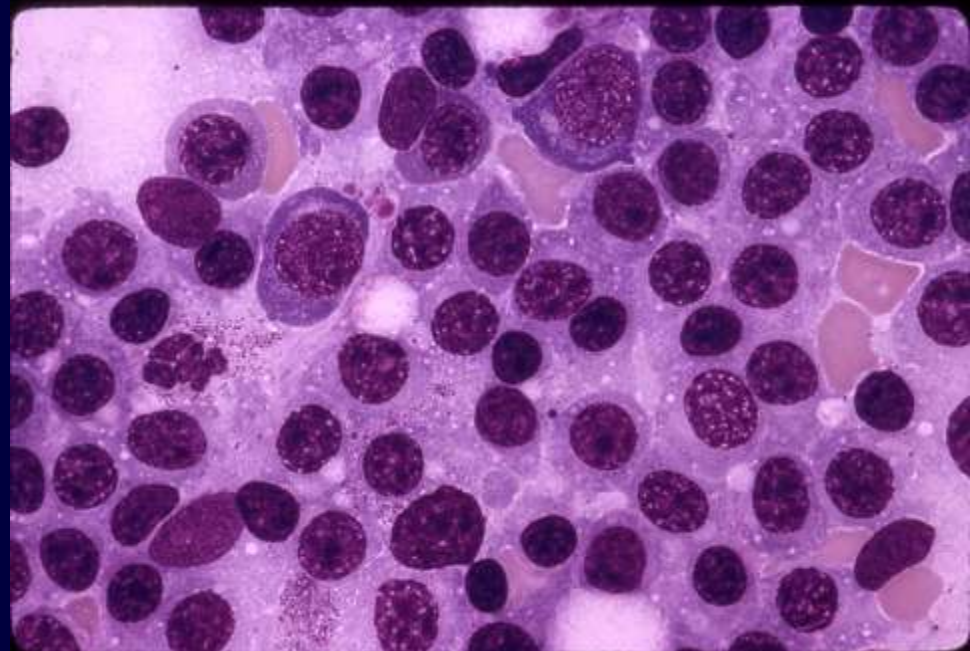


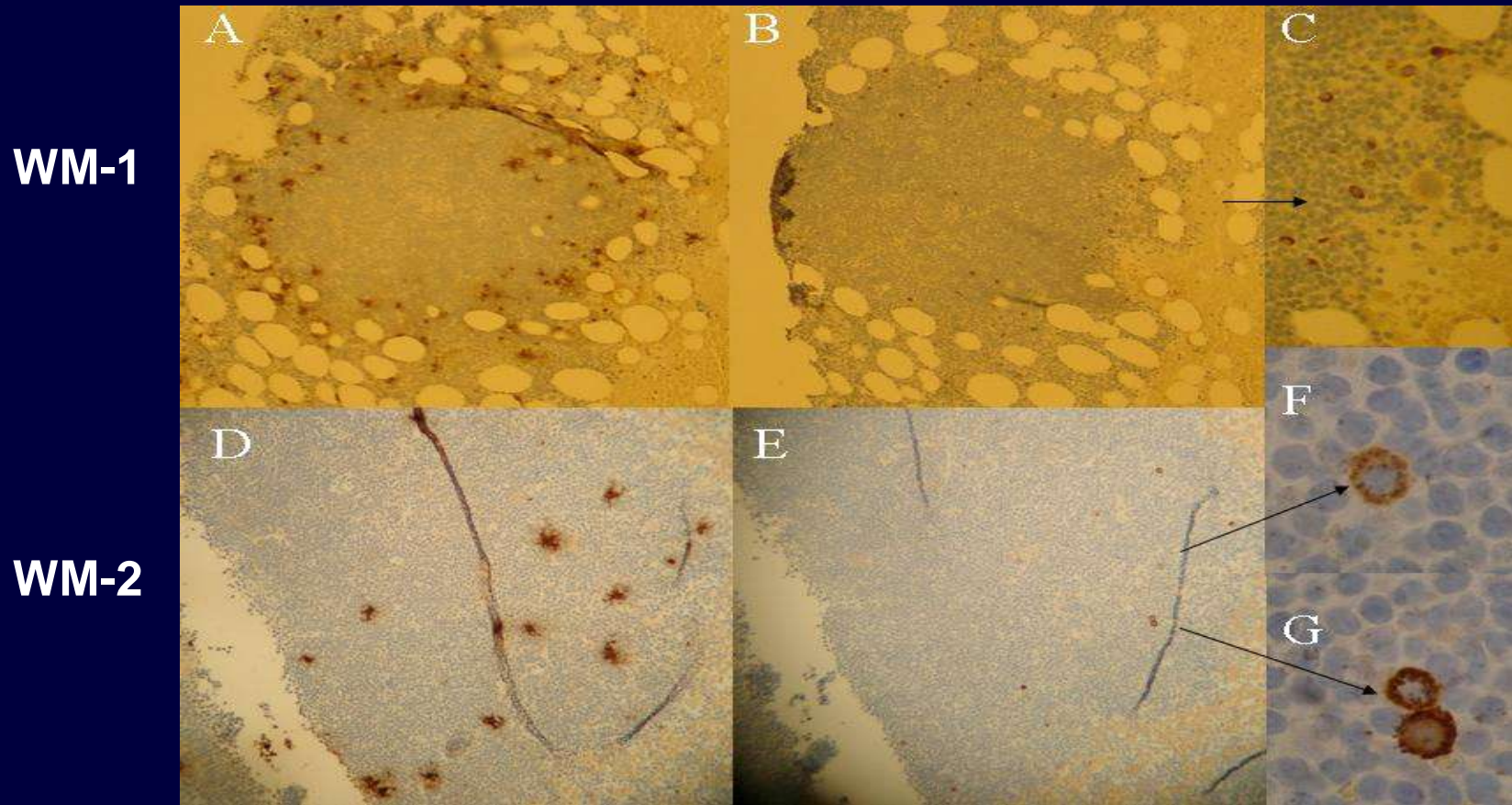
Mast Cells and sCD27 in Waldenström's Macroglobulinemia

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Increased Mast Cells in BM biopsies of WM Patients Express CD40L

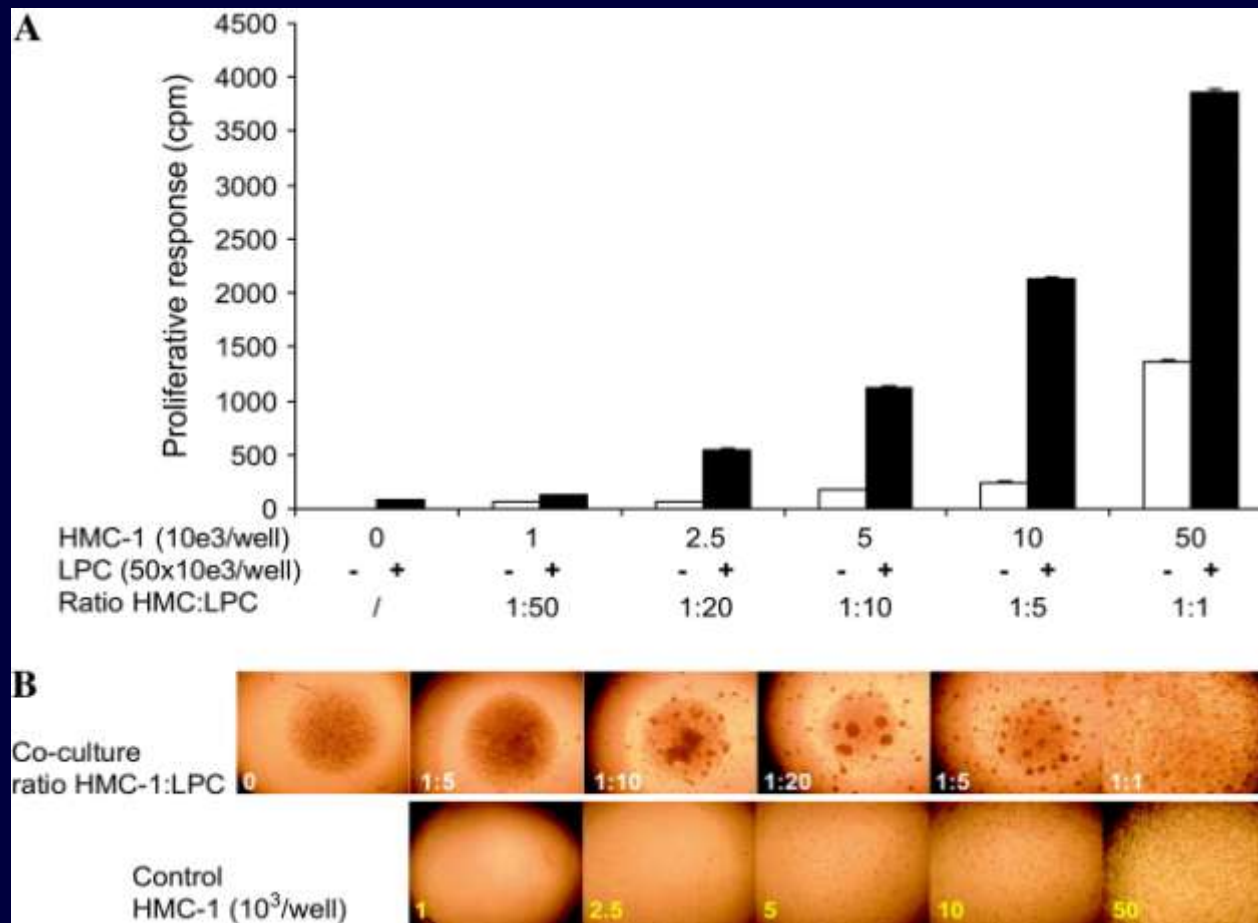


Tryptase

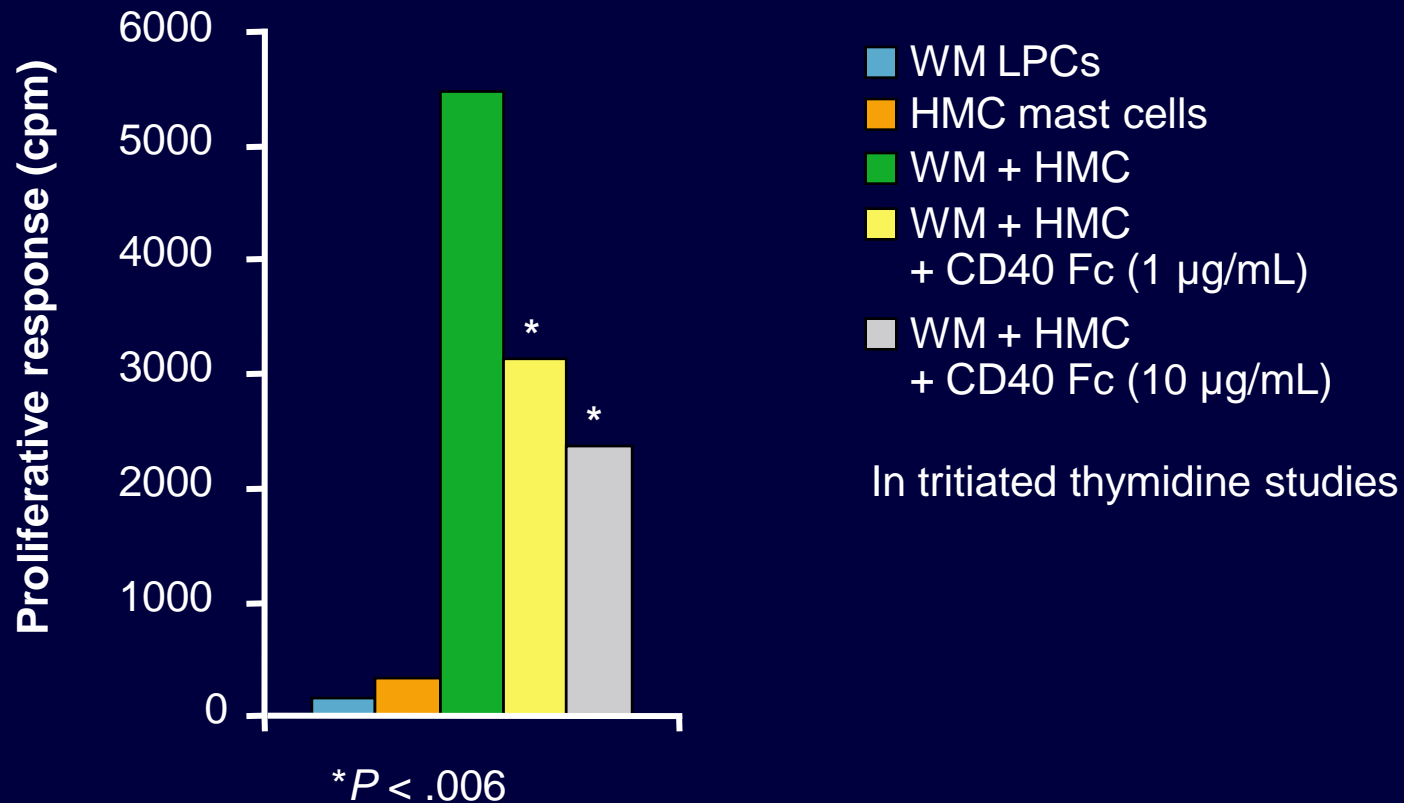
CD40 Ligand

Tournilhac et al,
Ann Oncol 2006

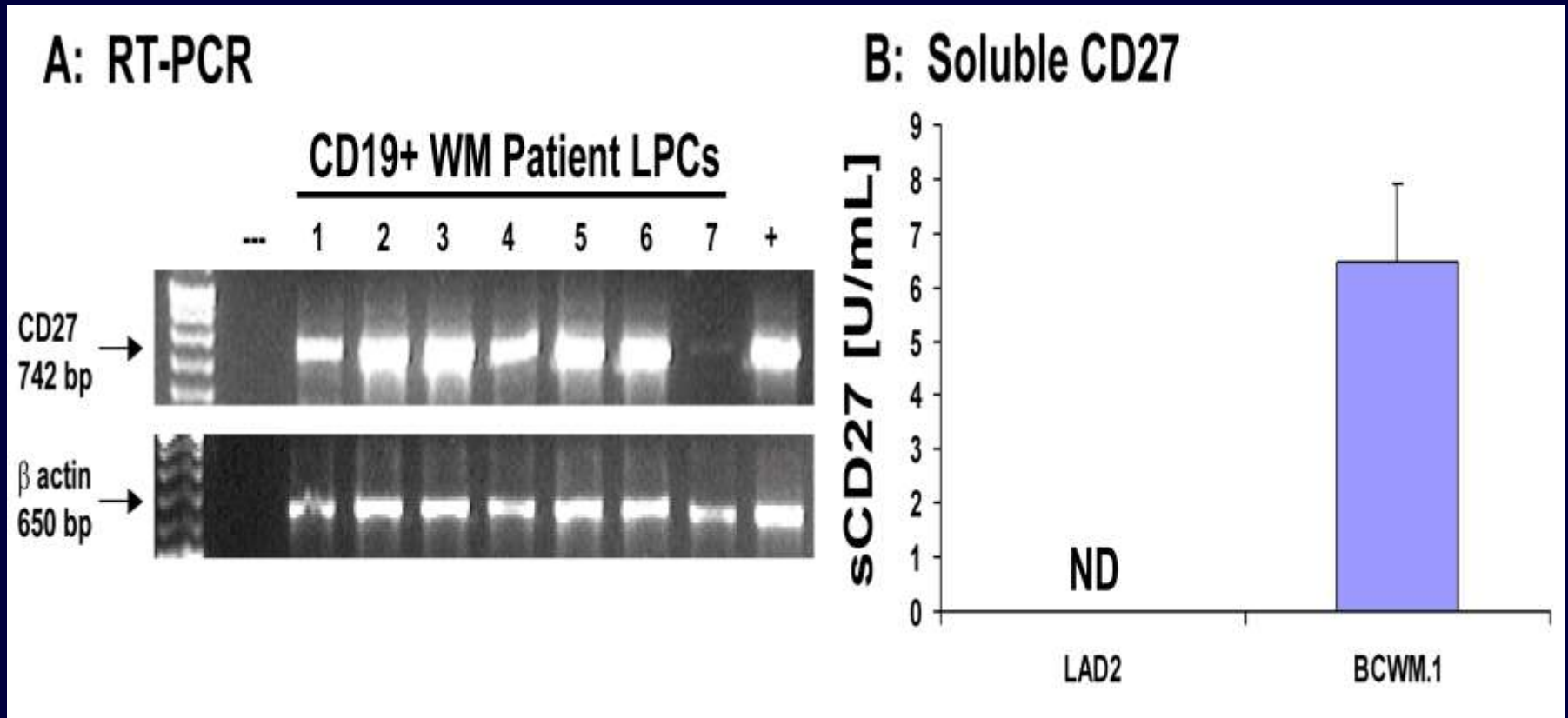
Mast Cells Induce Proliferation of WM Cells



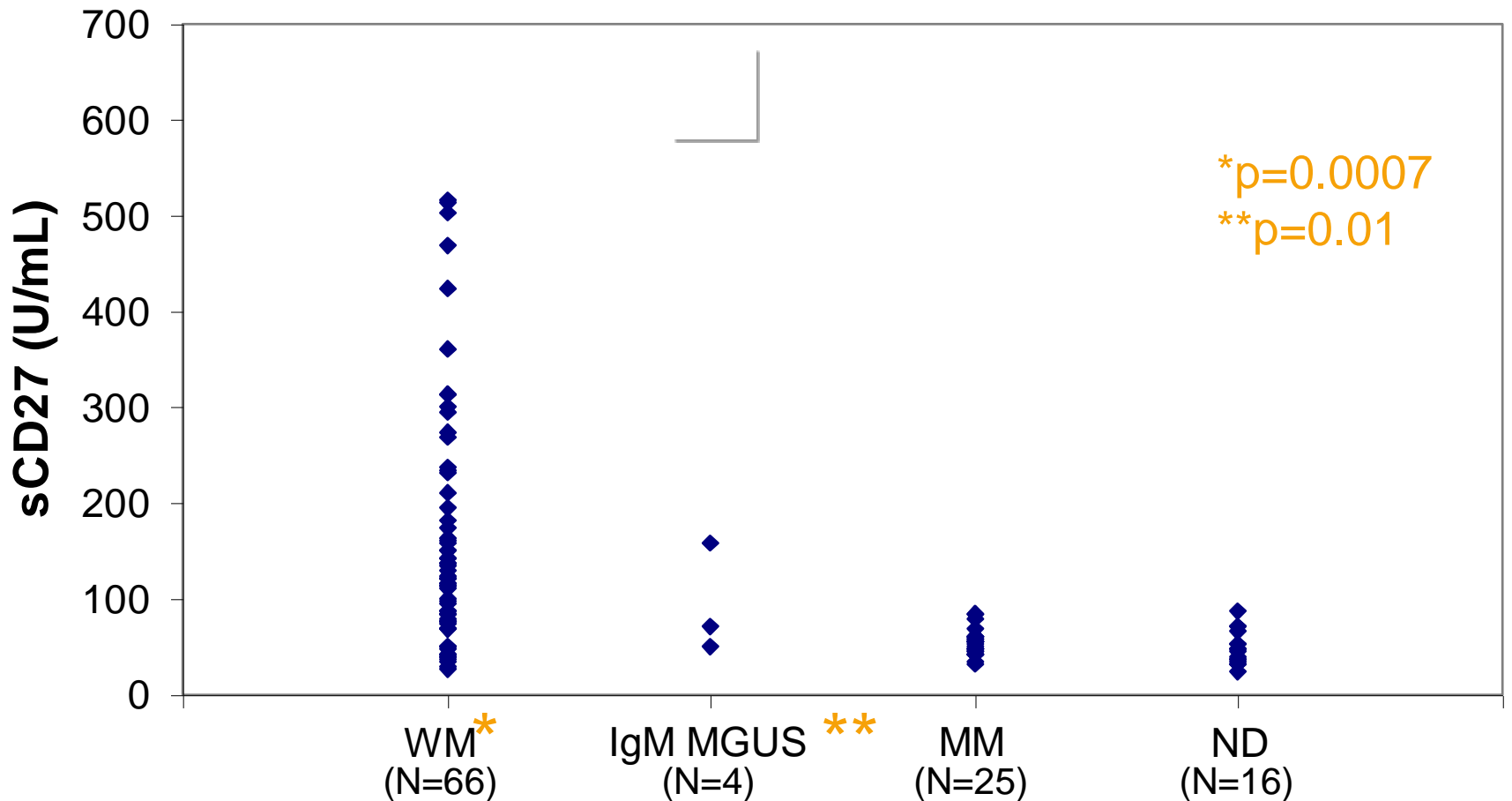
Mast Cell–Induced Proliferation of WM Cells Inhibited by Blocking CD40L



WM LPCs Express and Produce Soluble CD27

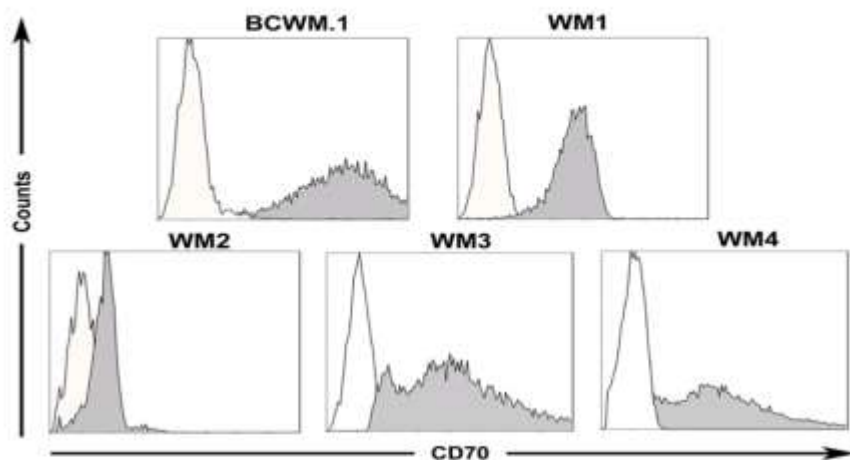


Soluble CD27 Levels are Elevated in WM

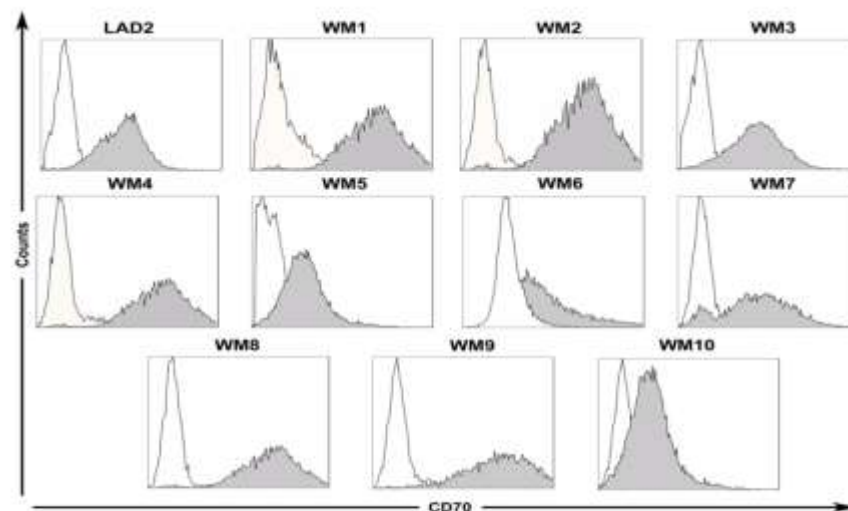


Expression of the CD27 Ligand (CD70) on WM Mast Cells by Flow Cytometric Analysis

A: WM Pt LPCs



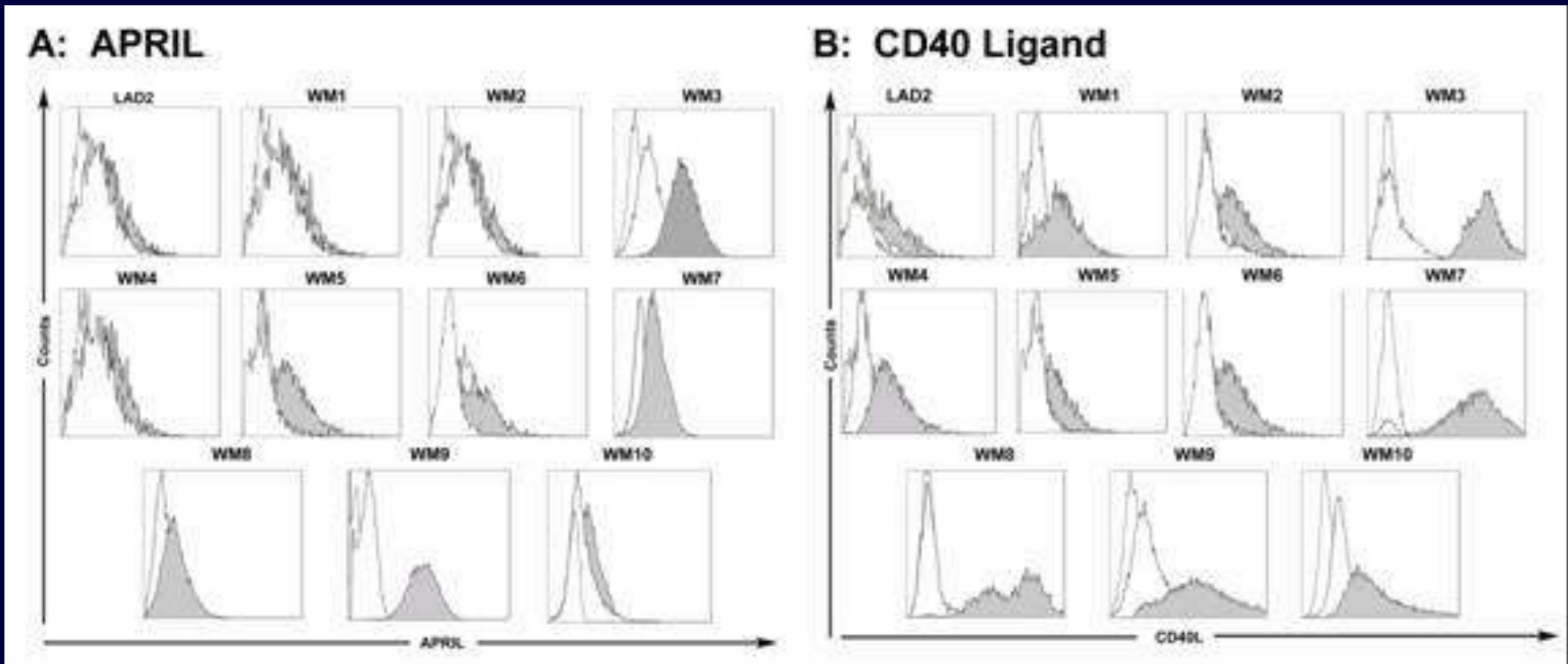
B: WM Pt Mast Cells



C: Expression of CD27 and CD70

	Flow Cytometry	
	WM	MC
CD27	5/12 (42%)	2/8 (25%)
CD70	6/6 (100%)	10/11 (91%)

sCD27 Induces Expression of APRIL and CD40L on WM Patient BM Mast Cells through CD70.

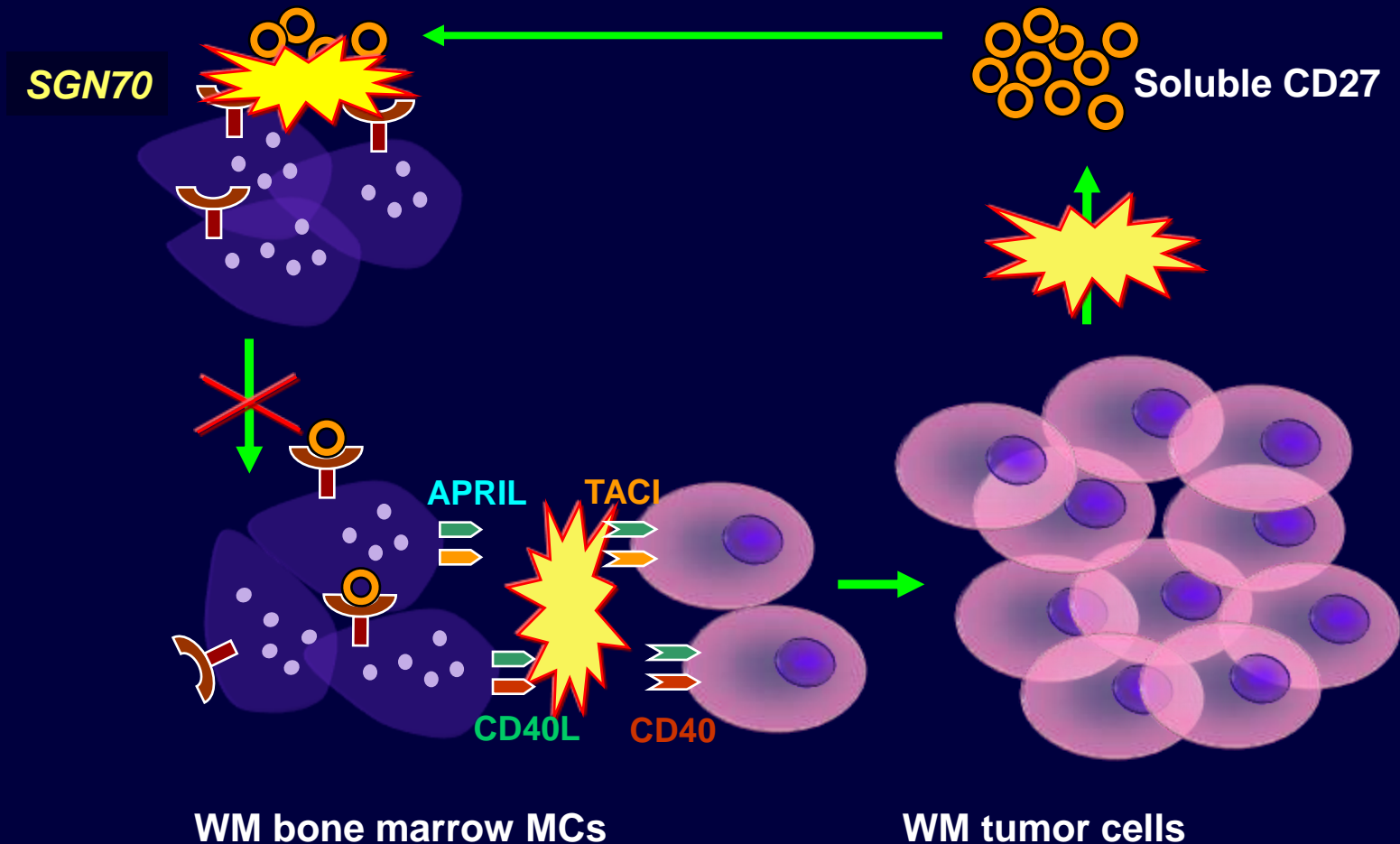


A. Baseline (dashed)

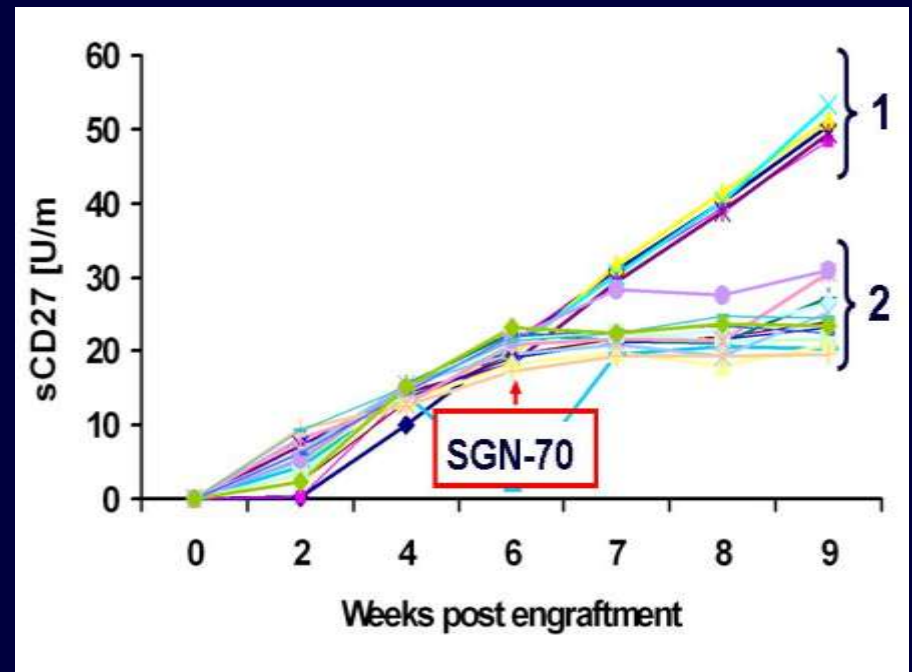
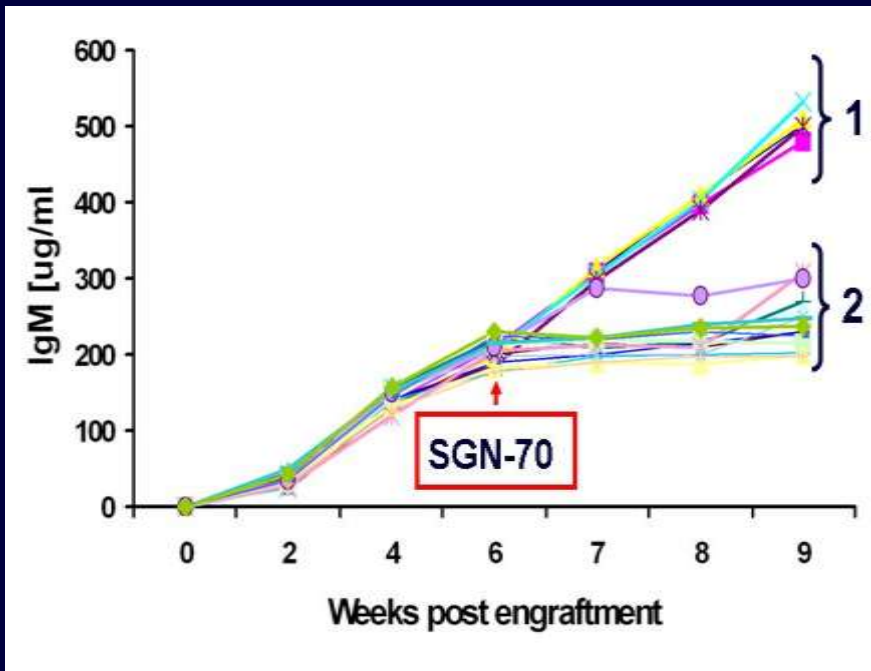
B. sCD27 (shaded)

C. sCD27 and SGN-70 mAb (solid)

WM-Mast Cell Interactions in Waldenstrom's Macroglobulinemia



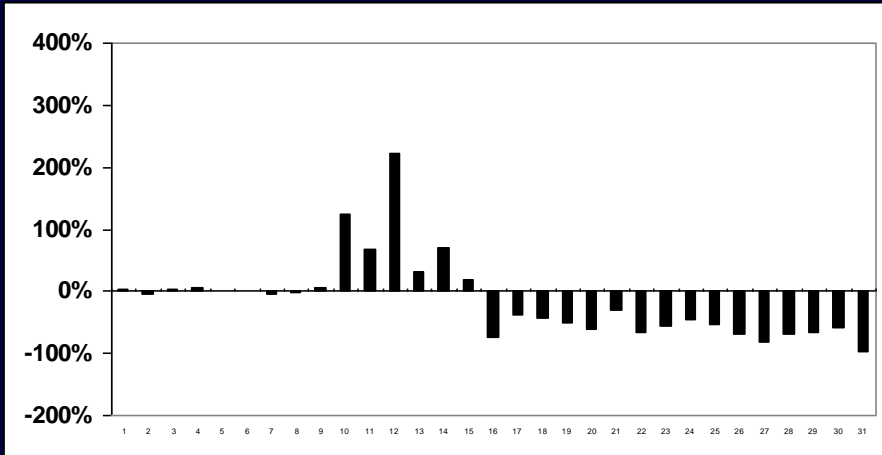
Human IgM and sCD27 after Engraftment and Treatment of BCWM.1 Bearing SCID-hu Mice with SGN-70.



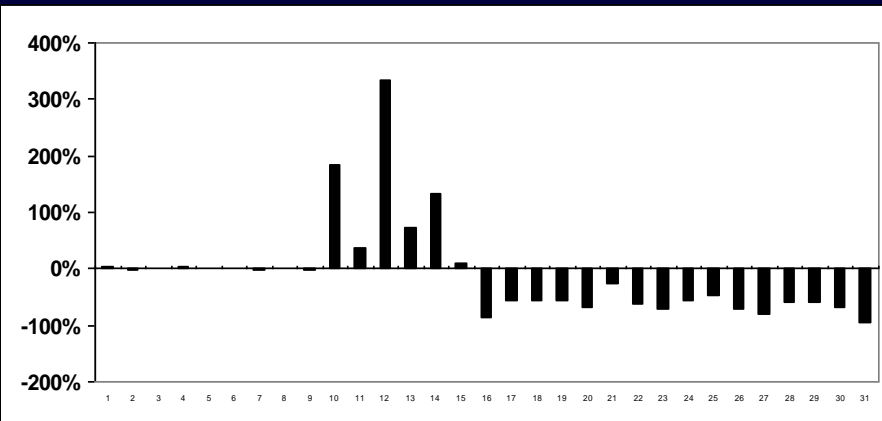
SCID, severe combined immunodeficiency
Ho AW, Blood 2008.

sCD27 is a Marker of Disease in WM

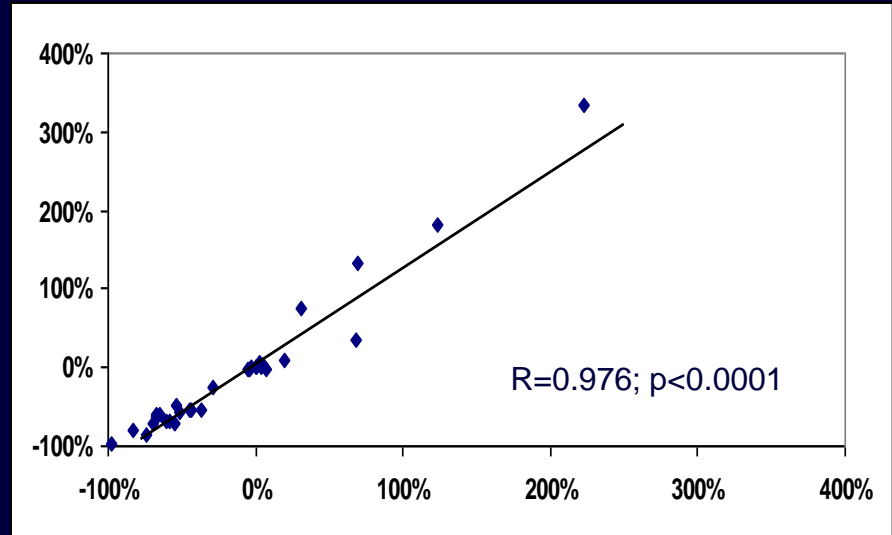
A. Serum sCD27 levels



B. Serum IgM levels

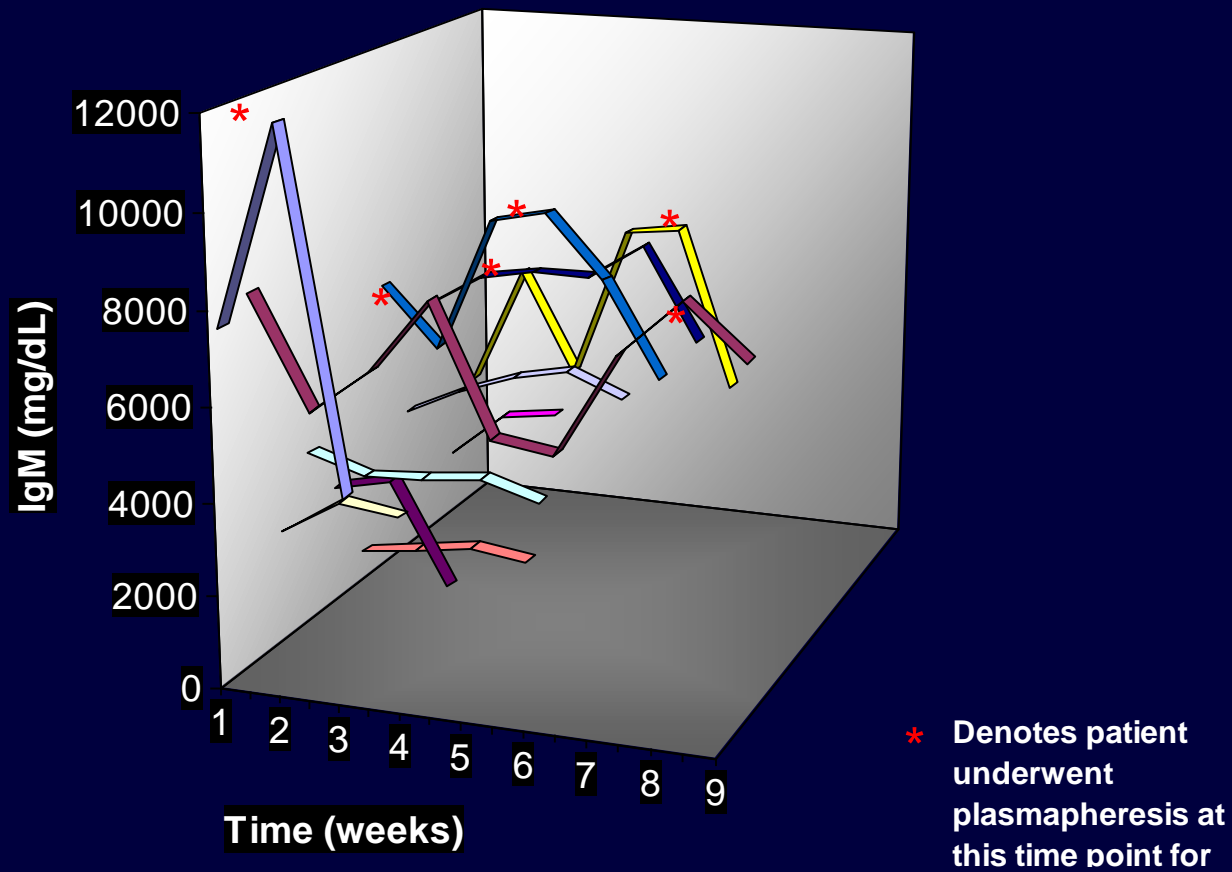


C. Correlative changes in sCD27 and IgM levels



Ho et al, ASCO 2006;
Ciccarelli et al, IWMW 2007

Serum IgM Levels Following Rituximab in Patients with WM.

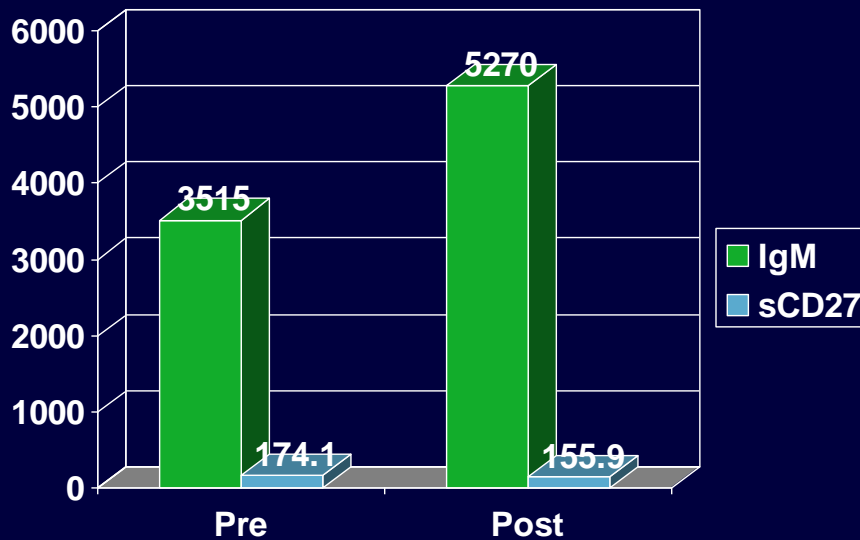


Rituximab Induced IgM Flare Occurs in Patients Receiving Combination Therapy.

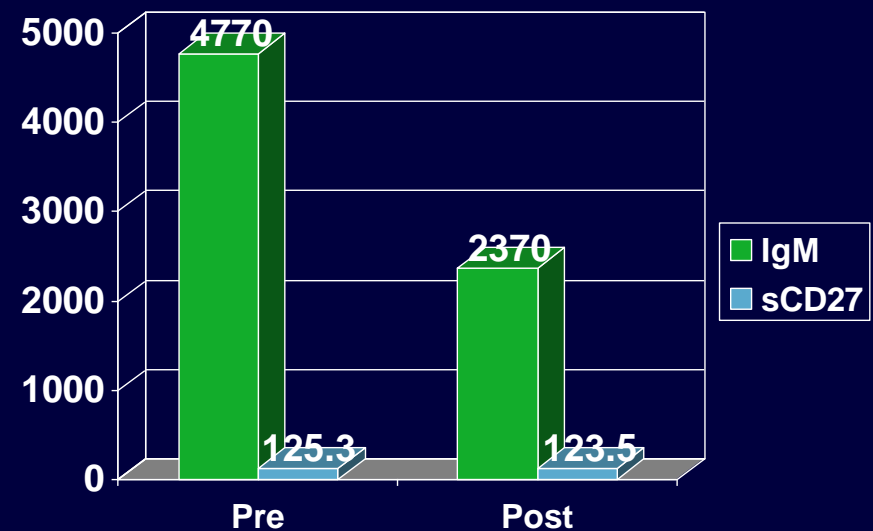
- Monotherapy (40-60%)
- Fludarabine/Rituximab (40%)
- Cyclophosphamide/Prednisone/Rituximab (25-30%)
- Thalidomide/Rituximab (50%)
- Lenalidomide/Rituximab (75%)
- Bortezomib/Dexamethasone/Rituximab (9%)

Treon et al, Ann Oncol 2004; Ghobrial et al, Cancer 2004; Nichols et al, ASH 2004; Ioakimidis et al, ASH 2008; Treon et al, Blood 2008; Treon et al, Clin Cancer Res 2008.

sCD27 is a Faithful Disease Marker and is Unaffected by Rituximab-induced IgM Flare or Plasmapheresis in WM



N= 8 WM patients who responded to rituximab based therapy after IgM flare



IgM and sCD27 levels in a WM pt pre- and 48 hrs post-PP

Concordance of sCD27 and Bone Marrow Findings in Patients Experiencing Rituximab Mediated IgM Flare

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Pre-Rituximab sIgM	1900	3520	3510	3460	2880	3880	3890	3560
Post-Rituximab sIgM	2340	4910	7340	3700	3430	5630	6900	7000
Pre-Rituximab sCD27	222	267	199	167	198	175	299	171
Post-Rituximab sCD27	174	171	153	158	160	147	127	120
Pre-Rituximab BMBx	50%	40%	30%	10%	5%	40%	40%	80%
Post-Rituximab BMBx	40%	30%	30%	NA	NA	NA	30%	70%

Concordance of sCD27 and Bone Marrow Findings in Patients Experiencing Plasmapheresis

	Patient 1	Patient 2	Patient 3
Pre-plasmapheresis sIgM	6380	6940	12300
Post-plasmapheresis sIgM	4770	3910	9380
Pre-plasmapheresis sCD27	125	117	73
Post-plasmapheresis sCD27	123	126	78
Base line of BMBx	30%	5%	40%

Conclusions

- **sCD27 is a TNF family member secreted by WM cells, and induces the expression of CD40L and APRIL on mast cells of WM patients.**
- **Elevated levels of sCD27 are present in sera of WM patients, and correlate strongly with serum IgM and changes in disease burden in patients as well as in a murine WM model.**
- **sCD27 more faithfully reflect disease burden in WM patients experiencing the rituximab mediated IgM spike/flare and possibly those patients undergoing plasmapheresis.**
- **These studies provide the framework for testing of soluble CD27 in prospective studies in patients with WM.**

Acknowledgements

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