UPDATED RESULTS OF THE ASPEN TRIAL FROM A COHORT OF PATIENTS WITH *MYD88* WILD-TYPE WALDENSTRÖM MACROGLOBULINEMIA

Ramon Garcia Sanz, MD, PhD[1]; Meletios Dimopoulos, MD[2]; Hui-Peng Lee, MBChB, FRACP, FRCPA[3]; Marek Trneny, MD, CSc[4]; Marzia Varettoni, MD[5]; Stephen Opat, MBBS, FRACP, FRCPA[6,7]; Shirley D'Sa, MD, MRCP, FRCPath[8]; Roger G. Owen, MD[9]; Gavin Cull, MB, BS, FRACP, FRCPA[10,11]; Stephen Mulligan, MBBS, PhD, FRACP, FRCPA[12]; Jaroslaw Czyz, MD, PhD[13,14]; Jorge Castillo, MD[15,16]; Marina Motta, MD[17]; Tanya Siddiqi, MD[18]; Mercedes Gironella Mesa, MD[19]; Miquel Granell Gorrochategui, MD[20]; Dipti Talaulikar, PhD, FRACP, FRCPA, MBBS[21]; Pier Luigi Zinzani, MD, PhD[22]; Elham Askari, MD[23]; Sebastian Grosicki, MD, PhD[24]; Albert Oriol, MD[25]; Janusz Kloczko, MD[26]; Alessandra Tedeschi, MD[27]; Christian Buske, MD[28]; Veronique Leblond, MD[29]; Wai Y. Chan, PhD[30]; Jingjing Schneider, PhD[30]; Aileen Cohen, MD, PhD[30]; Jane Huang, MD[30]; and Constantine S. Tam, MBBS, MD, FRACP, FRCPA[31,32,33,34]

[1]Hospital Universitario de Salamanca, Salamanca, Spain; [2]National and Kapodistrian University of Athens, Athens, Greece; [3]Flinders Medical Centre, Adelaide, South Australia, Australia; [4]Vseobecna fakultni nemocnice v Praze, Prague, Czech Republic; [5]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [6]Monash Health, Clayton, Victoria, Australia; [7]Monash University, Clayton, Victoria, Australia; [8]University College London Hospital Foundation Trust, London, United Kingdom; [9]St James University Hospital, Leeds, United Kingdom; [10]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [11]University of Western Australia, Perth, Western Australia, Australia; [12]Royal North Shore Hospital, Sydney, New South Wales, Australia; [13]Szpital Uniwersytecki nr 2 im dr. Jana Biziela, Kujawsko-pomorskie, Bydgoszcz, Poland; [14]Department of Hematology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]Harvard Medical School, Boston, MA, USA; [17]AO Spedali Civili di Brescia, Lombardia, Italy; [18]City of Hope National Medical Center, Duarte, CA, USA; [19]Hospital Universitario Vall d'Hebrón, Barcelona, Spain; [20]Hospital de La Santa Creu i Sant Pau, Barcelona, Spain; [21]Australian National University, Canberra, ACT, Australia; [22]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [23]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [24]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [25]Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [26]Uniwersytecki Szpital Kliniczny w Bialymstoku, Podlaskie, Poland; [27]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [28]Institute of Experimental Cancer Research - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [29]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [30]BeiGene USA, Inc., San Mateo, CA, USA; [31]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [32]St Vincent's Hospital, Fitzroy, Victoria, Australia; [33]University of Melbourne, Parkville, Victoria, Australia; and [34]Royal Melbourne Hospital, Parkville, Victoria, Australia

INTRODUCTION

- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
- First-generation BTK inhibitor ibrutinib has shown activity in Waldenström macroglobulinemia (WM) and has become a standard of care[4]
  - However, lower response rates,[5] no major responses,[5,6] and shorter survival[7] have been reported in patients (pts) who lack *MYD88*^{L265P} or other activating mutations (*MYD88*^{WT})
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases (**Figure 1**)
  - **Potent, selective, and irreversible**[8]
  - **Equipotent against BTK compared with ibrutinib**; fewer off-target effects due to higher selectivity for binding EGFR, ITK, JAK3, HER2, and TEC[9]
  - **Advantageous pharmacokinetic/pharmacodynamic properties**: complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[8]
  - **Favorable drug-drug interaction properties**: can be co-administered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and anti-thrombotic agents[10,11]

Zanubrutinib (BGB-3111)

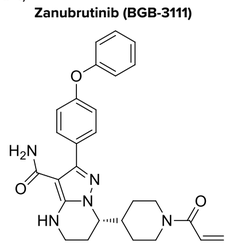
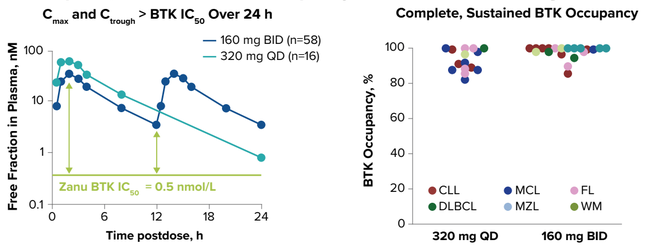


Figure 1a. Zanubrutinib: A Potent and Selective BTK Inhibitor[8,9]

	Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	3265	189	17
		p-PLCγ1 Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
		ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51
	HER2	HER2 Biochemical Assay	661	9.4	70
	TEC	TEC Biochemical Assay	1.9	0.8	2.4

Figure 1b. Complete, Sustained BTK Occupancy With BID or QD Dosing[8,9]



BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{max}, maximum concentration; C_{trough}, trough concentration; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HTRF, homogeneous time resolved fluorescence; IC_{50}, half maximal inhibitory concentration; ITK, IL-2–inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PLC, phospholipase C; QD, once daily; TEC, tyrosine protein kinase Tec; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

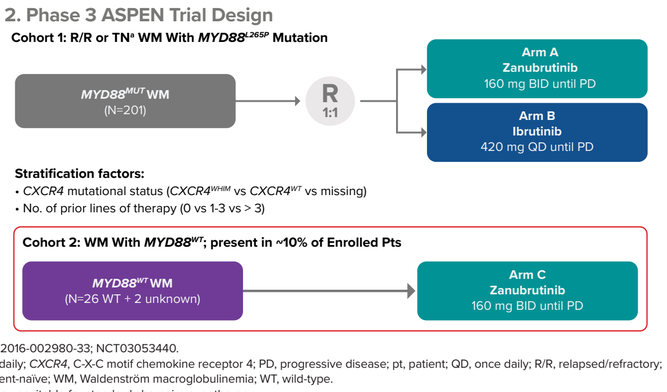
OBJECTIVE

- To assess the safety and efficacy of zanubrutinib in WM pts with *MYD88*^{WT} from an exploratory cohort of the ongoing phase 3 study of zanubrutinib vs ibrutinib in pts with WM (ASPEN; NCT03053440)

METHODS

- ASPEN is an open-label, multicenter, randomized, phase 3 study of zanubrutinib vs ibrutinib in pts with WM (**Figure 2**)

Figure 2. Phase 3 ASPEN Trial Design



EUDRACT 2016-002980-33; NCT03053440.
BID, twice daily; *CXCR4*, C-X-C motif chemokine receptor 4; PD, progressive disease; pt, patient; QD, once daily; R/R, relapsed/refractory; TN, treatment-naïve; WM, Waldenström macroglobulinemia; WT, wild-type.
[a]TN must be unsuitable for standard chemoimmunotherapy.

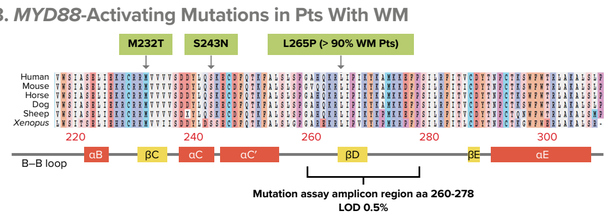
Eligibility

- Clinical and definitive histologic diagnosis of WM, with measurable disease (serum IgM >0.5 g/dL), and meeting ≥1 criterion for treatment according to consensus panel criteria from the Seventh International Workshop on WM[12]
- If treatment naïve, must be considered by treating physician unsuitable for standard chemoimmunotherapy regimens
- Eastern Cooperative Oncology Group performance status 0-2
- Absolute neutrophil count ≥750/μL, platelets ≥50000/μL (independent of growth factor/transfusions)
- Adequate renal, hepatic, and coagulation function
- No significant cardiac disease, active central nervous system involvement, or prior BTK inhibitors

Cohort Assignment

- Bone marrow *MYD88* and *CXCR4* mutations were assessed centrally at study entry (NeoGenomics Laboratory, Aliso Viejo, CA, USA)[13]
  - The *MYD88* mutation assay used detects all mutations in the region encompassing amino acid Ala[260]-Pro[278], which includes the predominant mutation in WM, *MYD88*^{L265P} (**Figure 3**)
- Pts were assigned to cohort 1 (*MYD88* mutated; randomized) or exploratory cohort 2 (*MYD88*^{WT} or *MYD88* unknown, nonrandomized) based on the central laboratory *MYD88* mutation assay results

Figure 3. *MYD88*-Activating Mutations in Pts With WM



Adapted from Treon et al[6] and Ngo et al[14]
aa, amino acid; LOD, limit of detection; *MYD88*, myeloid differentiation primary response gene 88; pt, patient; WM, Waldenström macroglobulinemia.

- Detection in the *MYD88* amplicon (Ala[260]-Pro[278]) by the NeoGenomics LDT assay includes a wild-type-allele–blocking approach (limit of detection [LOD], 0.5%)[13] versus standard polymerase chain reaction/bidirectional Sanger sequencing assay used to detect *CXCR4* mutations (LOD, 10%-15%)
- For *MYD88*^{WT} pts with available samples (12 of 26), *MYD88* mutations were also evaluated by next-generation sequencing (200×; LOD, 5%); no other activating mutations were detected

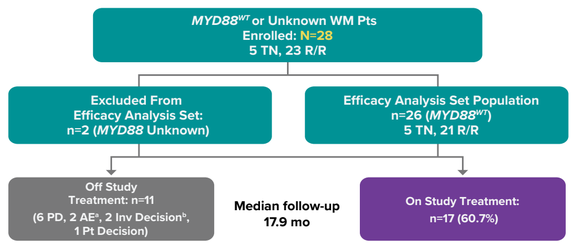
Exploratory Endpoints for Cohort 2

- Responses were assessed monthly by immunoglobulin M (IgM) with extramedullary disease assessment every 3 months, according to response criteria in the National Comprehensive Cancer Network WM guidelines[15] and modified Owen criteria[16] as assessed by the independent review committee
- Efficacy: response rates (overall and major response rate), duration of response, progression-free survival, and overall survival; safety assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

RESULTS

- In total, 28 pts (n=26 *MYD88*^{WT}; n=2 *MYD88* mutation status unknown) were enrolled into cohort 2
- The safety analysis set includes all 28 pts, and the efficacy analysis set includes 26 *MYD88*^{WT} pts, with a median follow-up of 17.9 months (range, 2.3-27.8; **Figure 4** and **Table 1**)

Figure 4. Disposition of Pts in Cohort 2



Data cutoff date: 31 Aug, 2019.
AE, adverse event; Inv, investigator; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; pt, patient; R/R, relapsed/refractory; TN, treatment-naïve; WM, Waldenström macroglobulinemia; WT, wild-type.
[a]Grade 4 subdural hemorrhage; grade 3 diarrhea.
[b]Investigator decided no further treatment needed (n=1); pt discharged to hospice for palliative care (n=1).

Table 1. Pt and Disease Characteristics

Characteristic	Total (N=28)
Age, median (range), y	70.1 (39-87)
>65 years, n (%)	19 (67.9)
>75 years, n (%)	12 (42.9)
Sex, n (%)	
Men	14 (50)
Women	14 (50)
IPSSWM, n (%)	
Low	5 (17.9)
Intermediate	11 (39.3)
High	12 (42.9)
Prior treatment status	
Treatment-naïve, n (%)	5 (17.9)
R/R, n (%)	23 (82.1)
No. of prior therapies for R/R pts, median (range)	1 (1-5)
Extramedullary disease present at baseline by IRC, n (%)	21 (75.0)
Genotype, n (%)	
MYD88^{WT}/*CXCR4*^{WT}	23 (82.1)
MYD88^{WT}/*CXCR4*^{WHIM}	1 (3.6)
MYD88^{WT}/*CXCR4* unknown	2 (7.1)
MYD88 unknown/*CXCR4* unknown	2 (7.1)
Hemoglobin ≤110 g/L, n (%)	15 (53.6)

CXCR4, C-X-C motif chemokine receptor 4; IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinemia; IRC, independent review committee; *MYD88*, myeloid differentiation primary response gene 88; pt, patient; R/R, relapsed/refractory; WT, wild-type.

Safety (n=28)

Table 2. AE Overview

Treatment-Emergent AE	n (%)
Pts with ≥1 AE grade ≥3	18 (64.3)
Pts with ≥1 serious AE	11 (39.3)
AE leading to death	0
AE leading to treatment discontinuation	2[a] (7.1)
AE leading to dose reduction	2[b] (7.1)

AE, adverse event; pt, patient.
[a]Grade 4 subdural hemorrhage (related) and grade 3 diarrhea (related).
[b]Grade 3 pneumonitis resolved and followed by grade 2 pneumonia (n=1); grade 1 diarrhea (n=1).

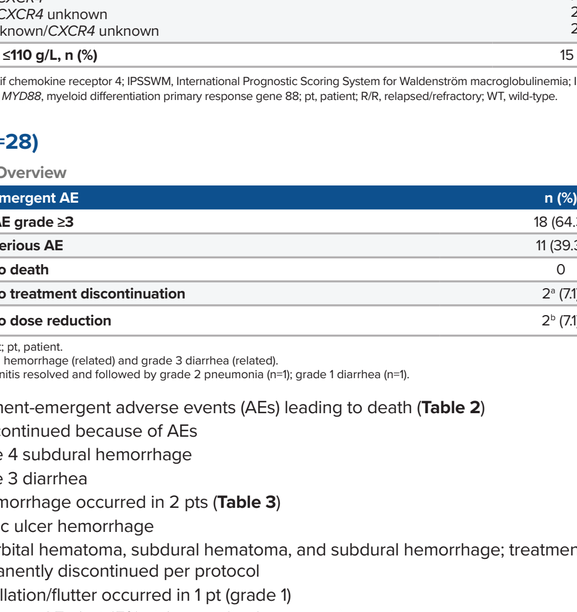
- No treatment-emergent adverse events (AEs) leading to death (**Table 2**)
- 2 pts discontinued because of AEs
  - Grade 4 subdural hemorrhage
  - Grade 3 diarrhea
- Major hemorrhage occurred in 2 pts (**Table 3**)
  - Gastric ulcer hemorrhage
  - Periorbital hematoma, subdural hematoma, and subdural hemorrhage; treatment was permanently discontinued per protocol
- Atrial fibrillation/flutter occurred in 1 pt (grade 1)
- Most common AEs (in >15% pts) were diarrhea, anemia, contusion, pyrexia, upper respiratory tract infection, respiratory tract infection, and cough (**Figure 5**)

Table 3. AE Categories of Interest (BTKi Class AEs)

AE Categories (Pooled Terms), n (%)	All Grade	Grade ≥3
Atrial fibrillation/flutter	1 (3.6)	0
Diarrhea (PT)	8 (28.6)	2 (7.1)
Hemorrhage	11 (39.3)	2 (7.1)
Major hemorrhage[a]	2 (7.1)	2 (7.1)
Hypertension	3 (10.7)	3 (10.7)
Neutropenia[b]	5 (17.9)	3 (10.7)
Infection	21 (75.0)	8 (28.6)
Second malignancy[c]	4 (14.3)	0

No tumor lysis syndrome or opportunistic infection was reported.
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
[a]Defined as any grade ≥3 hemorrhage or any grade central nervous system hemorrhage: gastric ulcer hemorrhage; and 1 patient had periorbital hematoma, subdural hematoma, and subdural hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.
[c]Basal cell carcinoma (n=3) and Queyrat erythroplasia (n=1).

Figure 5. Common AEs (Any Grade >10% or Grade ≥3 in >1 Pt), Regardless of Causality

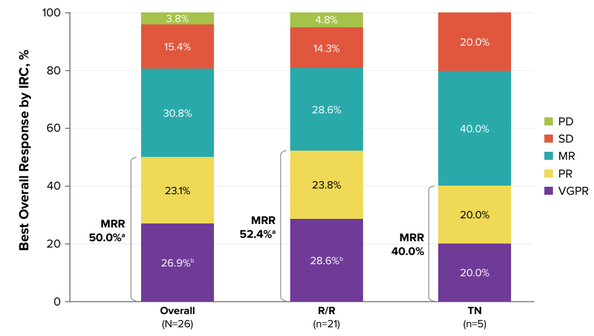


AE, adverse event; pt, patient.

Efficacy (n=26)

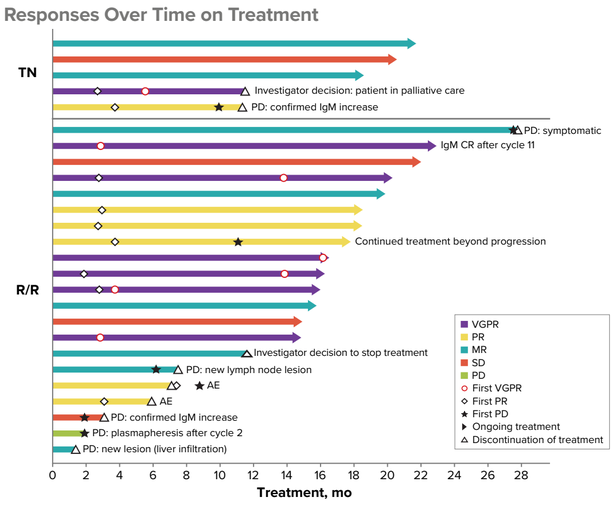
- Major response rate of 50.0% including 26.9% with VGPR (**Figure 6**)
- Median time to first major response (partial response or better, requiring reduction in extramedullary disease if present at baseline) was 2.9 mo (range, 1.9-16.1; **Figure 7**)
- IgM complete response (requiring normal IgM and immunofixation negative) was achieved in 1 pt
- Median progression-free and overall survival were not yet reached (**Figure 8**)

Figure 6. Best Responses by IRC in Patients With *MYD88*^{WT} WM



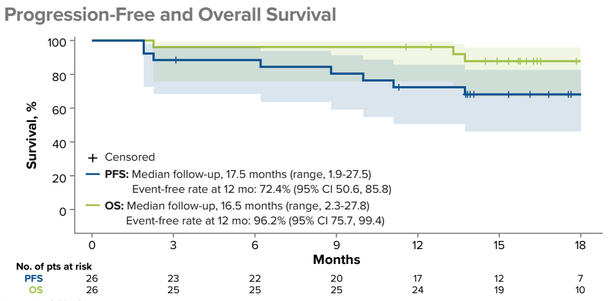
CR, complete response; IgM, immunoglobulin M; IRC, independent review committee; MR, minor response; MRR, major response rate (≥PR); *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; PR, partial response; pt, patient; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR; WM, Waldenström macroglobulinemia; WT, wild-type.
[a]Including pts confirmed by next-generation sequencing of no other activating *MYD88* mutations.
[b]One pt achieved IgM complete response (normalized IgM and negative immunofixation since cycle 11, with bulky extramedullary disease improving).

Figure 7. Responses Over Time on Treatment



Note: color of bars represents the best response for each patient.
AE, adverse event; CR, complete response; IgM, immunoglobulin M; MR, minor response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR.

Figure 8. Progression-Free and Overall Survival



Shaded areas show the 95% CI.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; pt, patient.

CONCLUSIONS

- Largest cohort of pts with WM with confirmed *MYD88*^{WT} (n=26) studied in terms of safety and efficacy of BTKi treatment
- Single-agent zanubrutinib resulted in major responses (including very good partial response)
  - Major response rate of 50.0% including 26.9% with very good partial response
  - IgM complete response achieved in 1 pt
  - Median time to first major response was 2.9 months (range, 1.9-16.1)
- Zanubrutinib was well tolerated
  - Discontinuation due to AEs occurred in 7.1% of pts (2/28)
  - Primary reason for discontinuation was progressive disease (3 of 6 within first 3 cycles)
  - No fatal AEs reported
  - Low incidences of atrial fibrillation
  - AE profile is consistent with cohort 1 finding in the ASPEN study

REFERENCES

1. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591.
2. Choe H, Ruan J. *Oncology (Williston Park)*. 2016;30:847-858.
3. Yang G, et al. *Blood*. 2013;122:1222-1232.
4. Treon SP, et al. *J Clin Oncol*. 2020;38:1198-1208.
5. Treon SP, et al. *N Engl J Med*. 2015;372:1430-1440.
6. Treon SP, et al. *N Engl J Med*. 2015;373;584-586.
7. Palomba ML, et al. IWWM-9 Session 9, October 7, 2016 [abstr].
8. Tam CS, et al. *Blood*. 2019;134:851-859.
9. Tam CS, et al. ICML Session 7, June 16, 2017 [abstr].
10. Mu S, et al. *Cancer Chemother Pharmacol*. 2020;85:391-399.
11. BeiGene, data on file.
12. Dimopoulos M, et al. *Blood*. 2014;124:1404-1411.
13. Albitar A, et al. *Int J Lab Hematol*. 2016;38:133-140.
14. Ngo VN, et al. *Nature*. 2011;470:115-119.
15. National Comprehensive Cancer Network (NCCN). NCCN Guidelines: Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia. 2015; version 2.
16. Owen RG, et al. *Br J Haematol*. 2013;160:171-176.

CORRESPONDENCE

rgarcias@usal.es

DISCLOSURES

RGS: Honoraria from Janssen, Novartis, MSD, Astellas. Payment for expert testimony for IVS technologies. Travel expenses from Janssen, Novartis, MSD, Astellas. Receipt of equipment from Diagnostica Longwood; **MD:** Honoraria from Amgen, Takeda, BeiGene, Janssen, BMS; **MT:** Honoraria from Janssen, Gilead, BMS, Amgen, Abbvie, Roche, AstraZeneca, MorphoSys, Incyte, Portolla, Takeda. Travel expenses from Gilead, Takeda, BMS, Roche, Janssen, Abbvie. Consulting/Advisory Role for Janssen, BMS, Abbvie, Roche, MorphoSys, Incyte, Portolla, Takeda; **SO:** Honoraria from Roche, Janssen, Abbvie, Celgene, Takeda, Merck, Gilead, and AstraZeneca. Consulting/Advisory Role for Roche, Janssen, Abbvie, Celgene, Takeda, Merck, Gilead, Mundipharma, AstraZeneca, CSL. Research funding from BeiGene, Roche, Janssen, Abbvie, Takeda, Merck, Gilead, Epizyme, AstraZeneca. Travel expenses from Roche; **SD:** Honoraria from BeiGene, Janssen. Travel expenses from Janssen, Sanofi. Consulting/Advisory Role for BeiGene, Janssen, Sanofi. Leadership or fiduciary role for WMUK, Lymphoma Action; **RGO:** Honoraria from BeiGene, Janssen, Celgene, AstraZenca. Consulting/Advisory Role for BeiGene, Janssen; **H-PL, MV, GC, MM, MGG, SM, JC, EA, SG, and JK:** nothing to disclose; **JC:** Research Funding and/or Honoraria from Abbvie, BeiGene, Janssen, Pharmacyclics, Roche and TG Therapeutics; **TS:** Funding from BeiGene. Honoraria from Pharmacyclics, Janssen, AstraZeneca. Consulting/Advisory Role for AstraZeneca, BeiGene, Juno therapeutics, BMS, Celgene, Kite Pharma, Pharmacyclics; **MGM:** Honoraria from Janssen, BMS, Amgen. Payment for expert testimony for GSK. Consulting/Advisory Role for Janssen, BMS, Amgen; **DT:** Consulting/Advisory Role for Roche, EUSA Pharma, George Clinical. Research Funding/Speakers Bureau/Travel Expenses for/from Roche; **PLZ:** Honoraria from EUSA Pharma, Takeda, Merck, Roche, Abbvie. Consulting/Advisory Role for Takeda, EUSA Pharma, Roche, Merck, Abbvie. Speakers Bureau for EUSA Pharma, Merck, Takeda, Gilead; **AO:** Honoraria from Celgene/BMS, Sanofi, Janssen. Consulting/Advisory Role for Celgene/BMS, Sanofi, GSK; **AT:** Consulting/Advisory Role and Speakers Bureau for Abbvie, AstraZeneca, Janssen and BeiGene; **CB:** Consulting/Advisory Role for BeiGene, Roche, Janssen, Abbvie, Pfizer, Celltrion, Novartis, BMS, Regeneron. Honoraria from BeiGene, Roche, Janssen, Abbvie, Pfizer, Celltrion, BMS, AbbVie, Regeneron. Research Funding from Roche, Janssen, MSD, Celltrion, Amgen. Leadership or Fiduciary Role for GLA, DGHO, ESMO; **VL:** Consulting Fees from AstraZeneca, Lilly, Abbvie. Honoraria from Roche, AstraZeneca, Amgen, BeiGene, Janssen, Abbvie. Advisory Board for AstraZeneca, BeiGene, Janssen, Abbvie; **WYC:** Employment, Stock or Other Ownership at BeiGene; **JS:** Employment, Stock or Other Ownership at BeiGene; **AC:** Employment, Stock or Other Ownership at BeiGene; **JH:** Employment, Stock or Other Ownership at BeiGene; **CST:** Honoraria from Janssen, Abbvie, BeiGene. Research funding from Janssen, Abbvie.

ACKNOWLEDGMENTS

We thank the investigators, site support staff, and especially the patients for participating in this study.
This study was sponsored by BeiGene. Editorial support was provided by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by BeiGene.