Inflammation is predictive of outcome in Waldenström macroglobulinemia treated by Bruton tyrosine kinase inhibitors: a multicentric real-life study

Pierre-Edouard Debureaux,[1,2] Nathalie Forgeard,[2,3+] Dikelele Elessa,[2+] Stéphanie Harel,[2] Laurent Frenzel,[4] Bruno Royer,[2] Alexis Talbot,[2] Sylvain Choquet,[3] Frederic Davi,[5] Florence Nguyen-Khac,[5,6] Wendy Cuccuini,[7] Morgane Cheminant,[4] Clotilde Bravetti,[5] Gregory Lazarian,[8] Sophie Kaltenbach,[9] Olivier Hermine,[4] Damien Roos-Weil,[3] Marion Espéli,[1#] Karl Balabanian[1#] and Bertrand Arnulf[2,10#]

[1]INSERM U1160 EMiLy, Institut de Recherche Saint-Louis, Université Paris-Cité; [2]Department of Immuno Hematology, Hospital Saint-Louis, Assistance Publique Hopitaux de Paris; [3]Department of Hematology, Sorbonne Université, Hospital Pitie-Salpetriere, Assistance Publique Hopitaux de Paris; [4]Department of Hematology, Hospital Necker, Assistance Publique Hopitaux de Paris; [5]Laboratory of Hematology, Hospital Pitie-Salpetriere, Assistance Publique Hopitaux de Paris; [6]Centre de Recherche des Cordeliers, Sorbonne Université, Université Paris Cité, INSERM UMRS1138, Drug Resistance in Hematological Malignancies Team; [7]Laboratory of Cytogenetic, Hospital Saint Louis, Assistance Publique Hopitaux de Paris; [8]Laboratory of Hematology, Hospital Avicenne, Assistance Publique Hopitaux de Paris; [9]Laboratory of Hematology, Hospital Necker, Assistance Publique Hopitaux de Paris and [10]Department of Immunology, University of Paris Cité, Paris, France

[+]NF and DE contributed equally.
[#]ME, KB and BA contributed equally as senior authors.

Correspondence:
P.-E. DEBUREAUX - Pierre-edouard.debureaux@aphp.fr
B. ARNULF - Bertrand.arnulf@aphp.fr

Inflammation is predictive of outcome in Waldenström macroglobulinemia treated by Bruton tyrosine kinase inhibitors: a multicentric real-life study

Pierre-Edouard Debureaux[1,2], Nathalie Forgeard[2,3*], Dikelele Elessa[2*], Stephanie Harel[2], Laurent Frenzel[4], Bruno Royer[2], Alexis Talbot[2], Sylvain Choquet[3], Frederic Davi[5], Florence Nguyen-Khac[5,6], Wendy Cuccuini[7], Morgane Cheminant[4], Clotilde Bravetti[5], Gregory Lazarian[8], Sophie Kaltenbach[9], Olivier Hermine[4**], Damien Roos-Weil[3**], Marion Espéli[1#], Karl Balabanian[1#] and Bertrand Arnulf[2,10#]

[1]INSERM U1160 EMiLy, Institut de Recherche Saint-Louis, Université Paris-Cité, Paris, France

[2]Department of Immuno Hematology, Hospital Saint-Louis, Assistance Publique Hopitaux de Paris, Paris, France;

[3]Sorbonne Université, Department of Hematology, Hospital Pitie-Salpetriere, Assistance Publique Hopitaux de Paris, Paris, France

[4]Department of Hematology, Hospital Necker, Assistance Publique Hopitaux de Paris, Paris, France

[5]Laboratory of Hematology, Hospital Pitie-Salpetriere, Assistance Publique Hopitaux de Paris, Paris, France

[6]Centre de Recherche des Cordeliers, Sorbonne Université, Université Paris Cité, Inserm UMRS1138, Drug Resistance in Hematological Malignancies Team, Paris, France

[7]Laboratory of Cytogenetic, Hospital Saint Louis, Assistance Publique Hopitaux de Paris, Paris, France

[8]Laboratory of Hematology, Hospital Avicenne, Assistance Publique Hopitaux de Paris, Paris, France

[9]Laboratory of Hematology, Hospital Necker, Assistance Publique Hopitaux de Paris, Paris, France

[10]University of Paris Cité, Paris, France;

*Co-second authors

**Co-before last authors

#Co-last authors

Supplementary Table 1A. Description of the global pooled cohort of WM patients who received a treatment and with CRP measure

| CRP (mg/L)	CRP <5 (n=170)	CRP 5-20 (n=104)	CRP ≥20 (n=124)
Men (n, %)	110 (65%)	60 (58%)	93 (75%)
Age at WM diagnosis (years, median, IQR)	67 [58; 76]	68 [58; 75]	66 [59; 76]
Year of first line treatment (year, median, IQR)	2013 [2008; 2016]	2014 [2011; 2017]	2014 [2010; 2016]
Age at first line treatment (years, median, IQR)	69 [60; 77]	72 [59; 78]	70 [61; 79]
MYD88 mutation (n, %, on 218 testing)	71 (84%)	54 (95%)	69 (91%)
CXCR4 mutation (n, %, on 159 testing)	21 (35%)	17 (36%)	8 (15%)
Del6q (n, %, on 205 testing)	8 (10%)	19 (31%)	33 (48%)

WM: Waldenström macroglobulinemia, IQR: interquartile

Supplementary Table 1B. Univariate analysis for time to next treatment (TTNT)

Variable	HR (95% CI for HR)	p-value
Sex	0.7 (0.35-1.4)	0.30
Age at WM diagnosis	1 (0.98-1.1)	0.32
Kappa (versus Lambda)	1.4 (0.44-4.7)	0.54
IMWW score Adverse (vs Low or Intermediate)	1.1 (0.4-3.2)	0.82
Age at WM diagnosis > 65 years	1.3 (0.68-2.4)	0.46
Hemoglobin < 11.5 g/dL	1.22 (0.41-3.5)	0.72
Platelets < 100 G/L	**2.38 (1.02-5.55)**	**0.04**
β2-microglobulin > 3 mg/L	1.6 (0.44-5.7)	0.48
Monoclonal IgM > 70 g/L	0.76 (0.1-5.7)	0.79
LDH > 250 UI/L	0.52 (0.23-1.2)	0.13
MYD88 mutation	0.48 (0.11-2.1)	0.33
***CXCR4* mutation**	**3.8 (1.5-9.6)**	**0.01**
Del6q	1.3 (0.49-3.4)	0.60
Line of WM treatment before BTKi	1.3 (0.97-1.8)	0.08
Age at BTKi initiation	1 (0.97-1)	0.9
Year of BTKi initiation	0.85 (0.7-1)	0.11
Inflammatory (CRP ≥ 20 mg/L) at BTKi initiation	**0.43 (0.22-0.81)**	**0.01**

BTKi: Bruton tyrosine kinase inhibitors, ISSWM: International prognosis Score System for Waldenström Macroglobulinemia, WM: Waldenström macroglobulinemia

Supplementary Figure 1. Global cohort analysis. (A) Time to next treatment (TTNT) survival curves at first line in the pooled cohort with 3 levels of CRP (0-5, 5-20 and 20 mg/L). Dotted line represents the median of TTNT survival. **(B) Maximally selected rank statistics on pooled global cohort for TTNT at first line. Standardized log-rank statistics was performed on CRP level (continuous variable) at different cut-off.** The dotted line (here at 22 mg/L of CRP) showed the best cut-off to separate the cohort into 2 groups of different survival (HR 4.9 for 22 mg/L). **(C-D) Del6q (C) and CXCR4 (D) incidence among the global pooled cohort of WM patients separated in 3 groups based on the CRP level (CRP < 5 mg/L, CRP 5-20 mg/L, CRP ≥ 20 mg/L)**
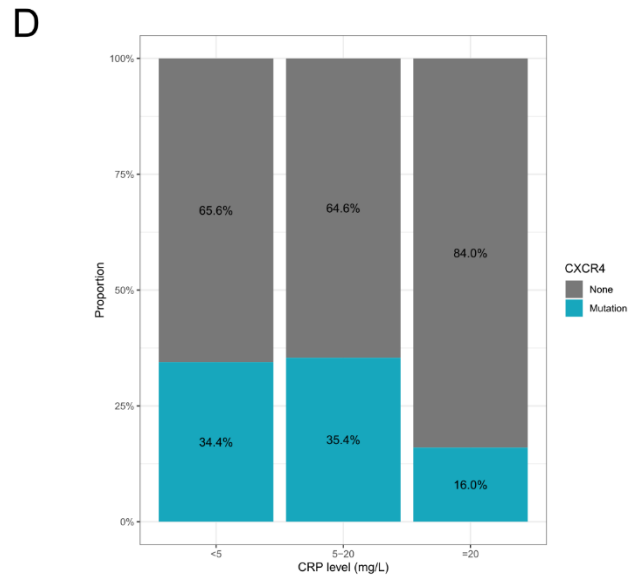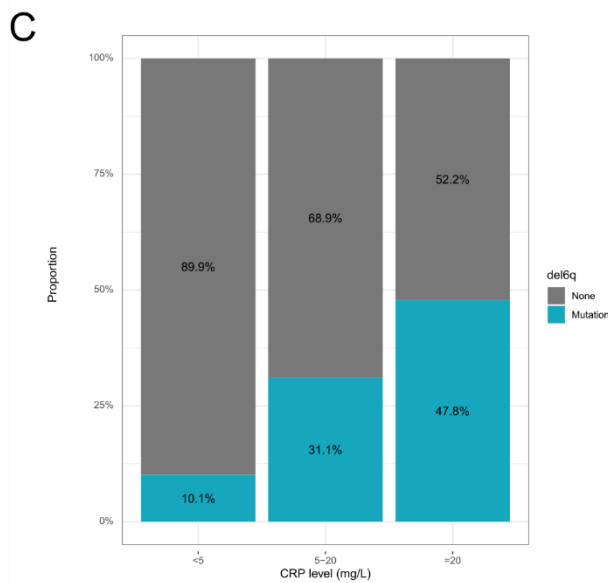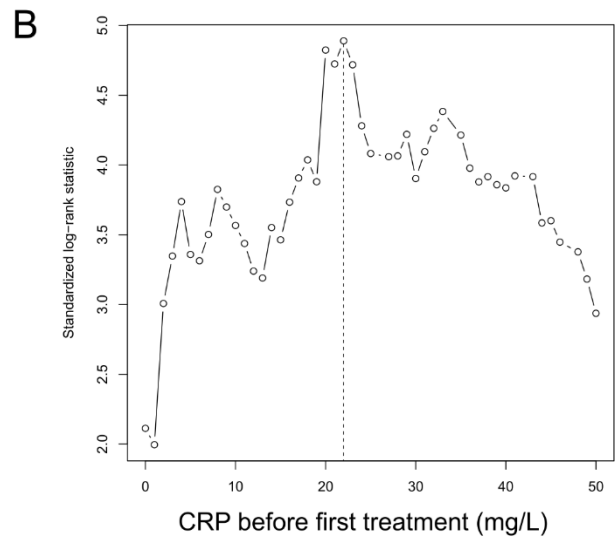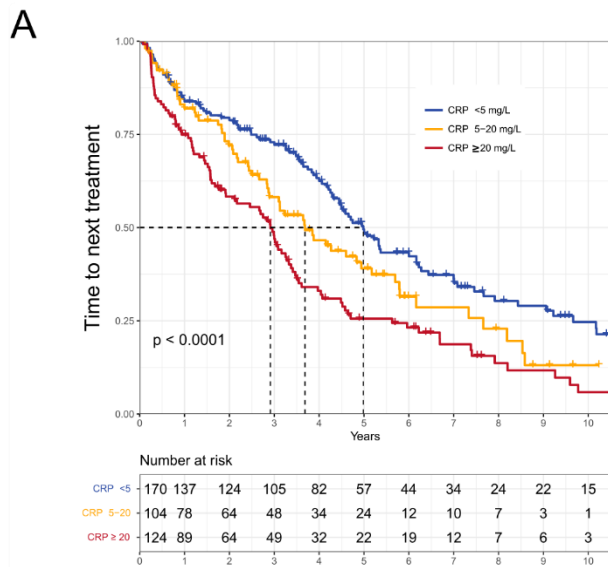
Supplementary Figure 2. BTK cohort analysis. (A) Time to next treatment (TTNT) survival curves after BTK treatment with 3 levels of CRP (0-5, 5-20 and 20 mg/L). Dotted line represents the median of TTNT survival. **(B) Maximally selected rank statistics on BTKi cohort for TTNT. Standardized log-rank statistics was performed on CRP level (continuous variable) at different cut-off (C) Overall survival between inflammatory WM (red) and non-inflammatory WM (blue) after BTKi treatment.**