

Keywords: myeloma; MGUS; biclonal gammopathy; plasma cells; immunoglobulins; M proteins

Active multiple myeloma suppresses and typically eliminates coexisting MGUS

John P Campbell^{1,2,9}, Jennifer L J Heaney^{1,9}, Sankalp Pandya¹, Zaheer Afzal¹, Martin Kaiser³, Roger Owen⁴, J Anthony Child⁴, Walter Gregory⁵, Gareth J Morgan⁶, Graham H Jackson⁷, Chris M Bunce⁸ and Mark T Drayson^{*.1}

¹Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham B15 2TT, UK; ²Department for Health, University of Bath, Bath BA2 7AY, UK; ³Institute of Cancer Research, London SM2 5NG, UK; ⁴St James's University Hospital, Leeds LS9 7TF, UK; ⁵Clinical Trials Research Unit, University of Leeds, Leeds LS2 9NL, UK; ⁶The Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; ⁷University of Newcastle, Newcastle upon Tyne NE1 7RU, UK and ⁸School of Biosciences, University of Birmingham, Birmingham B15 2TT, UK

Background: Myeloma is consistently preceded by premalignant monoclonal gammopathy of undetermined significance (MGUS). In >5% of MGUS patients there is a second MGUS clone (biclonal gammopathy of undetermined significance; BGUS), yet, at myeloma diagnosis, presentation of biclonal gammopathy myeloma (BGM_y) is considered less frequent, implying that myeloma eradicates coexisting MGUS.

Methods: In the largest study of its kind, we assessed BGM_y frequency amongst 6399 newly diagnosed myeloma patients enrolled in recent UK clinical trials.

Results: Compared to expected prevalence (i.e., >5% of MGUS have BGUS), only 58 of 6399 (0.91%) newly diagnosed myeloma patients had BGM_y, indicating myeloma typically eliminates coexistent MGUS. In these 58 BGM_y cases, the MGUS plasma cell clone was greatly suppressed in size compared to typical levels observed in conventional MGUS; contrarily, the MGUS clone did not inhibit the myeloma plasma cell clone in BGM_y.

Conclusion: Myeloma eliminates the majority of competing MGUS, and when it does not, the MGUS clone is substantially reduced in size.

Myeloma and the asymptomatic precursor that consistently precedes it, monoclonal gammopathy of undetermined significance (MGUS) (Landgren *et al*, 2009; Weiss *et al*, 2009), are characterised by monoclonal plasma cells (PCs) in the bone marrow and monoclonal antibody (MAB) in blood. In a population-based study of 12 482 persons, prevalence of MGUS was 3.7% in blacks, 2.3% in whites and 1.8% in Hispanics, and within these MGUS populations, the prevalence of two MGUS clones—termed biclonal gammopathy of undetermined significance (BGUS) (Kyle *et al*, 1981)—was 15.4%, 6.8% and 12.8%, respectively (Landgren *et al*, 2014). A proportion of new myeloma diagnoses also exhibit two MABs in immunofixation electrophoresis (IFE), termed myeloma

with biclonal gammopathy (BGM_y). This represents progression of one BGUS clone to active myeloma and the continued presence of a secondary MGUS clone (Kyle *et al*, 1981; Kyle *et al*, 2003). Given that the prevalence of MGUS in the general population—at the mean age of myeloma diagnosis—is ~5% (Dispenzieri *et al*, 2010; Wadhera and Rajkumar, 2010), and prevalence of BGUS amongst all MGUS is >5% (Landgren *et al*, 2014), one would also expect more than 5% of myeloma cases to be BGM_y. The frequency of BGM_y remains uncertain (Kyle *et al*, 1981; Nilsson *et al*, 1986; Riddell *et al*, 1986; Guastafierro *et al*, 2012; Garcia-Garcia *et al*, 2015). In a review of 1027 myeloma diagnoses in one centre, 2% of cases were BGM_y (Kyle *et al*, 2003). This lower than expected figure

*Correspondence: Professor MT Drayson; E-mail: M.T.Drayson@bham.ac.uk

⁹These authors contributed equally to this work.

Received 1 March 2017; revised 19 June 2017; accepted 22 June 2017; published online 20 July 2017

© 2017 Cancer Research UK. All rights reserved 0007–0920/17

warrants validation as it implies that when myeloma arises in an individual with BGUS, the malignant myeloma clone eliminates the competing MGUS clone. Here, in the largest study of its kind, we assessed 6399 newly diagnosed myeloma patients entered into three multicentre UK clinical trials to determine the frequency, and MAB sizes of, BGM_y at myeloma diagnosis.

MATERIALS AND METHODS

Trial patients. The BGM_y patients were identified from 6399 newly diagnosed myeloma patients enrolled in one of the following multicentre, phase III trials: the UK MRC Myeloma IX trial (N=1693; ISRCTN68454111); the CRUK Myeloma XI trial up to an induction randomisation date of 23 July 2015 (N=3880; ISRCTN49407852); or the UK NIHR TEAMM Trial up to a randomisation date of 23 July 2015 (N=826; ISRCTN51731976). All patients gave written informed consent. The study was approved by the institutional review boards of the participating centres and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Laboratory tests. The MABs in serum were identified by IFE (Sebia, Paris, France) and quantified by protein zone electrophoresis and densitometry (SPE; Interlab, Rome, Italy); please refer to Supplementary Information for more information. In patients with a light-chain (LC) MAB without a heavy-chain (HC) component (i.e., LC-only myeloma), MAB size was measured and monitored by involved free LCs (Binding Site, Birmingham, UK) expressed in g l⁻¹.

Statistical analyses. Differences between groups were analysed by one-way ANOVA for continuous variables (e.g., MAB size), and χ^2 for categorical variables and frequencies. One-sample *t*-tests were used to compare observed MAB sizes to previously observed mean MAB sizes in the literature; observed BGM_y MAB sizes were compared to reported MAB sizes in MGUS (Turesson *et al*, 2014) and myeloma using a combined data set from MIX and MXI UK trials. Correlational analyses were conducted using Pearson's for normally distributed data and Spearman's Rank where data was skewed. Significance was accepted at *P*<0.05. Data were analysed by IBM SPSS statistics version 21 (Armonk, NY, USA).

RESULTS

Frequency of BGM_y and demographics of BGM_y patients. A total of 58 patients had BGM_y (from MIX=18, MXI=33 and TEAMM=7) and 6341 had monoclonal gammopathy myeloma (MGMy) giving a BGM_y frequency of 58 out of 6399 patients (0.91%; 99% confidence interval: ±0.3%). Comparison of the 58 BGM_y patients with MGMy patients in the same trials found no differences in age: BGM_y median age (range) was 69 (45–86) years; and MGMy was 66 (28–90) years.

Distinguishing MGUS from myeloma MABs. The frequencies and concentrations of serum MABs in all 58 BGM_y patients at trial entry are presented in Table 1; the largest MAB is classified as the myeloma MAB and is referred to as 'M1', whereas the smaller MAB was classified as the MGUS MAB and is referred to as 'M2'. In 4 patients with a FLC MAB >500 mg l⁻¹ and intact

Table 1. Characteristics and frequencies of M1 and M2 in 58 BGM_y patients at myeloma diagnosis, compared to expected frequencies and characteristics of MGMy and conventional MGUS

MAB 1						MAB 2								
HC isotype		Frequency (N)	Proportion (%)	Conc. (g l ⁻¹) (median (range))	MGMy reference ranges ^a		HC isotype		Frequency (N)	Proportion (%)	Conc. (g l ⁻¹) (median (range))	MGUS reference ranges ^b		
					Proportion (%)	Conc. (g l ⁻¹) (median (range))						Kyle <i>et al</i> , 2006	Turesson <i>et al</i> , 2014	
												Conc. (g l ⁻¹) (median ± s.d.)		
IgG	Total	39	67.2	~36.1 (4.8–70.0)	59.9	34.4 (0.8–100.2)	IgG	Total	33	56.9	^d 2.6 (0.5–12.0)	68.9	68.8	7.0 ± 6.0
	IgGκ	26	66.7	32.6 (4.8–70.0)				IgGκ	17	51.5	2.5 (0.5–12.0)			
	IgGλ	13	33.3	39.7 (10.2–60.0)				IgGλ	16	48.5	2.8 (0.5–9.0)			
IgA	Total	14	24.1	^c 25.4 (1.8–60.0)	23.6	33.0 (0.2–96.6)	IgA	Total	11	19.0	^d 1.7 (0.5–11.6)	10.8	14.7	8.0 ± 5.0
	IgAκ	8	57.1	26.9 (1.8–60.0)				IgAκ	5	45.5	1.3 (0.5–3.9)			
	IgAλ	6	42.9	23.2 (3.9–53.0)				IgAλ	6	54.5	2.5 (0.5–11.6)			
IgD	Total	1	1.7	2.6 (2.6–2.6)	1.7	4.2 (0.2–36.9)	IgM	Total	14	24.1	^d 1.3 (0.5–6.0)	17.2	16.2	7.0 ± 6.0
	IgDκ	0	0.0	—				IgMκ	12	85.7	1.3 (0.5–6.0)			
	IgDλ	1	100	2.6 (2.6–2.6)				IgMλ	2	14.3	1.6 (0.6–2.7)			
FLC	Total	4	6.9	1.0 (0.5–1.9)	13.1	2.6 (0.02–46.7)								
	FLCκ	3	75.0	1.4 (0.5–1.9)										
	FLCλ	1	25.0	0.7 (0.7–0.7)										
LC isotype		Frequency (N)	Proportion (%)	Conc. (g l ⁻¹) (median (range))	MGMy reference proportion ^a (%)		LC isotype		Frequency (N)	Proportion (%)	Conc. (g l ⁻¹) (median (range))	MGUS reference proportion (%) Kyle <i>et al</i> , 2006		
κ		37	63.8	26.0 (0.5–70.0)	66.0		κ		34	58.6	1.8 (0.4–12.0)	62.0		
λ		21	36.2	27.0 (0.7–60.0)	34.0		λ		24	41.4	2.7 (0.5–11.6)	37.9		

Abbreviations: BGM_y = biconal gammopathy myeloma; Conc. = concentration; FLC = free light chain; HC = heavy chain; LC = light chain; MAB = monoclonal antibody; MGMy = monoclonal gammopathy myeloma; MGUS = monoclonal gammopathy of undetermined significance.
^aReference ranges aggregated from 3248 patients with MGMy diagnosed at entry into Myeloma IX and Myeloma XI trials; data set cutoff June 2013.
^bReference ranges derived from 728 MGUS patients (Turesson *et al*, 2014) or 694 MGUS patients (Kyle *et al*, 2006).
^cSignificant difference between M1 and M2 concentration (IgG *P*<0.001; IgA *P*<0.001).
^dSignificant difference between M2 concentration and expected MAB concentration in MGUS (IgG *P*<0.001; IgA *P*<0.001; IgM *P*<0.001) (Turesson *et al*, 2014). No significant differences observed between M1 and expected MAB concentrations in MGMy (*P*>0.05) based on observations from Myeloma IX and XI.

Table 2. Frequency of M1 and M2 combinations observed in BGM_y

MAB 1	MAB 2	MAB 2 frequency		MAB 2 proportion	
		Observed BGM _y frequency (N)	Expected MGUS ^a frequency (N)	Observed BGM _y proportion (%)	Expected MGUS ^a proportion (%)
IgG κ (N = 26)	IgG κ	0 ^b	12	0	46
	IgG λ	10	6	38	23
	IgA κ	3	3	12	10
	IgA λ	4	1	15	5
	IgM κ	7	3	27	11
	IgM λ	2	1	8	5
IgG λ (N = 13)	IgG κ	6	6	46	46
	IgG λ	0	3	0	23
	IgA κ	2	1	15	10
	IgA λ	2	1	15	5
	IgM κ	3	1	23	11
	IgM λ	0	1	0	5
IgA κ (N = 8)	IgG κ	5	4	63	46
	IgG λ	1	2	13	23
	IgA κ	0	1	0	10
	IgA λ	0	0	0	5
	IgM κ	2	1	25	11
	IgM λ	0	0	0	5
IgA λ (N = 6)	IgG κ	4	3	67	46
	IgG λ	2	1	33	23
	IgA κ	0	1	0	10
	IgA λ	0	0	0	5
	IgM κ	0	1	0	11
	IgM λ	0	0	0	5

Abbreviations: BGM_y=biclonal gammopathy myeloma; FLC=free light chain; MAB=monoclonal antibody; MGUS=monoclonal gammopathy of undetermined significance. Because of low frequency, data not shown from one patient with IgD MAB 1 and four patients with FLC MAB 1.
^aReference range proportions obtained from Turesson *et al* (2014), with assumed 2:1 proportion of kappa:lambda for each heavy-chain isotype.
^bχ²-analyses revealed significant differences between the observed frequency of IgGκ pairs in BGM_y compared to those expected in MGUS (P<0.001; χ²=15.60). A trend (P=0.065; χ²=3.391) was observed for frequency of observed IgGλ pairs in BGM_y and those expected in MGUS.

immunoglobulin <5 g l⁻¹, the FLC MAB was selected as M1. M1s were 10- to 20-fold larger than M2s with median M1 IgG 34.4 g l⁻¹ compared to M2 IgG 2.6 g l⁻¹; and M1 IgA 33 g l⁻¹ compared to M2 IgA 1.7 g l⁻¹.

M1 and M2 MAB combinations in BGM_y are presented in Table 2 where it can be seen that 37 out of 58 BGM_y (65%) combinations exhibited different LC isotypes; assessment of available serum FLC levels in these patients (illustrated in Supplementary Figure 1) demonstrated that elevated FLC levels were predominantly associated with the M1 clone.

In Table 2, we show that two independent IgG MABs was the most common M1 and M2 combination (16 out of 58 patients), but not as common as expected (27 out of 58), and we did not observe any patients with two IgG MABs with the same LC isotype (15 out of 58 expected; P<0.001; χ²=17.228). In 6 BGM_y patients with two IgG MABs, the electrophoretic mobilities of the MABs

Table 3. Comparison of M1 and M2 concentrations in BGM_y with expected MAB sizes in conventional MGMy and in MGUS

Size	M1 proportion and frequency ^a	Expected proportion in MGMy (%) ^{b,c}	M2 proportion and frequency	Expected proportion in MGUS (%) ^d
<4.99 g l ⁻¹	7% (N=4)	7	83% (N=48)	24
5.00-9.99 g l ⁻¹	7% (N=4)	5	14% (N=8)	19
10.00-14.99 g l ⁻¹	7% (N=4)	5	3% (N=2)	33
15.00-19.99 g l ⁻¹	7% (N=4)	6	0% (N=0)	18
20.00-24.99 g l ⁻¹	13% (N=7)	9	0% (N=0)	5
>25.00 g l ⁻¹	57% (N=31)	68	0% (N=0)	1

Abbreviations: BGM_y=biclonal gammopathy myeloma; MAB=monoclonal antibody; MGMy=monoclonal gammopathy myeloma; MGUS=monoclonal gammopathy of undetermined significance.
^aExcludes four patients diagnosed with a FLC myeloma M1 (all four patients had a whole MAB <4.99 g l⁻¹).
^bReference range represents aggregated data from patients with MGMy diagnosed at entry into Myeloma IX and Myeloma XI trials.
^cExcludes patients with FLC myeloma and non-secretory myeloma.
^dReference range derived from 694 MGUS patients (Kyle *et al*, 2006).

were very similar and so these MABs were only reliably distinguishable by their different LC isotype. Accordingly, we may have missed a third of the 15 out of 58 expected IgG MAB pairs of the same LC isotype, because of electrophoretic mobility similarities.

MGUS MAB isotypes and levels in BGM_y compared to conventional MGUS. The most frequent M2 was IgG (33 out of 58), and a quarter of M2 clones (14 out of 58) secreted IgM. The frequency of different M2 HC isotypes was closest to the patterns observed in two MGUS studies of 728 and 694 MGUS patients, rather than the different HC frequencies seen in myeloma (Kyle *et al*, 2006; Turesson *et al*, 2014) (Table 1). There were, however, less IgG M2s than would be expected in a typical MGUS population (33 *versus* 41) and more IgM and IgA isotypes (25 *versus* 16; trend observed: P=0.092; χ²=2.83).

The level of the MGUS-associated MAB (M2) in BGM_y was smaller than sizes reported in MGUS (Turesson *et al*, 2014) by 2.5-fold for IgG and 5-fold for IgA and IgM MABs (P<0.001). Thus, whereas coexistent MGUS (i.e., M2) did not appear to suppress the myeloma clone (i.e., M1) in BGM_y, the presence of myeloma (M1) significantly suppressed MGUS (M2) MAB levels. The magnitude of this suppression is illustrated in Table 3 where 83% of M2's were below 5 g l⁻¹ compared to the observed 24% in a prior MGUS study.

Serum levels of myeloma MABs are the same in MGMy and BGM_y. The most prevalent M1 was IgG, followed by IgA, FLC and then IgD; no IgM or IgE M1's were observed; please refer to Supplementary Information for more information. The HC frequencies were very similar to those of 3248 patients in the same clinical trials who had MGMy (Table 1). Notably, IgG and IgA M1 MAB concentrations were not significantly different to those observed in the MGMy patients from the same trials. This indicates that the presence of a second neoplastic PC clone (i.e., M2) does not competitively suppress the expansion of the neoplastic myeloma clone (i.e., M1) (Table 3).

DISCUSSION

This is the largest study of BGM_y frequency in a large cohort of newly diagnosed myeloma patients, and demonstrates that

myeloma eliminates or greatly suppresses coexisting MGUS. As the prevalence of MGUS in the general population – at the typical age of myeloma diagnosis – is ~5% (Dispenzieri *et al*, 2010; Wadhera and Rajkumar, 2010) and the prevalence of BGUS amongst all individuals with MGUS is >5% (Landgren *et al*, 2014), it would also be expected that >5% of myeloma cases would be BGMy. However, despite rigorous central laboratory analysis, it was found to be just 0.91%.

This shortfall is unlikely to be the result of myeloma being fivefold more likely to arise in individuals with a single MGUS clone than from individuals with two MGUS clones. A recent study reported the rate of progression from BGUS to myeloma was ~1% per year, which is similar to the incidence of MGUS progression to myeloma (Mullikin *et al*, 2016). Thus, when myeloma arises from BGUS, in ~80% of cases, the other MGUS clone must be eliminated or suppressed below the limits of detection on IFE (0.1 g l^{-1}).

In the BGMy cases reported herein, MGUS-associated MAB levels were smaller than expected levels typically observed in conventional MGUS (Turesson *et al*, 2014), by 2.5-fold for IgG and 5-fold for IgA and IgM. The degree of suppression of MGUS clones in BGMy appears comparative to the immunoparesis of non-malignant polyclonal PC that occurs in the majority of newly diagnosed myeloma patients (Pruzanski *et al*, 1980; Wang, 1987; Wang and Young, 2001; Kastiris *et al*, 2014). Of 3248 MGMy patients from the same Myeloma IX and XI trials reported in this study, we found that polyclonal immunoglobulin levels were below the normal range in >80% of patients and levels were lower than the median level found in healthy controls by 2.5-fold for IgG and 7-fold for IgA and IgM. Despite their larger relative presence, MGUS clones appear to only compete effectively with polyclonal PC in ~20% of cases, as evidenced by incidence of immunoparesis in MGUS (Turesson *et al*, 2014). As only a fifth of MGUS clones exhibit competitiveness for the normal PC niche, we hypothesise that these are the only MGUS clones that survive when myeloma arises in the wider marrow environment and that they are subject to the same suppression of clonal size and antibody secretion as normal polyclonal PCs; this would also be applicable to the MGUS PC clone from which myeloma arose. In a separate observation, we observed in this study that two IgG MABs was the most common BGMy combination (16 out of 58 patients) but not as common as expected (27 out of 58) indicating that the presence of IgG myeloma PC clones suppresses IgG MGUS PC clones more than IgA or IgM PC clones. There is evidence from both MGUS and myeloma that neoplastic IgG PC clones exert a greater degree of suppression on normal polyclonal IgG PC than they do on IgA and IgM isotypes (Bradwell *et al*, 2013; Katzmman *et al*, 2013; Ludwig *et al*, 2016).

A limitation of our study is that we were unable to conduct longitudinal measurement of BGUS before myeloma diagnosis; this excluded the possibility of investigating elimination of MGUS clones at the time of myeloma clone proliferation. Future prospective studies may seek to explore differences between BGUS that progress to myeloma, and BGUS that do not progress to myeloma, and measurements should incorporate bone marrow tumour samples as well as stroma to investigate possible mechanisms of tumour eradication. In summary, our findings confirm that BGMy is rare, and the survival of a coexisting MGUS clone is hallmarked by reduced MAB size.

ACKNOWLEDGEMENTS

We are grateful to the NCRI Haemato-oncology subgroup and to all principle investigators for their dedication and commitment to recruiting patients to Myeloma IX, XI and TEAMM trials. We thank the Clinical Trials Research Unit at The University of Leeds

(Myeloma IX and XI) and the Clinical Trials Unit at the University of Warwick (TEAMM). We are grateful to the staff of the Clinical Immunology Service in Birmingham with Tim Plant, Karen Walker, Alison Adkins and Nicola Newnham. Finally we are grateful to all patients and their clinical teams at centres throughout the UK whose participation made this study possible.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JPC, CMB and MTD wrote the manuscript; MTD, JPC and JLJH designed the investigation into BGMy; JPC, JLJH, SP and ZA conducted the experiments; JPC, JLJH, SP and MTD interpreted the data; MK, RO, GJM, GHJ, AC and MTD designed the Myeloma IX, XI and/or TEAMM trials. All authors approved the manuscript.

REFERENCES

- Bradwell A, Harding S, Fourrier N, Mathiot C, Attal M, Moreau P, Harousseau JL, Avet-Loiseau H (2013) Prognostic utility of intact immunoglobulin Ig κ /Ig λ ratios in multiple myeloma patients. *Leukemia* **27**(1): 202–207.
- Dispenzieri A, Katzmman JA, Kyle RA, Larson DR, Melton 3rd LJ, Colby CL, Therneau TM, Clark R, Kumar SK, Bradwell A, Fonseca R, Jelinek DF, Rajkumar SV (2010) Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. *Lancet* **375**(9727): 1721–1728.
- Garcia-Garcia P, Enciso-Alvarez K, Diaz-Espada F, Vargas-Nunez JA, Moraru M, Yebra-Bango M (2015) Biclinal gammopathies: Retrospective study of 47 patients. *Rev Clin Esp* **215**(1): 18–24.
- Guastafierro S, Ferrara MG, Sica A, Parascandola RR, Santangelo S, Falcone U (2012) Serum double monoclonal components and hematological malignancies: only a casual association? Review of 34 cases. *Leuk Res* **36**(10): 1274–1277.
- Kastiris E, Zagouri F, Symeonidis A, Roussou M, Sioni A, Pouli A, Delimpasi S, Katodritou E, Michalis E, Michael M, Hatzimichael E, Vassou A, Repousis P, Christophoridou A, Kartasis Z, Stefanoudaki E, Megalakaki C, Giannouli S, Kyrtonis MC, Konstantopoulos K, Spyropoulou-Vlachou M, Terpos E, Dimopoulos MA, Greek Myeloma Study G (2014) Preserved levels of uninvolved immunoglobulins are independently associated with favorable outcome in patients with symptomatic multiple myeloma. *Leukemia* **28**(10): 2075–2079.
- Katzmann JA, Clark R, Kyle RA, Larson DR, Therneau TM, Melton 3rd LJ, Benson JT, Colby CL, Dispenzieri A, Landgren O, Kumar S, Bradwell AR, Cerhan JR, Rajkumar SV (2013) Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. *Leukemia* **27**(1): 208–212.
- Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR (2003) Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* **78**(1): 21–33.
- Kyle RA, Robinson RA, Katzmman JA (1981) The clinical aspects of biclinal gammopathies. Review of 57 cases. *Am J Med* **71**(6): 999–1008.
- Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, Dispenzieri A, Katzmman JA, Melton 3rd LJ (2006) Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* **354**(13): 1362–1369.
- Landgren O, Graubard BI, Katzmman JA, Kyle RA, Ahmadizadeh I, Clark R, Kumar SK, Dispenzieri A, Greenberg AJ, Therneau TM, Melton 3rd LJ, Caporaso N, Korde N, Roschewski M, Costello R, McQuillan GM, Rajkumar SV (2014) Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutritional Examination Survey. *Leukemia* **28**(7): 1537–1542.

- Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, Dispenzieri A, Kumar S, Clark RJ, Baris D, Hoover R, Rajkumar SV (2009) Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* **113**(22): 5412–5417.
- Ludwig H, Milosavljevic D, Berlanga O, Zojer N, Hubl W, Fritz V, Harding S (2016) Suppression of the noninvolved pair of the myeloma isotype correlates with poor survival in newly diagnosed and relapsed/refractory patients with myeloma. *Am J Hematol* **91**(3): 295–301.
- Mullikin TC, Rajkumar SV, Dispenzieri A, Buadi FK, Lacy MQ, Lin Y, Dingli D, Go RS, Hayman SR, Zeldenrust SR, Russell SJ, Lust JA, Leung N, Kapoor P, Kyle RA, Gertz MA, Kumar SK (2016) Clinical characteristics and outcomes in biconal gammopathies. *Am J Hematol* **91**(5): 473–475.
- Nilsson T, Norberg B, Rudolphi O, Jacobsson L (1986) Double gammopathies: incidence and clinical course of 20 patients. *Scand J Haematol* **36**(1): 103–106.
- Pruzanski W, Gidon MS, Roy A (1980) Suppression of polyclonal immunoglobulins in multiple myeloma: relationship to the staging and other manifestations at diagnosis. *Clin Immunol Immunopathol* **17**(2): 280–286.
- Riddell S, Traczyk Z, Paraskevas F, Israels LG (1986) The double gammopathies. Clinical and immunological studies. *Medicine (Baltimore)* **65**(3): 135–142.
- Tureson I, Kovalchik SA, Pfeiffer RM, Kristinsson SY, Goldin LR, Drayson MT, Landgren O (2014) Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies: 728 cases followed up to 30 years in Sweden. *Blood* **123**(3): 338–345.
- Wadhera RK, Rajkumar SV (2010) Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. *Mayo Clin Proc* **85**(10): 933–942.
- Wang L, Young DC (2001) Suppression of polyclonal immunoglobulin production by M-proteins shows isotype specificity. *Ann Clin Lab Sci* **31**(3): 274–278.
- Wangel A (1987) Multiple myeloma and polyclonal hypogammaglobulinaemia. *Acta Med Scand* **221**(5): 421–425.
- Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM (2009) A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood* **113**(22): 5418–5422.

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 4.0 Unported License.

Supplementary Information accompanies this paper on British Journal of Cancer website (<http://www.nature.com/bjc>)