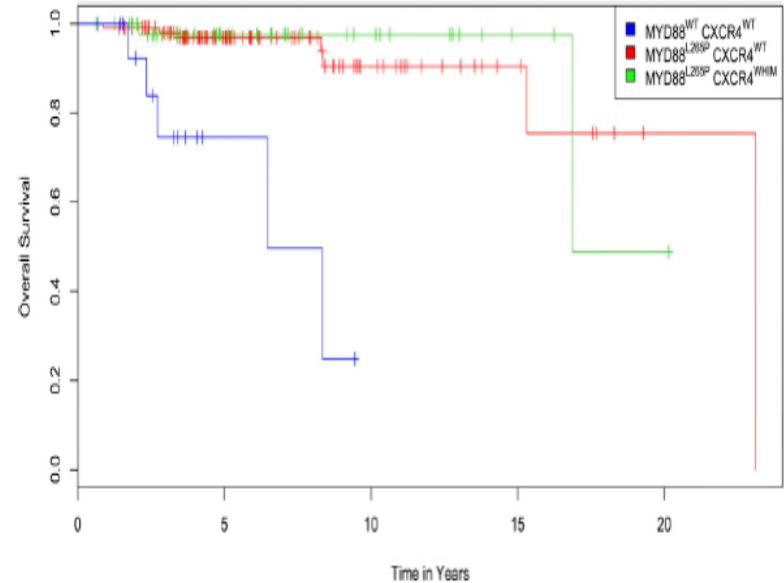
Disease presentation

- » higher IgM levels^{1,*2}
- » higher incidence of hyperviscosity^{1*}
- » higher BM infiltration^{1*}
- » lower PLT,^{2,3} Hb,³ WBC³ count
- » less adenopathy^{1,3}

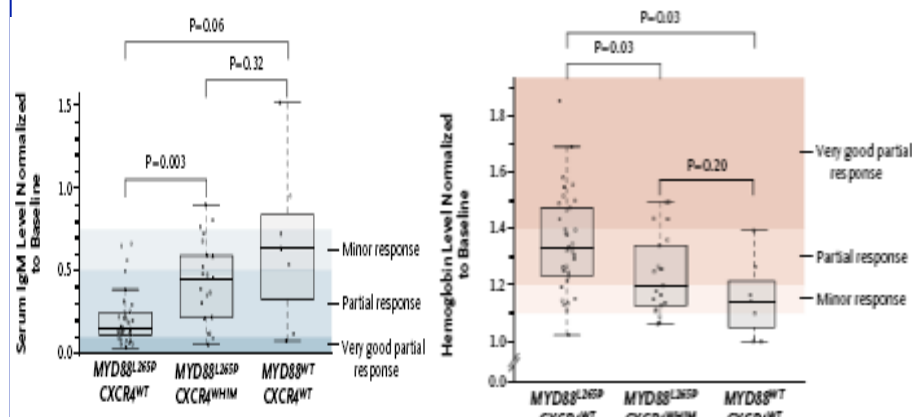
*CXCR4/NS

Outcome

- No impact on OS^{1,2}



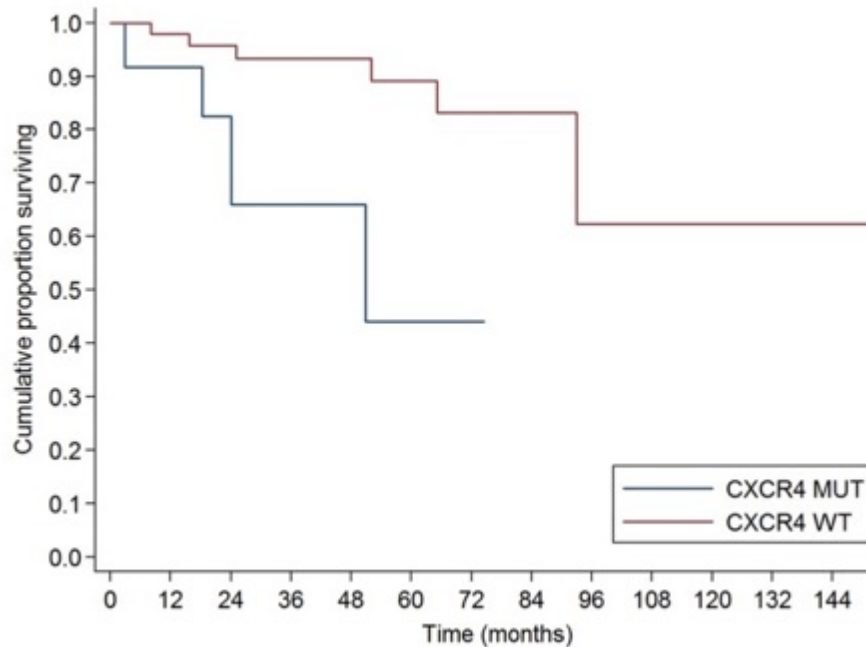
Clinical resistance to Ibrutinib⁴



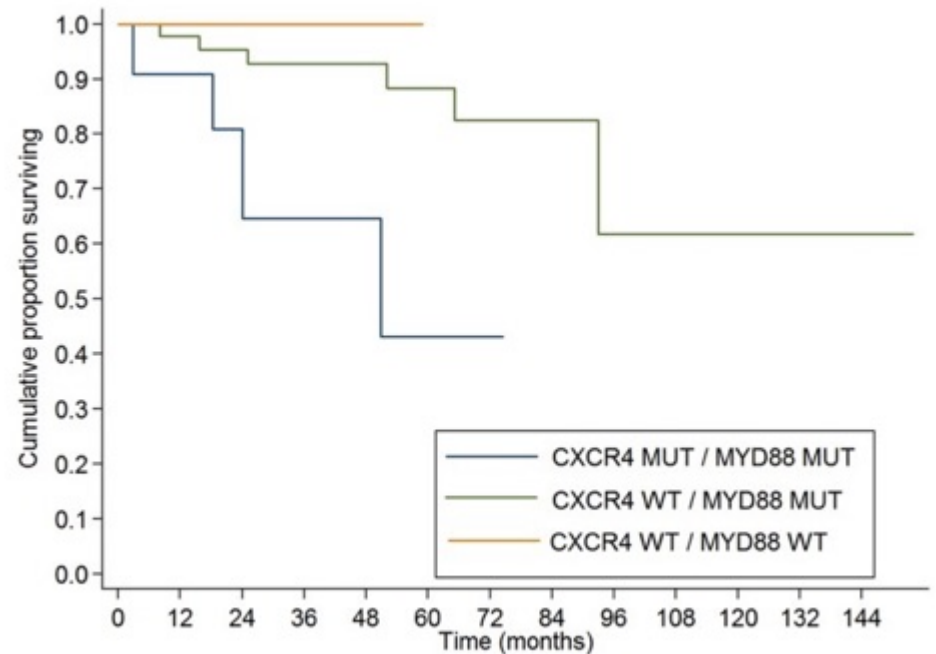
- 1 Treon SP et al, *Blood* 2014; 123: 2791-96
- 2 Poulain S et al, *Clin Cancer Res* 2016; 22: 1480-88
- 3 Schmidt J et al, *Br J Haematol* 2015; 169: 795-803
- 4 Treon SP et al, *NEJM* 2015; 372: 1430-40

Treatment-free survival in asymptomatic WM patients according to CXCR4 mutation status

CXCR4



CXCR4 and MYD88

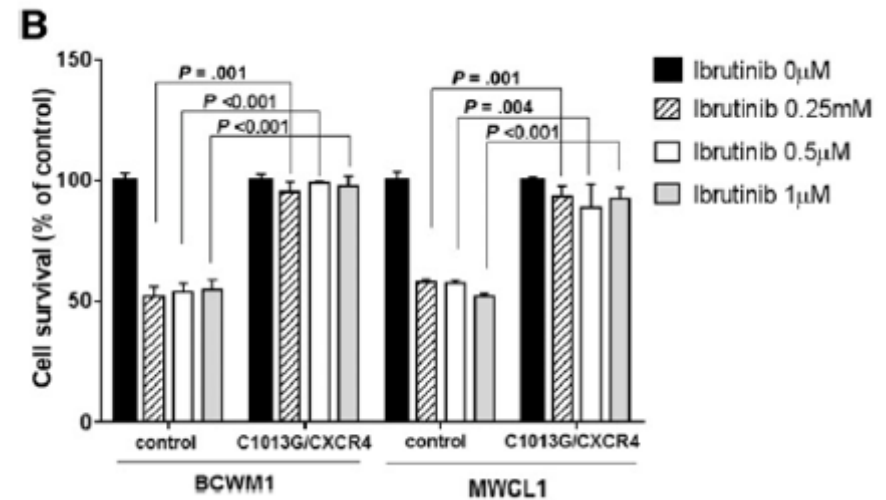
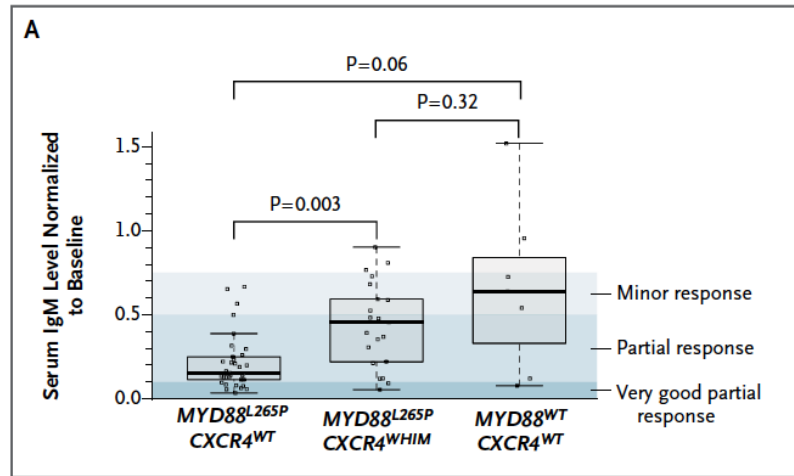


ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

MYD88^{WT} and/or CXCR4^{WHIM} predict resistance to ibrutinib, idelalisib and temsirolimus

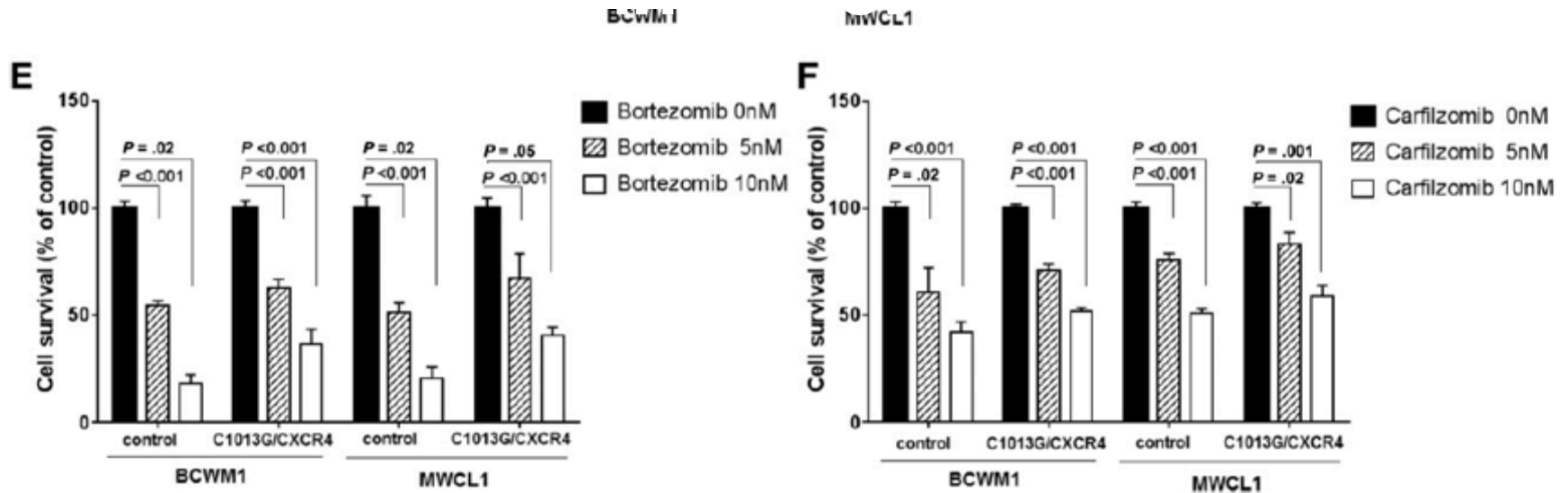


Roccaro AM et al., Blood 2014

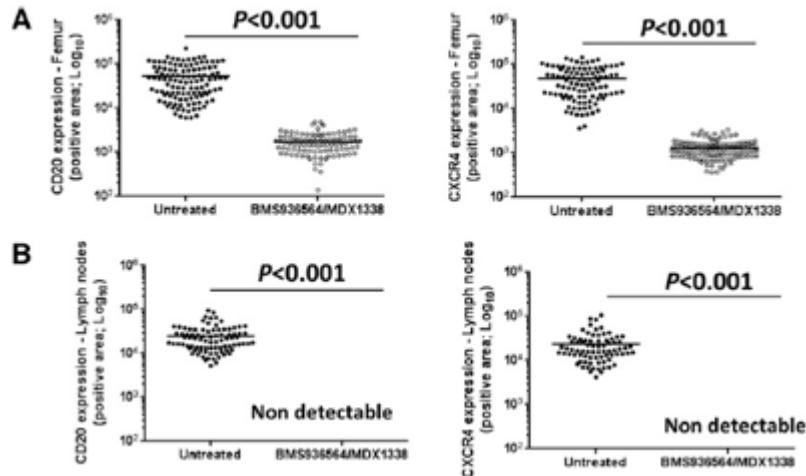
CONCLUSIONS

Ibrutinib was highly active, associated with durable responses, and safe in pre-treated patients with Waldenström's macroglobulinemia. MYD88 and CXCR4 mutation status affected responses to this drug. (Funded by Pharmacyclics and others; ClinicalTrials.gov number, NCT01614821.)

CXCR4^{WHIM} cells are sensitive to proteasone



Roccaro AM et al., Blood 2014



BMS936564/MDX1338, a novel anti-CXCR4 moAb, successfully targets WM cells, either C1013G/CXCR4 mutated or wild-type.



EUROPEAN
HEMATOLOGY
ASSOCIATION

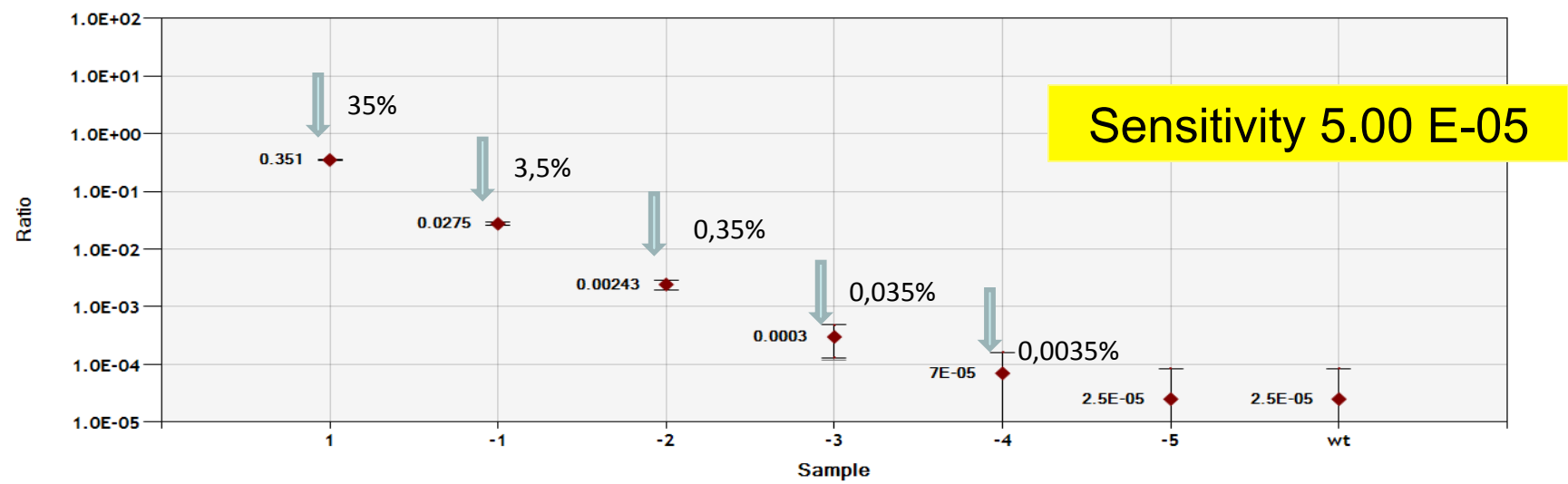
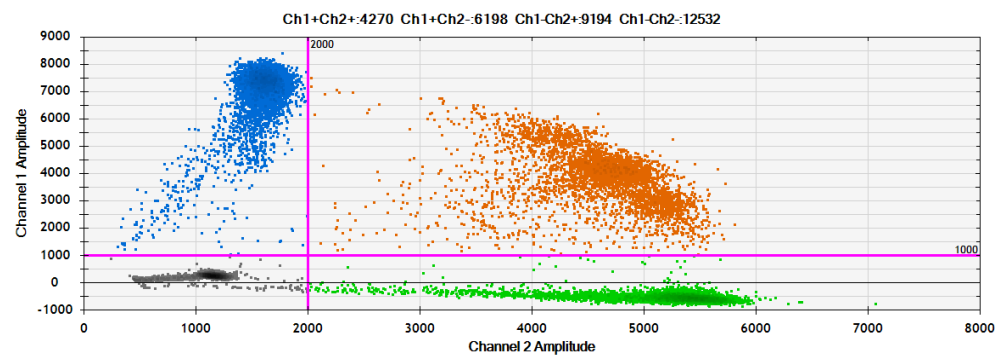
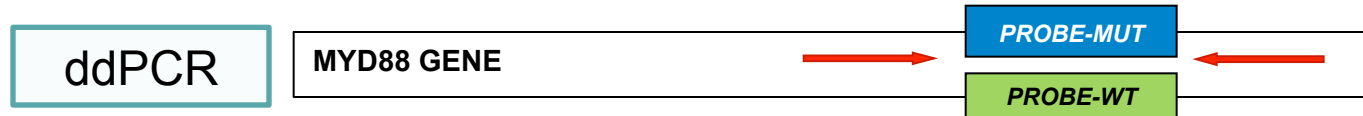


Highly sensitive MYD88^{L265P} mutation detection by droplet digital PCR in Waldenström Macroglobulinemia

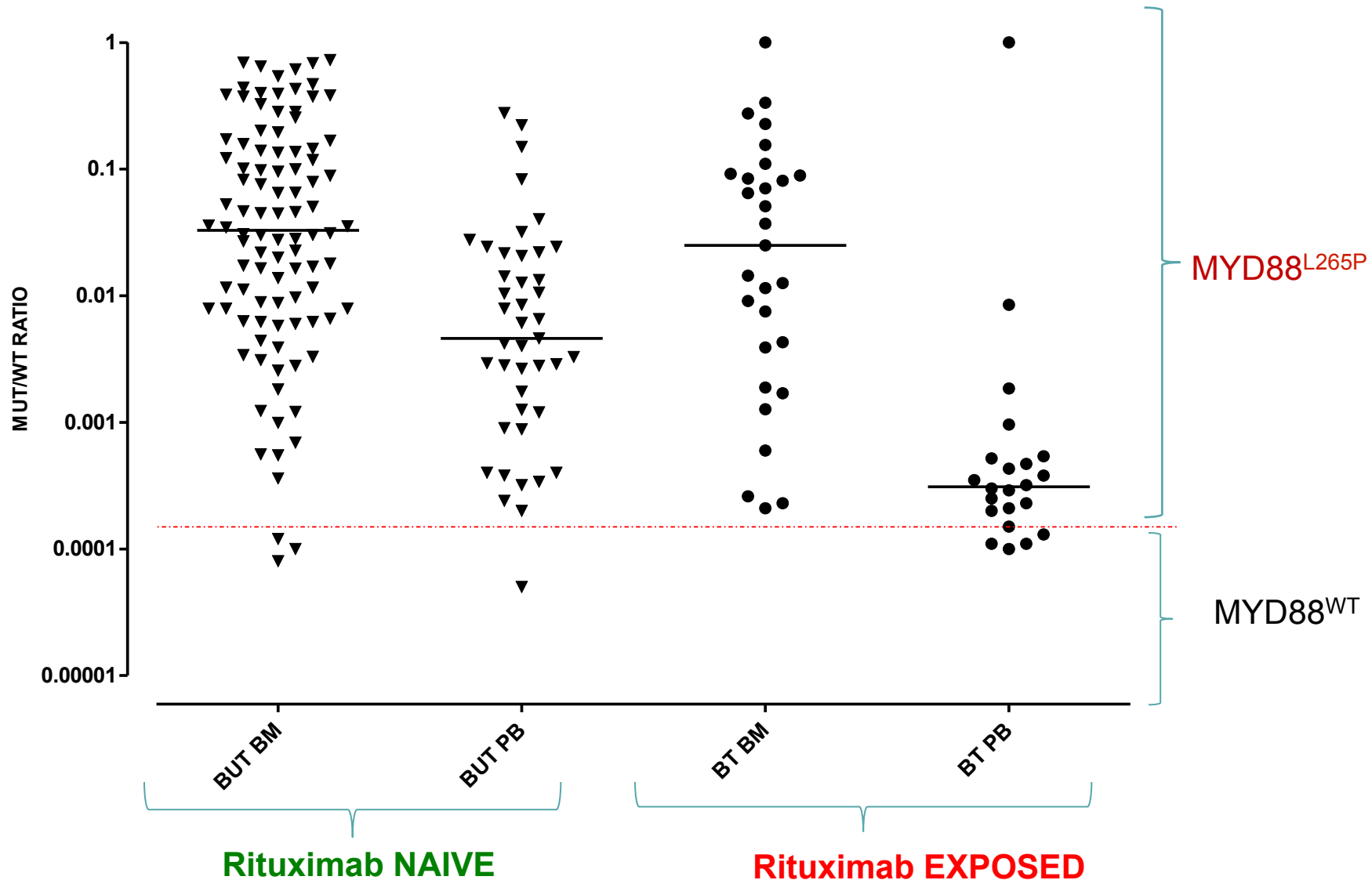
by Daniela Drandi, Elisa Genuardi, Irene Dogliotti, Martina Ferrante, Cristina Jiménez, Francesca Guerrini, Mariella Lo Schirico, Barbara Mantoan, Vittorio Muccio, Giuseppe Lia, Gian Maria Zaccaria, Paola Omedè, Roberto Passera, Lorella Orsucci, Giulia Benevolo, Federica Cavallo, Sara Galimberti, Ramón García-Sanz, Mario Boccadoro, Marco Ladetto, and Simone Ferrero

Haematologica 2018 [Epub ahead of print]

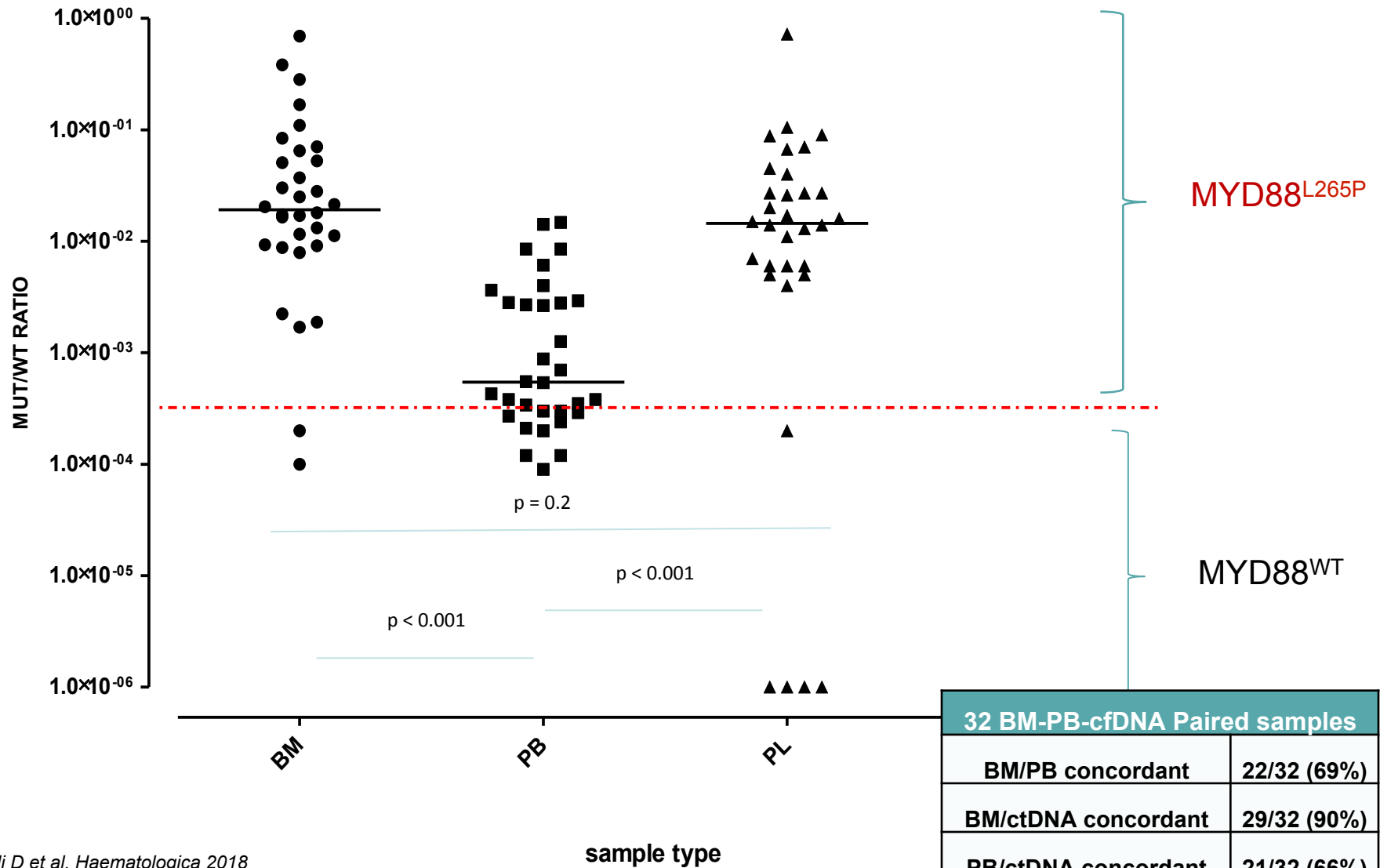
A ddPCR strategy for MYD88^{L265P} mutation detection in Waldenström's macroglobulinemia



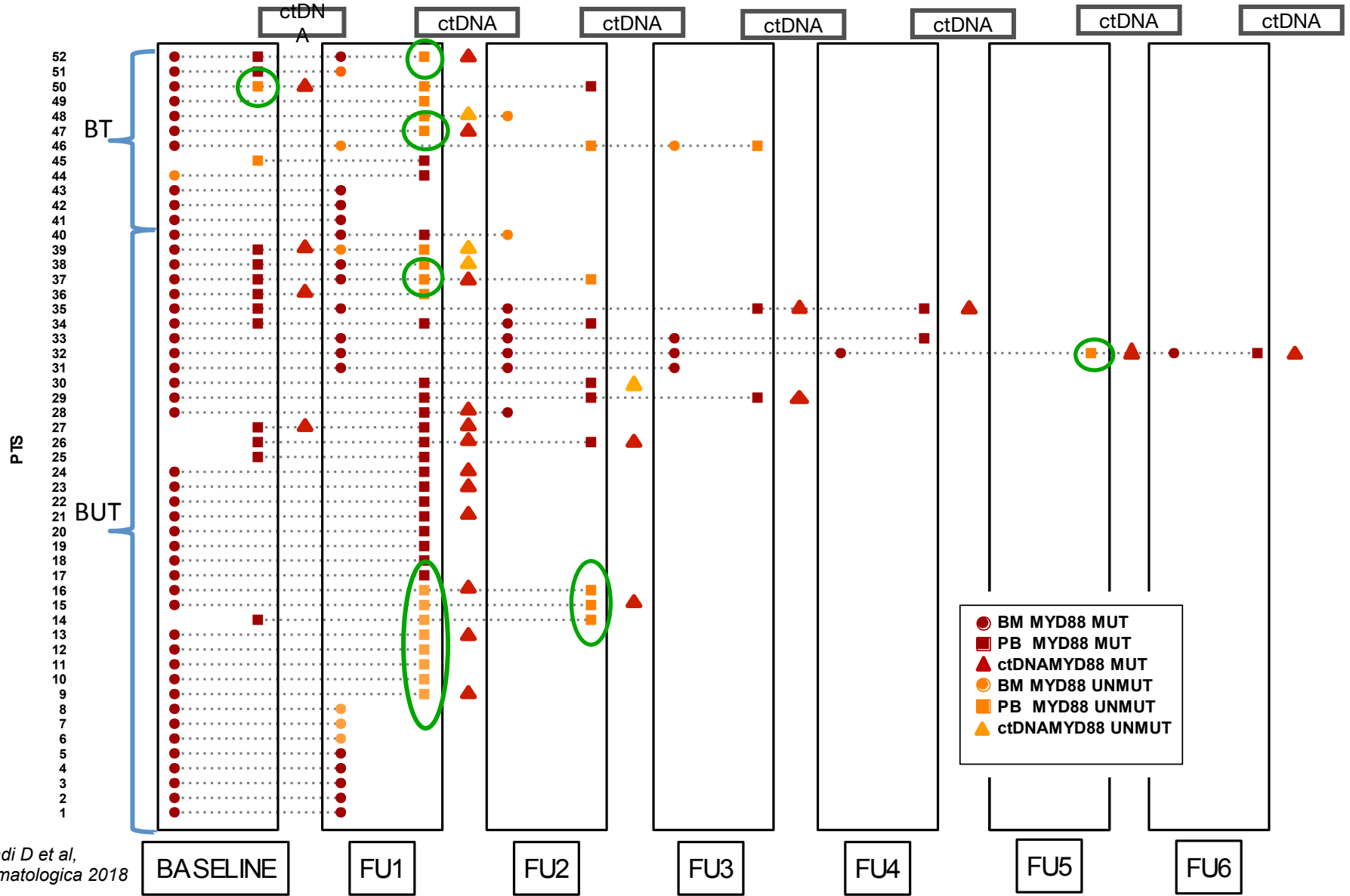
MYD88^{L265P} MUT/WT RATIO AT BASELINE



MYD88^{L265P} QUANTIFICATION BM vs PB vs PLASMA cfDNA

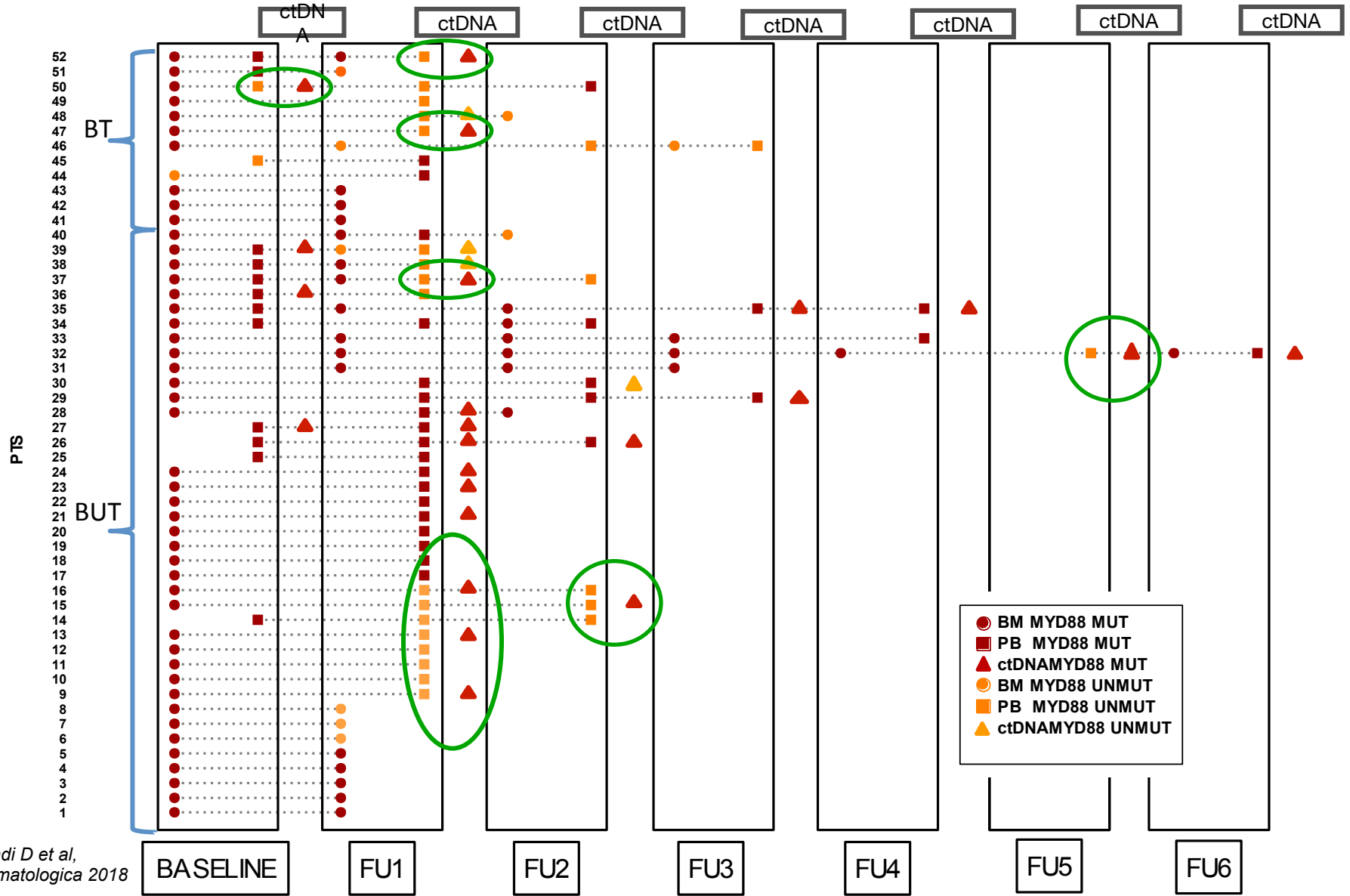


Feasibility of MYD88^{L265P} as MRD marker: 52 patients monitored



Drandi D et al, Haematologica 2018

Feasibility of MYD88^{L265P} as MRD marker: 52 patients monitored



Drandi D et al, Haematologica 2018

URINARY cell-free nucleic acids

Copy number variations in urine cell free DNA as biomarkers in advanced prostate cancer

Yun Xia^{1,2}, Chiang-Ching Huang³, Rachel Dittmar², Meijun Du², Yuan Wang², Hongyan Liu², Niraj Shenoy⁴, Liang Wang² and Manish Kohli⁴

¹ Department of General Surgery, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

² Department of Pathology and MCW Cancer Center, Medical College of Wisconsin, Milwaukee, WI, USA

³ Joseph J. Zilber School of Public Health, University of Wisconsin, Milwaukee, WI, USA

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Correspondence to: Manish Kohli, email: kohli.manish@mayo.edu

Keywords: prostate cancer, liquid biopsy, urine, cell free DNA, next generation sequencing

Received: December 08, 2015

Accepted: April 16, 2016

Published: April 26, 2016

REVIEWS

Extracellular Nucleic Acids in Urine: Sources, Structure, Diagnostic Potential

O. E. Bryzgunova¹, P. P. Laktionov^{1,2}

¹Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences, 8 Lavrentiev Avenue, 630090, Novosibirsk, Russia

²E.N. Meshalkin Novosibirsk Research Institute of Circulation Pathology, st. Rechkunovskaya 15, 630055, Novosibirsk, Russia

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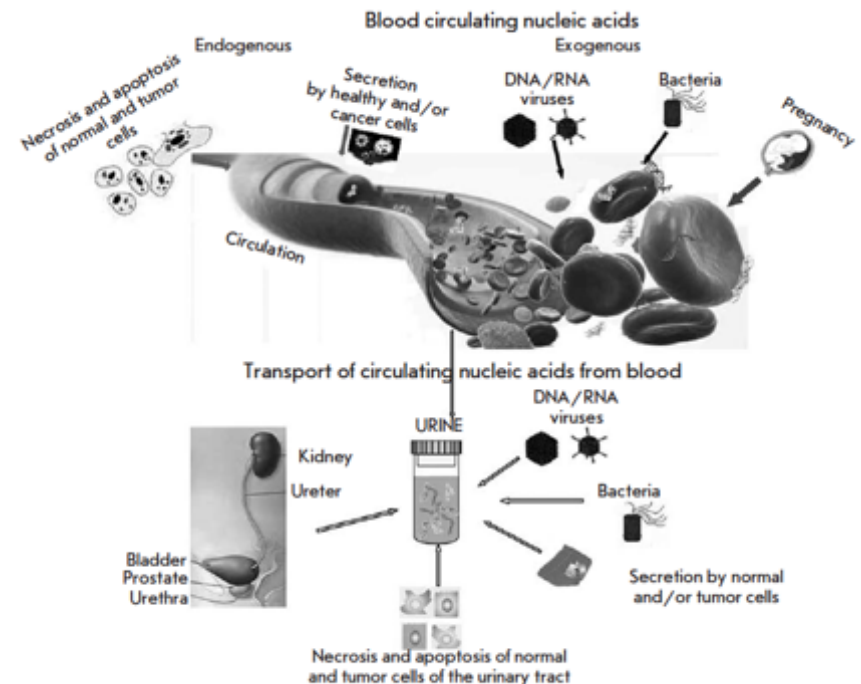
Received: 29.10.2014

Revision received: 19.05.2015

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Urinary Cell-Free DNA Quantification as Non-Invasive Biomarker in Patients with Bladder Cancer

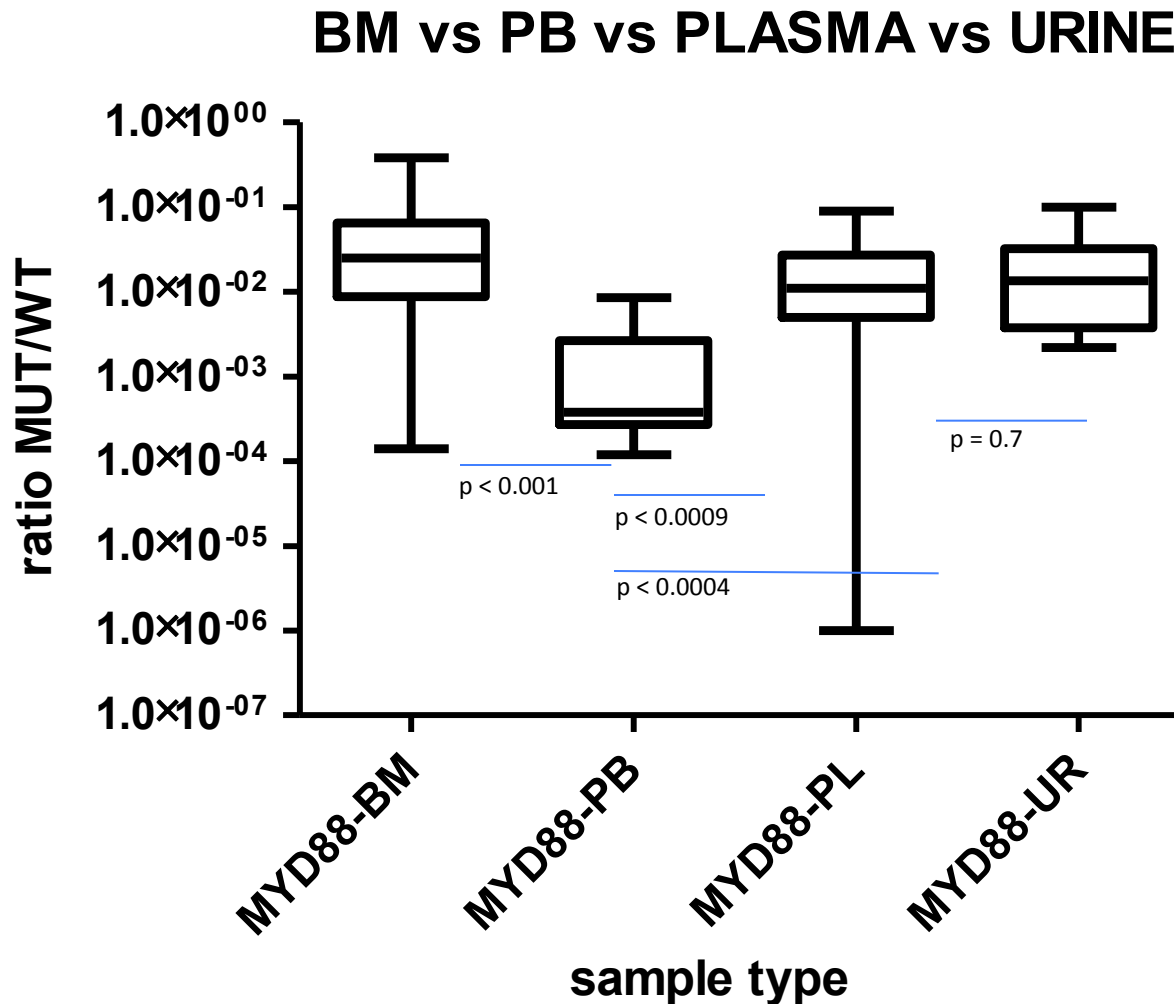
Antonin Brisuda^a, Eva Pazourkova^b, Viktor Soukup^c, Ales Horinek^{d,e}, Jan Hrbáček^a, Otakar Capoun^c, Iveta Svobodova^d, Sarka Pospisilova^d, Marie Korabecna^d, Jaroslav Mares^f, Tomáš Hanuš^c, Marek Babjuk^a



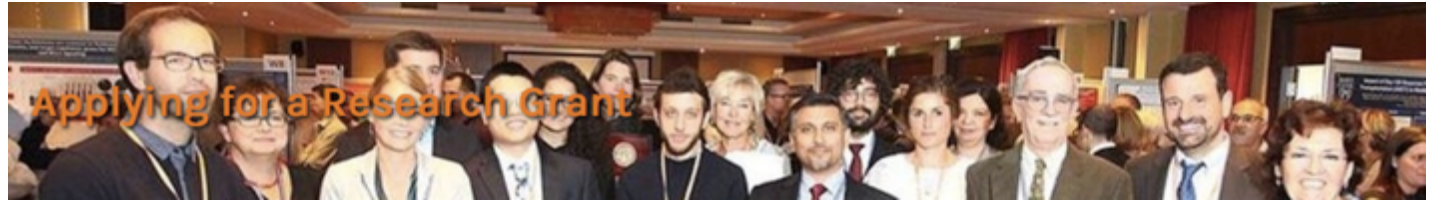
Sources of cell-free nucleic acids in the urine and blood

Preliminary comparison of MYD88^{L265P} quantification in cfDNA from plasma and urine

20 PTs



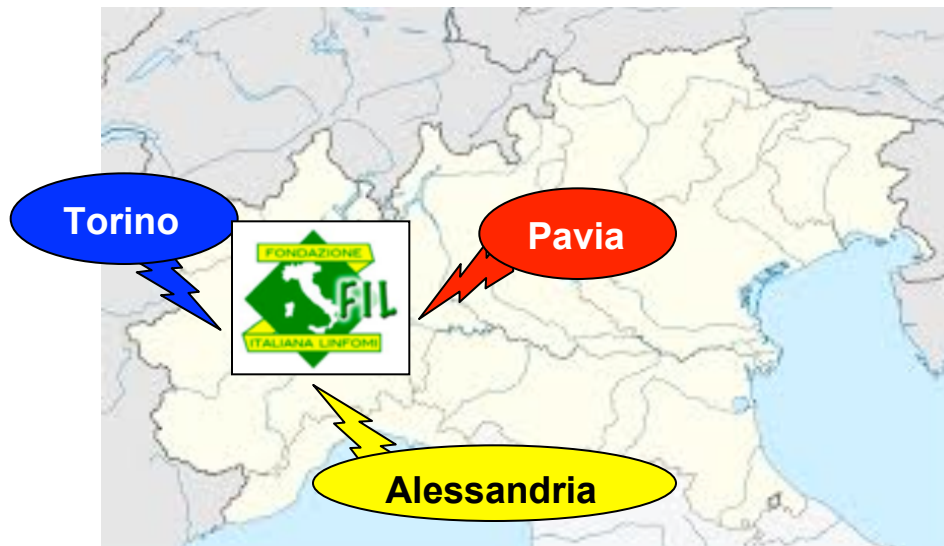
Biological Studies & Indolent Lymphomas FIL Committees joined application



“Non-invasive diagnostics and monitoring of MRD and clonal evolution in Waldenström’s Macroglobulinemia”

INVOLVED CLINICAL AND BIOLOGICAL UNITS

Marzia Varettoni (PI), Luca Arcaini, Marco Ladetto, Simone Ferrero, Ramòn Garcia-Sanz



Non-invasive diagnostics and monitoring of MRD and clonal evolution in Waldenstrom's Macroglobulinemia

International Waldenstrom

Macroglobulinemia Foundation (IWMF)

Grant 400.000 \$ (200.000/year for 2 years)

FIL approval: 3th October 2017

Investigators:

Marzia Varettoni (PI)

Simone Ferrero

Marco Ladetto

Ramon Garcia-Sanz

Financial/administrative assistance:

Alessandro Levis

Valentina Lenti

Sonia Perticone

Study Coordinator:

Stefania Badiali

Statistics:

Luigi Marcheselli



Rationale: WM diagnostics

- No clear cut-off in the size of monoclonal component between WM and IgM-MGUS
- Overlapping clinical and phenotypic features of WM and other B-cell secreting LPD (especially MZL)
- MYD88 (L265P) mutation highly recurrent but not restricted to WM
- Mutations of CXCR4 are present only in 25-30% of WM patients and are not a hallmark of the disease

Bone marrow biopsy still necessary for the diagnosis

Razionale: MRD assessment

- MRD negativity is a strong predictor of outcome, both by RT-qPCR (FL and MCL) and by MFC (MM)
- Due to high prevalence at diagnosis, MYD88 represents a suitable marker for MRD assessment
- After treatment, MYD88 (L265P) is detectable by RT-qPCR only on BM samples not allowing disease monitoring on PB samples
- ddPCR has higher sensitivity over RT-qPCR (5×10^{-5} vs 1×10^{-3}) and is feasible also on cf-DNA recovered from plasma and urine even in diseases with infrequent leukemization
- 8-color MFC has higher sensitivity as compared with 4-color MFC (more than 1×10^{-4})

Aims of the study

- ◆ **Non-invasive diagnostics:** assess whether a reliable diagnosis of WM and IgM MGUS is feasible on PB or plasma or urine by means of highly sensitive techniques (dd-PCR, MFC, NGS) overcoming the need of invasive procedures
- ◆ **Minimal residual disease:** assess MRD after treatment using dd-PCR, MFC and IGH-based NGS and assess whether the achievement of MRD negativity translates into longer progression-free survival
- ◆ **Dynamics of clonal evolution:** testing a panel of recurrent mutations by means of NGS in samples collected at different timepoints during the disease course

Study design and patient population

Study design

- Observational
- Retrospective and prospective
- Multicentric

Patient population

- Patients with Waldenstrom's Macroglobulinemia or IgM-monoclonal gammopathy of undetermined significance (IgM MGUS)

Duration of the study

- 22 months for enrollment + 2 years of follow-up from the enrollment of the last patient

Sample size

- 300 patients: 150 retrospective (learning cohort) and 150 prospective (validation cohort)

Inclusion and exclusion criteria

Inclusion criteria

- Diagnosis of Waldenstrom's Macroglobulinemia (symptomatic or asymptomatic) or IgM MGUS according to criteria established during the second IWWM (Owen et al, Semin Oncol 2003)
- No prior treatment for WM
- Age \geq 18 years
- Informed consent

Exclusion criteria

- Prior treatment with immunotherapy and/or chemotherapy and/or novel agents
- Active HBV, HCV, HIV infection

Biological studies and timepoints



Study timepoints

at diagnosis (BM, PB, urine)
 every 12 months (PB, urine)
 before & after therapy (BM, PB, urine)

CD19+ MNCs

Plasma

Genomic DNA

cell-free DNA

Multiparameter Flow Citometry

Mutation analysis

- AS qPCR for MYD88 (L265P)
- Sanger sequencing of CXCR4
- Targeted deep sequencing (NGS)
- Droplet digital PCR

Clinical data

- eCRF

MIDOLLO



15 ml



Suddividere in 5 provette



SANGUE

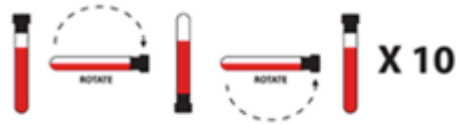


1°

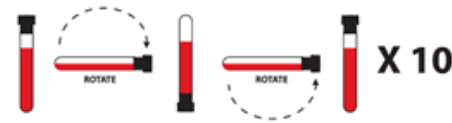
2°



7 ml



2 x 10 ml



Agitare GENTILMENTE



Mantenere a Temp. Ambiente
NON raffreddare

URINE



20 ml



NON le prime del mattino,
NON raffreddare

Mutational studies

Targeted deep sequencing for mutation discovery and evaluation of clonal evolution

- 15-gene panel: MYD88, CXCR4, ARID-1A, KMT2D, TP53, PRDM1, CD79b, NOTCH2, TRAF3, MYBBP1A, HIST1H1E, CARD11, PLC γ 2, BTK, KLF2
- Will be performed at diagnosis and then every 12 months on
 - Genomic DNA from BM CD19+ MNCs and cell-free DNA from plasma
 - Cel-free DNA recovered from plasma
- PB CD19- MNCs will be used as control tissue
- Validation with RT-qPCR for MYD88 (L265P) and Sanger for CXCR4 mutations

Droplet digital PCR for MYD88 (L265P) and CXCR4 (S338X)

- Will be performed at diagnosis and after therapy on:
 - genomic DNA extracted from BM and PB CD19+ MNCs
 - cell-free DNA from plasma and urine

IGH-based NGS

- Will be performed at diagnosis and after therapy on BM and PB CD19+ MNCs

Multiparameter flow cytometry



Paired BM and PB samples will be stained with the following 8-color panels at diagnosis, before and after therapy

WM-screening panel

FITC	PE	PERCP-Cy5.5	PE-Cy7	APC	APCC750	BV450	OC515
clgM	CD56	CD5	CD19	CyK	CyL	CD38	CD45

WM-characterization panel

Tube	FITC	PE	PERCP-Cy5.5	PE-Cy7	APC	APCH7	BV450	OC515
1	CyIgM	CyL	CD3	CD19	CyK	CD38	CD20	CD45
2	CD23	CD10	CD79B	CD19	CD200	CD38	CD20	CD45
3	CD31	LAIR1	CD11c	CD19	SIgM	CD38	CD20	CD45
4	CD103	CD25	CD22	CD19	CXCR5	CD38	CD20	CD45
5	CD62L	CD39	DR	CD19	CD27	CD38	CD20	CD45
6	CD81	CD117	CD138	CD19	CD56	CD38	CD20	CD45

WM-MRD panel

FITC	PE	PERCP-Cy5.5	PE-Cy7	APC	APCH7	BV450	OC515
CyIgM	CyL	CD3	CD19	CyK	CD38	CD20	CD45



Study Protocol

Non-invasive diagnostics and monitoring of minimal residual disease and clonal evolution in Waldenström's Macroglobulinemia and in IgM monoclonal gammopathy of undetermined significance

ID Study: FIL_BIOWM

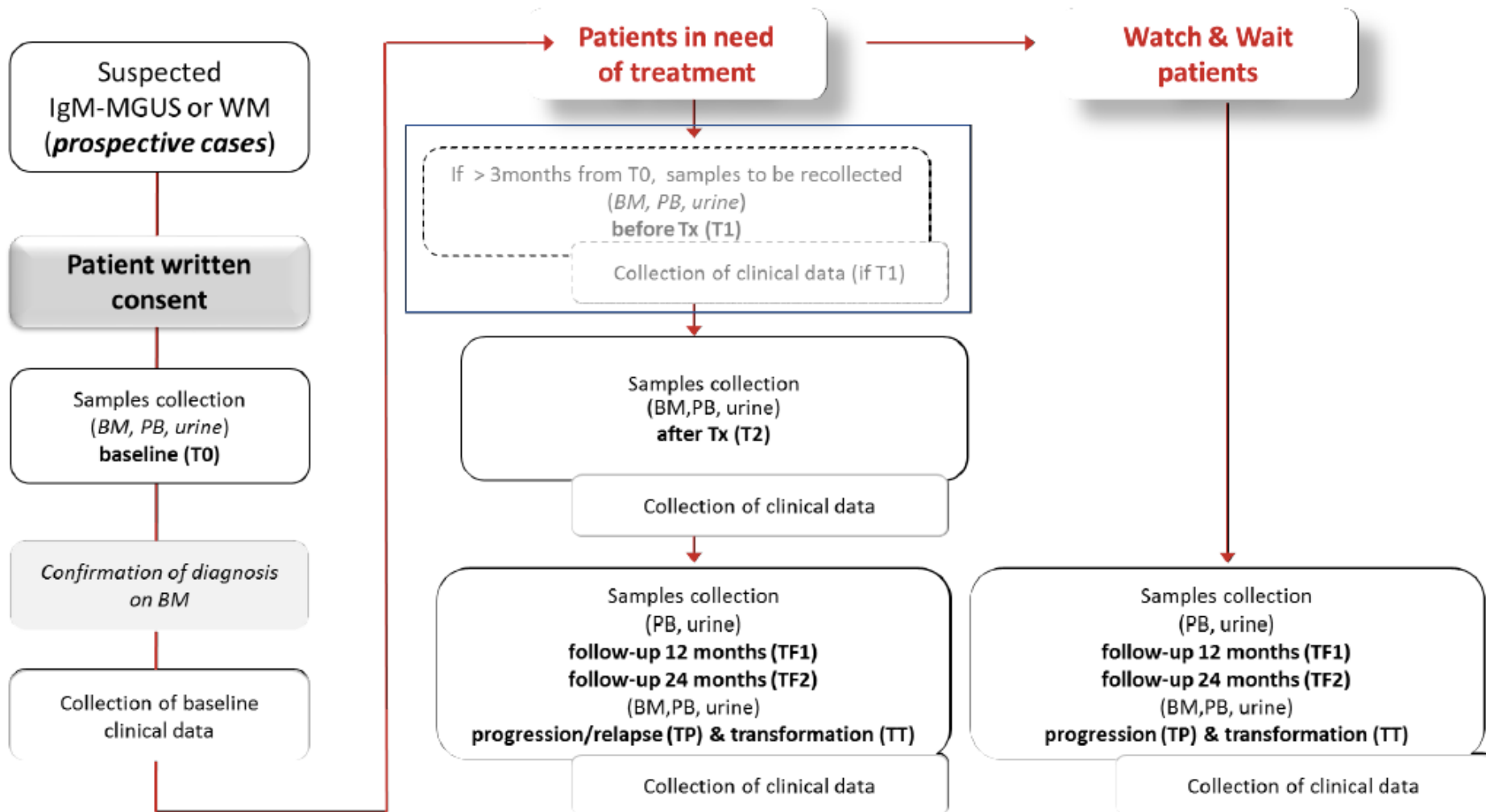
INVESTIGATOR SPONSOR

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REGISTRATION (SEE SECTION 12)	www.filinf.it
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6. STUDY FLOW CHART



16.8. Schedule of specimens' collection and assessment for biological studies



SAMPLE		TIMEPOINTS	QUANTITY
BM	Appendices A-B	<ul style="list-style-type: none"> • At diagnosis (T0); • Before treatment (T1)(see below); • After treatment (T2); • At progression (TP) or transformation (TT) 	15 ML
PB	Appendices A-B	<p>Untreated patients</p> <ul style="list-style-type: none"> • At diagnosis (T0); • At month 12 (TF1) and month 24 (TF2) from diagnosis; • At progression (TP) or transformation (TT); <p>Patients requiring treatment</p> <ul style="list-style-type: none"> • At diagnosis (T0); • Before treatment (T1)(see below); • After treatment (T2); • At month 12 (TF1) and month 24 (TF2) from end of treatment • At progression/relapse (TP) or at transformation (TT) 	27 ML
URINE	Appendices A-B	<p>Untreated patients</p> <ul style="list-style-type: none"> • At diagnosis (T0); • At month 12 (TF1) and month 24 (TF2) from diagnosis; • At progression (TP) or transformation (TT); <p>Patients requiring treatment</p> <ul style="list-style-type: none"> • At diagnosis (T0); • Before treatment (T1)(see below); • After treatment (T2); • At month 12 (TF1) and month 24 (TF2) from end of treatment • At progression/relapse (TP) or transformation 	20 ML



Logged in as **sferrero2** | [Log out](#)
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Project status: **Development**

Data Collection

- [Record Status Dashboard](#)
- View data collection status of all records
- [Add / Edit Records](#)
- Create new records or edit/view existing ones

Applications

- [Calendar](#)
- [Data Exports, Reports, and Stats](#)
- [Data Import Tool](#)
- [File Repository](#)
- [Resolve Issues](#)
- [Longitudinal Reports](#)
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FIL_BIOWM

Add / Edit Records

You may view an existing record/response by selecting it from the drop-down lists below. To create a new record/response, click the button below.

Total records: **21**

Choose an existing Record ID	Arm 1: PROSPECTIVE	-- select record --
<input type="button" value="Add new record for the arm selected above"/>		

Data Search


Choose a field to search <small>(excludes multiple choice fields)</small>	All fields
Search query <small>Begin typing to search the project data, then click an item in the list to navigate to that record.</small>	<input type="text"/>

NOTICE:
This project is currently in Development status. **Real data should NOT be entered** until the project has been moved to Production status.



 Editing existing Record ID 7

Event Name: **BIOLOGICAL ANALYSIS (Arm 1: PROSPECTIVE)**

Record ID	7
Laboratory <small>* must provide value</small>	<input type="text"/>
Time points <small>* must provide value</small>	<input type="text"/>
Sample analyzed? <small>* must provide value</small>	<input checked="" type="radio"/> Yes <input type="radio"/> No
Date sample taken <small>* must provide value</small>	<input type="text"/>  D-M-Y
Type of sample (tissue) <small>* must provide value</small>	<input type="text"/>
MYD88^{L256p} - Methodology <small>* must provide value</small>	<input type="text"/>
CXCR4 - Methodology <small>* must provide value</small>	<input type="text"/>
CXCR4 - Type of mutation	<input type="text"/>

reset

BIOMOLECULAR QUALITATIVE ANALYSIS