Abstract Title: Updated results of the ASPEN trial from a cohort of patients with wild-type *MYD88* Waldenström macroglobulinemia

Authors: 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]

Affiliations: [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: Inhibitors of Bruton's tyrosine kinase (BTK) have shown significant activity in patients with *MYD88*-mutation–positive (*MYD88*$^{mut+}$) Waldenström macroglobulinemia (WM). However, lower response rates and shorter progression-free survival have been reported in patients with WM who lack such mutations (*MYD88*^{WT}). The ASPEN trial (NCT03053440) evaluated zanubrutinib, a potent and selective BTK inhibitor, in patients with *MYD88*$^{mut+}$ and *MYD88*^{WT} WM.

Objective: The objective of this abstract is to evaluate the safety and efficacy of zanubrutinib in patients with *MYD88*^{WT} WM from the ASPEN trial.

Material and Methods: In the ASPEN trial, *MYD88* gene mutations were assessed in bone marrow at study entry by a central laboratory (NeoGenomics). Based on these results, patients were assigned to cohort 1 (*MYD88*$^{mut+}$) or cohort 2 (*MYD88*^{WT} or unknown mutation status). In cohort 2, patients received zanubrutinib 160 mg twice daily until disease progression.

Results: In total, 28 patients were enrolled in cohort 2, of which 26 were centrally confirmed as *MYD88*^{WT}. Median age of patients was 72 years; five patients were treatment-naïve and 23 patients had relapsed/refractory (≥1 prior therapy) WM. Most patients had intermediate-risk (39.3%) or high-risk (42.9%) disease, as defined by the International Prognostic Scoring System for WM. At a median follow-up of 17.9 months, two patients discontinued zanubrutinib due to adverse events (AEs) and six experienced disease progression; there were no cases of disease transformation. In 26 confirmed *MYD88*^{WT} patients, the overall response rate by independent central review was 80.8%, with a major response rate of 50.0%, including a very good partial response rate of 26.9% (**Table**). The progression-free survival rate at 12 months was 72.4%. The most frequently reported AEs were diarrhea, anemia, contusion, pyrexia, and upper respiratory tract infection. Major hemorrhage was reported in two patients, and atrial fibrillation was reported in one patient. There were no fatal AEs.

Conclusions: Zanubrutinib showed clinically meaningful antitumor activity, including achieving major responses and durability of responses, and was considered well tolerated with a low discontinuation rate due to AEs in patients with *MYD88*^{WT} WM.

Some authors declare conflicts of interest.
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Table. Best Overall Response by Independent Central Review in Patients With *MYD88*^{WT} WM

	Treatment-naïve WM (n=5)	Relapsed/refractory WM (n=21)	Overall (N=26)
Median follow-up, months	19.3	17.1	17.9
Best overall response, n (%)			
Complete response	0	0	0
Very good partial response	1 (20.0)	6 (28.6)	7 (26.9)
Partial response	1 (20.0)	5 (23.8)	6 (23.1)
Minor response	2 (40.0)	6 (28.6)	8 (30.8)
Stable disease	1 (20.0)	3 (14.3)	4 (15.4)
Progressive disease	0	1 (4.8)	1 (3.8)

WM, Waldenström macroglobulinemia; WT, wild-type.