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

AUTHORS

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INTRODUCTION

- The monoclonal antibody KappaMab (formerly MDX-1097) specifically binds to kappa myeloma antigen (KMA). The LambdaMabs, designated 10B3 and 7F11, specifically bind to lambda myeloma antigen (LMA). These Mabs bind to conformational epitopes found in the constant regions of KMA and LMA that are associated with lipid rafts.[1-3]
- KMA has been identified on kappa restricted myeloma plasma cells (PCs), some lymphomas and on amyloidosis PCs, whereas LMA is restricted to lambda PCs in the same B cell malignancies.
- In normal human tissues LMA and KMA have been identified on occasional mononuclear cells and plasmablasts in tonsils, salivary gland and secondary mucosal lymphoid tissue by using immunohistochemistry and flow cytometry techniques[1-3].
- LMA and KMA are NOT present on normal B cells or any other normal immune cells[1-3].
- In a Phase I single dose escalation clinical trial KappaMab (0.3-10mg/kg) showed no antibody-related hematologic toxicities and there was evidence of efficacy at the higher doses. There were statistically significant antibody dose-related decreases in three serum chemokines CXCL-9, CXCL-10 and MIF and in three growth factors including HGF, CCL27 and G-CSF, all of which support myeloma cell survival in the bone marrow environment (BME). No other cytokines (n=47) were affected.[4]
- In a Phase IIa study with 8 weekly doses of KappaMab at 10mg/kg, and no monthly maintenance treatment given, there were no hematologic toxicities and only grade 1-2 infusion reactions were observed. Nineteen patients were treated and the ORR was 1 VGPR, 2 PRs and 3 MRs[5].
- A recently completed Phase IIb combination study with KappaMab and lenalidomide + dexamethasone (KMRd) in relapsed refractory patients (n=40) showed an ORR of 83% versus 45% in the matched control arm (Rd). There was one grade 3 and seven grade 1-2 infusion reactions; importantly there were no antibody-related haematologic toxicities or lymphopenias[6].
- Following a successful in vivo study, a KMA.CAR T cell phase I clinical trial will be initiated in 2024[7].
- Here, we present data on a larger series of patients with myeloma and plasma cell dyscrasias and show that KMA and LMA are found on BM PCs at all stages of disease and their range of antigen densities is greater than BCMA. In addition, KMA and LMA are not always co-expressed with BCMA.

METHODS

- Patient bone marrow samples (κ=82 and λ=51*) were analysed using multiparametric FCM immunophenotyping with APC labelled LambdaMab (10B3) and KappaMab Fab'2 fragments, CD38, CD138, CD269 (BCMA), CD56 and CD45 monoclonal antibodies.
- PCs were identified as previously described by initial gating using CD38 and CD138[2]. It has been suggested that aberrant CD56 expression is an important prognostic marker in myeloma[8].
- LMA and KMA expression was determined and compared with the other plasma cell markers.
- Immunohistochemistry (ICH) was performed on snap frozen, unfixed human tissue samples to support sensitive detection of non-target tissue binding (cross-reactivity) by the antibody, as the targets were conformational epitopes prone to denaturation by cross-linking reagents.

RESULTS

Percent of Positive Cases for KMA, BCMA and CD56

Diagnosis N=82*	CD269 (BCMA) n(%)	KMA n(%)	CD56 n(%)	KMA & BCMA co-expression n(%)	KMA & CD56 co-expression n(%)
NDMM n=37	33[b] (89)	26[c] (70)	28[b] (76)	24[c] (65)	20[b] (54)
RRMM n=19[a]	13 (68)	14 (74)	12[b] (63)	12 (63)	9 (47)
MGUS n=16	15 (94)	11[b] (73)	9[c] (56)	11 (73)	7[b] (44)
SMM n=4	4 (100)	3 (75)	4 (100)	3 (75)	3 (75)
Plasmacytoma n=6	6 (100)	6 (100)	5 (83)	6 (100)	5 (83)

[a]Two patients each had 2 timepoints. [b]Includes 1 patient with both positive and negative PC populations, [c] Includes 3 patients with both positive and negative PC populations.

- KMA and BCMA were detected at all stages of disease but were not always co-expressed
- All plasmacytomas expressed KMA and co-expressed KMA and BCMA

Percent of Positive Cases for LMA, BCMA and CD56

Diagnosis N=51*	CD269 (BCMA) n(%)	LMA n(%)	CD56 n(%)	LMA & BCMA co-expression n(%)	LMA & CD56 co-expression n(%)
NDMM n=24	23 (96)	15 (63)	17[d] (71)	15 (63)	9[b] (38)
RRMM n=6	5 (83)	2[b] (50)	3[c] (50)	3 (50)	1 (17)
MGUS[a] n=13	12[c] (92)	10[c] (77)	7[c] (54)	10[c] (77)	5[c] (38)
SMM n=2	2 (100)	2 (100)	1 (50)	2 (100)	1 (50)
Amyloidosis n=6	3 (50)	6 (100)	4[b] (66)	3 (50)	4[c] (66)

[a]One patient had 4 timepoints. [b]Includes 2 patients with both positive and negative PC populations, [c] Includes 3 patients with both positive and negative PC populations, [d]Includes 4 patients with both positive and negative PC populations.

- LMA and BCMA were detected at all stages of disease but were not always co-expressed
- All amyloidosis samples expressed LMA and only 50% co-expressed LMA & BCMA

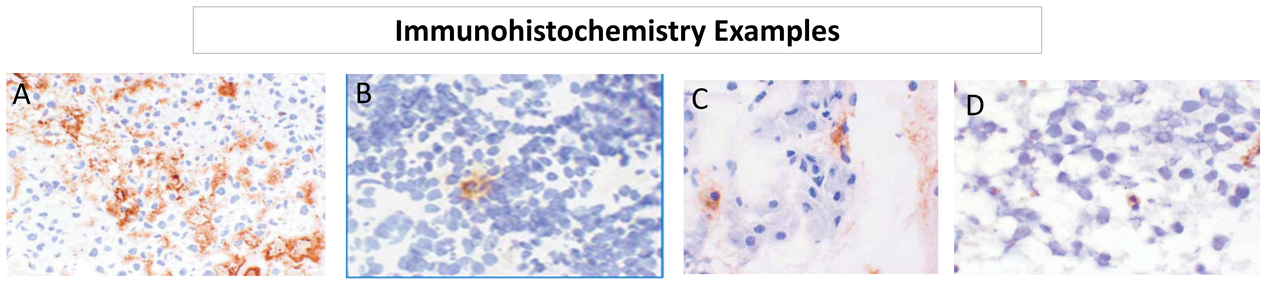
KMA, LMA and BCMA Ag Densities

Antigen Density (molecules of PE/cell) n=42*		
Diagnosis (BM samples)	LMA mean (range)	BCMA mean (range)
MGUS n=13	1703 (132-5714)	1402 (511-4716)
NDMM n=24	2056 (50-8949)	1943 (395-6990)
RRMM n=5	1941 (263-6664)	1425 (537-4418)

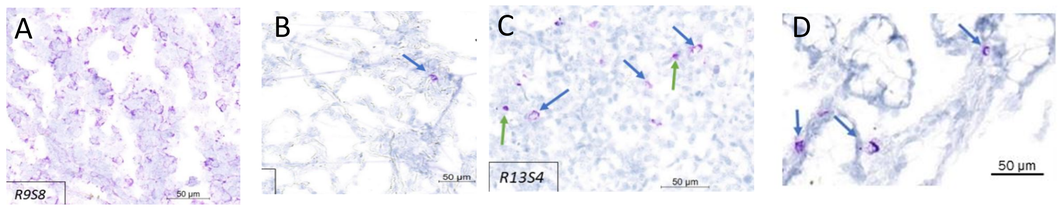
Antigen Density (molecules of PE/cell) n=60*		
Diagnosis (BM samples)	KMA mean (range)	BCMA mean (range)
MGUS n=10	1368 (200-6441)	1192 (500-4079)
NDMM n=23	1741 (204-12022)	1486 (250-5370)
RRMM n=15	1843 (468-7943)	1486 (350-3004)

- The KMA and LMA antigen density ranges on PCs were greater compared to BCMA.

Immunohistochemistry Examples

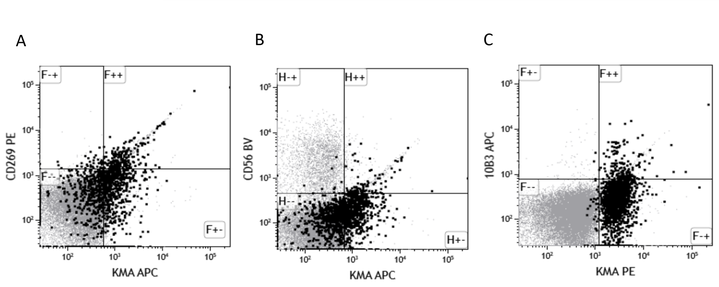


Immunohistochemistry staining for KMA using KappaMab. Panel A shows extensive staining in kappa myeloma BM PCs. Occasional mononuclear staining occurred in normal tonsil (panel B) and normal salivary gland (panel C) and was negative in normal BM (panel D). (Charles River Laboratories, Pathology Associates (PAI), Maryland, USA).



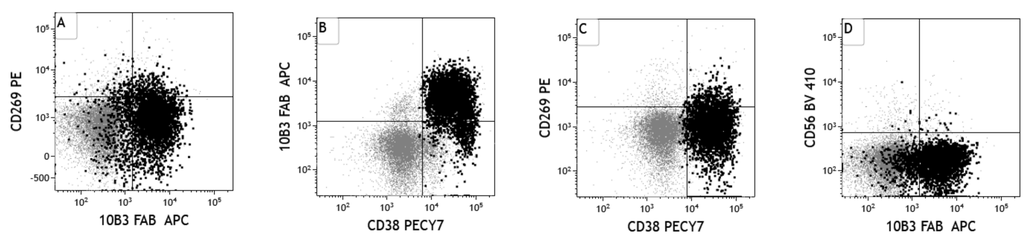
Immunohistochemistry staining for LMA using 10B3. Panel A shows extensive staining in a lung plasmacytoma. Occasional mononuclear staining occurred in normal lung (panel B), normal tonsil (panel C) and normal colon (panel D). (TPL Path Labs GmbH Sasbacher Str. 10 D-79111, Freiburg, Germany).

Flow Cytometry of Relapsed, Refractory MM bone marrows : Two Examples



KMA+ RRMM case currently in remission. KMA antigen density=2859, BCMA antigen density=313. Patient is currently KMA positive with dim BCMA expression (A). First autologous transplant in 2014, 06/2022 commenced carfilzomib, 08/2022 commenced carfilzomib + dex, 2nd autologous transplant in 2023.

LMA+ RRMM case. LMA (10B3) expression was positive (A-D) compared to CD269 (A and C) and CD56 (D) which were negative.



CONCLUSIONS

- KMA or LMA are expressed on malignant PCs at all stages of MM, however they were not always co-expressed with BCMA.
- IHC showed abundant KMA or LMA staining in myeloma and plasmacytoma patient tissues and occasional staining of mononuclear cells in normal secondary lymphoid tissue.
- The combination of increased, persistent KMA/LMA Ag density and the Phase I, IIa and IIb observation of KappaMab specificity, safety and reduction in myeloma growth promoting cytokines could provide a significant benefit in the KappaMab and LambdaMab treatment of MM and PCDs.

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, **k**=kappa, **λ**=lambda, **BCMA**=B cell Maturation Antigen, **Len**=lenalidomide, **Dex**=dexamethasone, **IHC**=Immunohistochemistry, **BME**=bone marrow microenvironment

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*Note: In this ongoing analysis, sample numbers presented here have increased since publication of the abstract.

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