



Novel antigens LMA and KMA are expressed on malignant bone marrow plasma cells from patients at all stages of multiple myeloma

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Introduction

The lambda myeloma antigen (LMA) and kappa myeloma antigen (KMA) are unique antigens on the surface of malignant plasma cells (PCs) in multiple myeloma and other plasma cell dyscrasia (PCD) bone marrow samples, as well as in human myeloma cell lines. In addition:

- LMA and KMA are also found on occasional mononuclear cells in tonsillar tissue and secondary mucosal lymphoid tissue.

- LMA and KMA are NOT present on normal B cells or other normal immune cells¹⁻³.

Characteristics of the antibodies called KappaMab and LambdaMabs (10B3 and 7F11) that bind to specific conformational epitopes in the constant regions of these surface-bound light chains have been described in clinical trials and in vitro experiments^{1, 2, 4-6}.

Here we present data on a larger series of patients with PCDs, and show the expression of LMA versus BCMA on PCs from patients in whom myeloma evolves from monoclonal gammopathy of unknown significance (MGUS).

We also describe the difference in phenotype between LMA and KMA expressing malignant PCs and the frequent expression of KMA in relapsed refractory myeloma patient (RRMM) samples.

Methods

- Patient bone marrow samples (κ =59 and λ =35*) were analysed using multiparametric FCM immunophenotyping with APC labelled LambdaMab (10B3) and KappaMab Fab'2 fragments, CD38, CD138, CD269 (BCMA), CD319 (SLAM F7), CD56 and CD45 monoclonal antibodies.
- PCs were identified as previously described by initial gating using CD38 and CD138².
- LMA and KMA expression was determined and compared with the other plasma cell markers.
- Antigen density was calculated using QuantiBrite beads in PE.

*Since publication of the abstract, a further 10 kappa+ and 4 lambda+ samples were analysed; note only MGUS, SMM, NDMM and RRMM data are presented here.

Abbreviations: PCDs=Plasma cell dyscrasias, **LMA**=Lambda Myeloma Antigen, **KMA**=Kappa Myeloma Antigen, **NDMM**=newly diagnosed multiple myeloma, **RRMM**=relapsed, refractory multiple myeloma, **PCs**=plasma cells, **MGUS**=monoclonal gammopathy of unknown significance, **SMM**=smoldering multiple myeloma, κ =kappa, λ =lambda, **BCMA**=B cell Maturation Antigen

Results

Percent of Positive Cases for KMA or LMA and BCMA, SLAMF7 and CD56

Number and % of Positive Cases						
Diagnosis n=50	KMA n(%)	CD269 (BCMA) n(%)	CD319 (SLAMF7) n(%)	CD56 n(%)	Co-exp of KMA & BCMA n(%)	Co-exp of KMA & CD56 n(%)
MGUS n=10	5**(50)	9(90)	10(100)	6***(60)	5(50)	2**(20)
SMM n=2	1(50)	2(100)	2(100)	2(100)	1(50)	1(50)
NDMM n=23	15**(65)	21(91)	23(100)	17(74)	15(65)	11(48)
RRMM n=15*	12(80)	11(73)	15(100)	10***(67)	10(67)	9(60)
Post HSCT n=6	4(66)	4(66)	6(100)	2**(33)	3(50)	2(33)

*Two patients each have 2 timepoints, thus n=15 samples from 13 patients. **Includes 1 patient with both positive and negative PC populations. ***Includes 4 patients with both positive and negative PC populations, Co-exp=Co-expression.

- The percent of samples expressing KMA was lowest in MGUS and SMM cases, was increased in NDMM (untreated) cases and was highest in RRMM (treated) cases.
- Conversely, the percent of samples expressing BCMA was highest in MGUS, SMM and NDMM, then decreased in RRMM.
- In the RRMM subset who had bone marrow samples taken post stem cell transplant, KMA was expressed in 4/6 cases.

Number and % of Positive Cases						
Diagnosis n=29	LMA n(%)	CD269 (BCMA) n(%)	CD319 (SLAMF7) n(%)	CD56 n(%)	Co-exp of LMA & BCMA n(%)	Co-exp of LMA & CD56 n(%)
MGUS n=11*	8***(73)	10***(91)	11(100)	7***(66)	6***(55)	4***(36)
SMM n=2	2(100)	2(100)	2(100)	1(50)	2(100)	1(50)
NDMM n=12	6(50)	11(92)	12(100)	5**(42)	6(50)	1(8)
RRMM n=4	2**(50)	4(100)	4(100)	2***(50)	2(50)	0(0)

*One patient has 2 timepoints, thus n=11 samples from 10 patients. **Includes 1 patient with both positive and negative PC populations, ***Includes 3 patients with both positive and negative PC populations, Co-exp=co-expression.

- Co-expression of LMA, and KMA, with BCMA was not consistent across MM stages.
- In all stages of disease, co-expression of LMA with CD56 was lower compared to KMA and CD56.

Antigen Densities

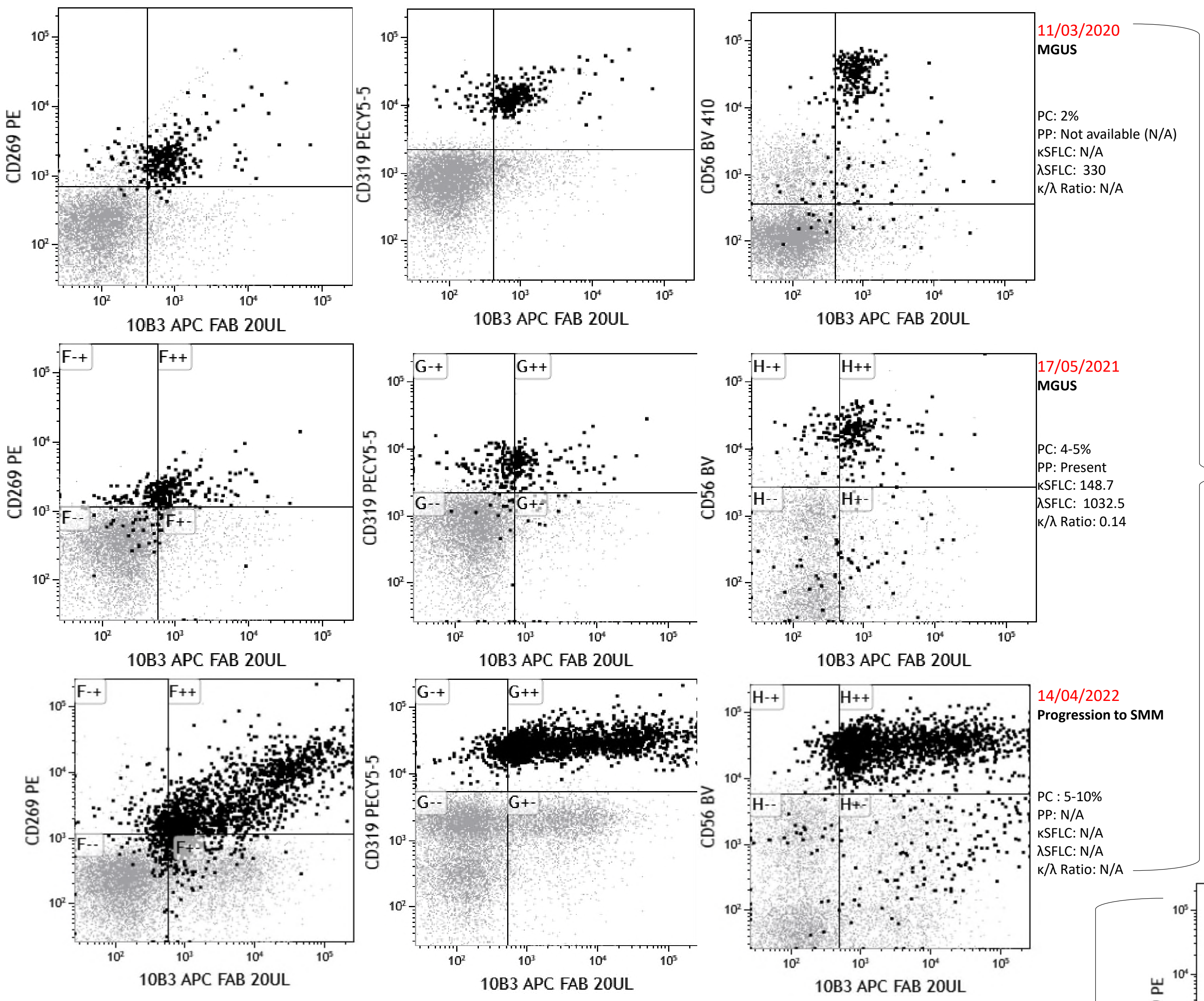
Antigen Density (molecules of PE/cell) n=27			Antigen Density (molecules of PE/cell) n=48		
Diagnosis (BM samples)	LMA mean (range)	BCMA mean (range)	Diagnosis (BM samples)	KMA mean (range)	BCMA mean (range)
MGUS n=11	1406 (132-5714)	1478 (511-4716)	MGUS n=10	687 (200-2187)	1031 (500-1412)
NDMM n=12	1652 (130-8949)	1897 (395-6990)	NDMM n=23	1447 (204-12022)	1439 (364-5370)
RRMM n=4	2439 (263-6664)	817 (537-1065)	RRMM n=15	1899 (468-7943)	1426 (350-2630)

Mean LMA antigen density was lowest in MGUS, was increased in NDMM and was highest in RRMM, while BCMA increased in NDMM relative to MGUS, and decreased in RRMM cases.

Mean KMA antigen density was lowest in MGUS, was increased in NDMM and was highest in RRMM, while BCMA was lowest in MGUS and remained the same in NDMM and RRMM cases.

References: ¹Asvadi P et al. *Br J Haematol.* 2015;169(3):333-343. ²Sartor et al. *Blood.* 2021; 138(Supplement 1):1595. ³Boux et al. *J Exp Med* 1983;158(5):1769-74. ⁴Spencer et al. *BCJ* 2019;9(8):58. ⁵Kaliff A et al. *Blood* (2019) 134 (Supplement 1): 3144 ⁶Asvadi et al. *Haematologica*, 2013; 98(s1):316. Abstract no. P756.

Two Longitudinal Cases: LMA Increases with Disease Stage

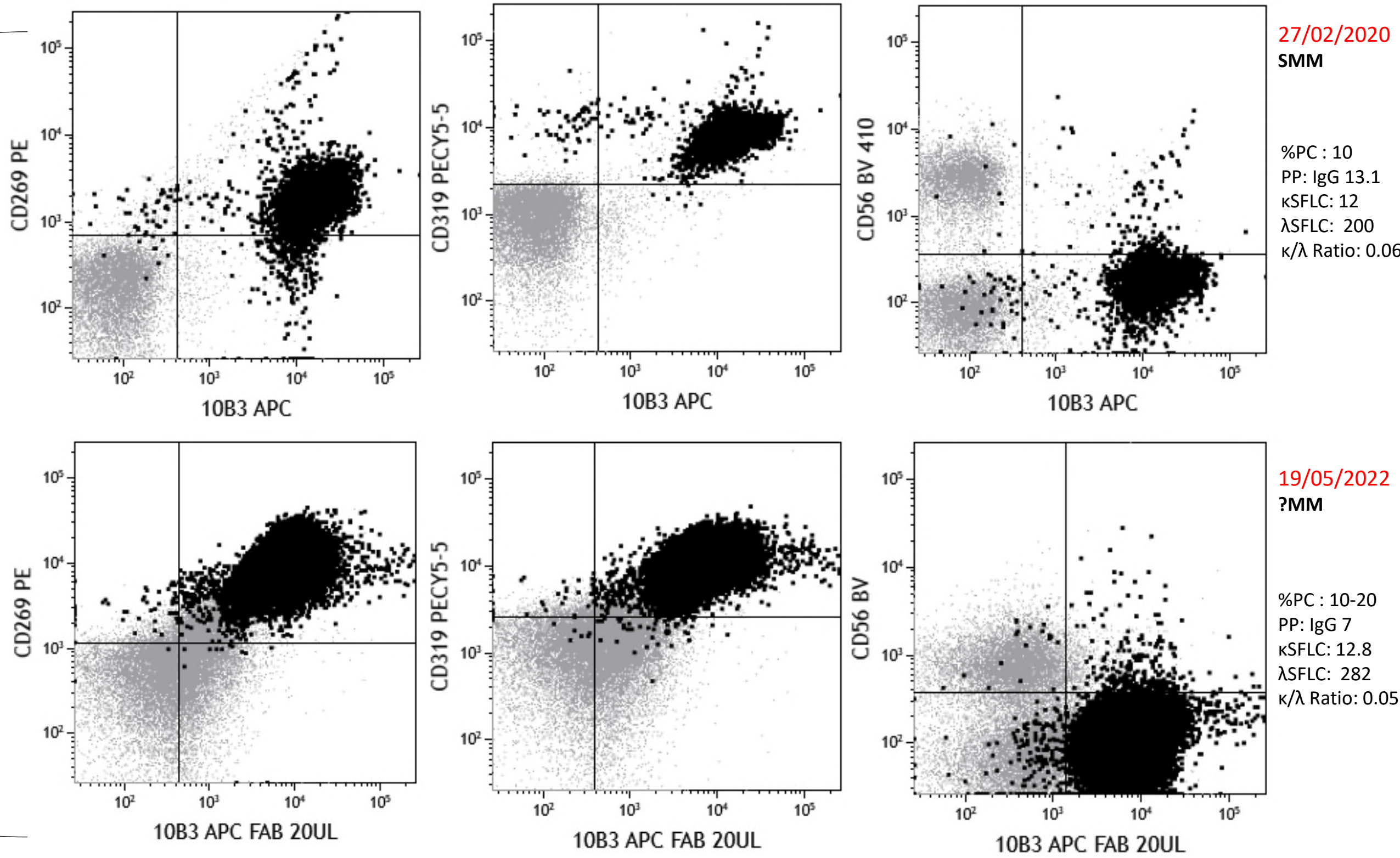


Longitudinal case #2

- Patient showed LMA expression and antigen density increased on bone marrow plasma cells during progression from SMM (2020) to myeloma (2022).
- Percent of plasma cells positive for LMA rose from 94% to 100%.
- LMA antigen density increased from 3981 to **8941** molecules PE/cell.
- BCMA Ag Density increased from 1259 to **6990** molecules PE/cell.

Longitudinal case #1

- Patient showed LMA expression and antigen density increasing on the surface of bone marrow plasma cells during progression from MGUS (2020) to smoldering myeloma (SMM) (2022).
- Percent of plasma cells positive for LMA increased from 61% to 92%.
- LMA antigen density increased from 532 to **5164** molecules PE/cell.
- BCMA Ag density increased from 631 to **2357** molecules PE/cell.



Discussion and Conclusions

- In an enlarged cohort of patients with myeloma, we have confirmed that KMA and LMA are expressed at all stages of disease.
- Our data examining longitudinal expression in two LMA+ patients suggests that expression of LMA on bone marrow PCs increases from MGUS to MM.
- The majority of patients with κ RRMM expressed KMA. Further data is required to confirm LMA expression in the λ RRMM population.
- LMA and KMA densities are enriched, while BCMA densities are reduced or remain the same in RRMM relative to NDMM samples, indicating a possible treatment-resistant clone.
- Co-expression of LMA or KMA with BCMA is not consistent, KMA is more consistently co-expressed with CD56 compared to LMA.
- Due to the lack of LMA and KMA expression on normal immune cells, targeting KMA and LMA through cellular and immunological therapies has the potential to leave normal PCs untouched and may minimise the risk of serious post-treatment infection.
- These data show that KappaMab and LambdaMab have therapeutic potential in the treatment of myeloma patients, especially in the setting of relapsed refractory disease where the combination of high antigen density and restriction of the target antigen to the malignant subpopulation of plasma cells may confer valuable clinical benefit.

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