Prospective, Multicenter Study of the MTOR inhibitor Everolimus (RAD001) as Primary Therapy in Waldenstrom's Macroglobulinemia.

Treon SP, Tripsas CK, Meid K, Patterson CJ, Heffner LT, Eradat H, Gregory S, Thomas S, Advani R, Baz R, Badros A, Matous J, Murphy TJ, Ghobrial IM.

Dana Farber Cancer Institute, Boston MA, USA; Winship Cancer Institute, Emory University Atlanta GA, USA; University of California, Los Angeles Medical Center, Los Angeles CA, USA; Rush University Medical Center, Chicago IL, USA; MD Anderson Cancer Center, Houston TX, USA; Stanford University Medical Center, Palo Alto CA, USA; H. Lee Moffitt Cancer Center, Tampa, FL, USA; University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA; Rocky Mountain Cancer Center, Denver CO, USA.

INTRODUCTION

Everolimus (RAD001) is an inhibitor of MTORC1, a component of the Akt-MTOR pathway which regulates growth and survival of lymphoplasmacytic cells in Waldenstrom's Macroglobulinemia (WM). Everolimus also exhibits activity in WM patients with relapsed/refractory disease (Ghobrial et al, JCO 2010; 28:1408-14). We therefore initiated this multicenter, prospective study to delineate the efficacy and tolerability of Everolimus as primary therapy in WM.

mTOR Pathway

PATIENTS AND METHODS

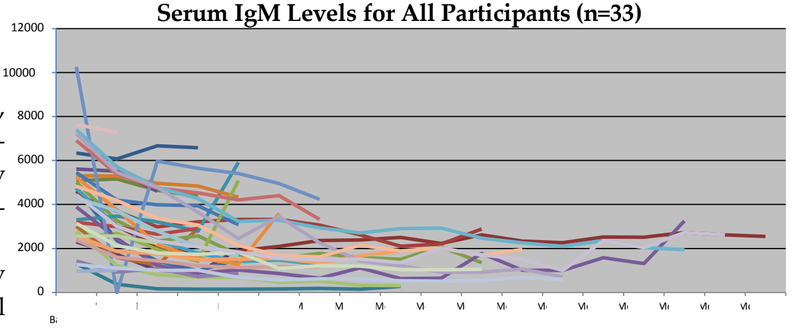
WM patients with symptomatic disease, adequate organ function, who were not previously treated, and who did not have symptomatic hyperviscosity were eligible for this study Intended therapy consisted of 10 mg of oral Everolimus administered daily with sequential dose de-escalation to 7.5 mg daily 5 mg daily and 5 mg every other day permitted for toxicity Patients were treated until progression or unacceptable toxicity Patients were encouraged to use 5 mL of an oral dexamethasone solution (0.5 mg/5mL) to swish and spit up to 4 times daily for prevention of oral ulcerations associated with Everolimus. Study participants were assessed monthly for the first 3 months, and thereafter every 3 months which included a physical examination, complete blood counts, chemistries, and serum IgM monitoring. Bone marrow biopsies and aspirations were performed at baseline, at months 3 - 6 and as required for response assessment.

Baseline and Post-Everolimus (Best Response) Characteristics

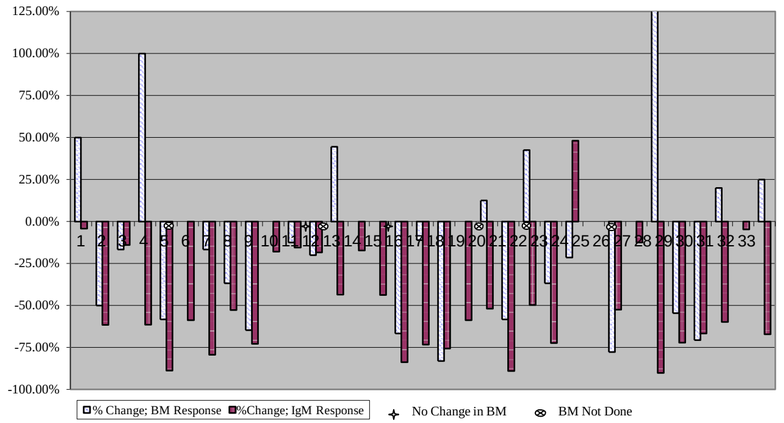
Characteristics	Baseline Median (range)	Post-Everolimus Median (range)
Age	62 years (41-80 years)	n/a
Hct $_{p}$=0.0015	31.3% (24.5-45.7%)	34.3 % (25.5.-46.7%)
Hgb $_{p}$=0.0017	10.8 g/dL (7.8-15.7 g/dL)	11.8 g/dL (8.7-15.5 g/dL)
Serum IgM*	4,440 mg/dL (959-10,256 mg/dL)	1360 mg/dL (146-7,280 mg/dL)
M-spike*	2.60 g/dL (0.31-5.31 g/dL)	0.93 g/dL (0- 4.31 g/dL)
B_2M	3.0 mg/L (1.6-6.7 mg/L)	n/a
BM involved p=0.0256	70% (1.65 -95%)	40% (0.75-100%)

*p-value<0.0001

Serum IgM Levels for All Participants (n=33)



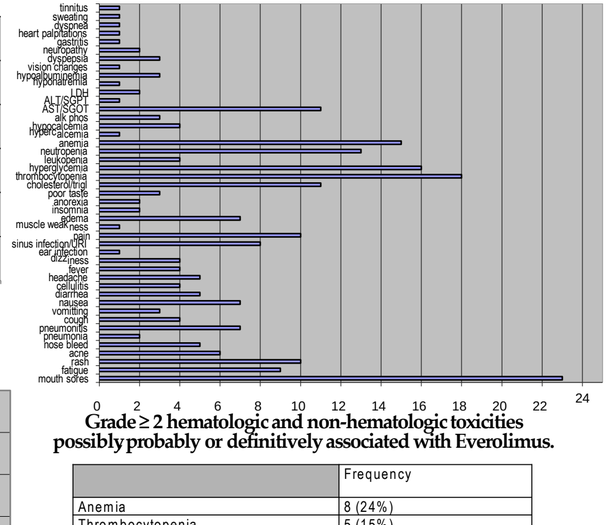
Best Bone Marrow Response vs. Serum IgM Response (n=33)



IgM and Bone Marrow Responses to Everolimus Therapy

	Overall response rate	Major response rate	VGPR	PR	MR	SD/PD
Serum IgM response (consensus criteria) (n=33)	72.7%	60.6%	1	19	4	11
Bone Marrow response (n=27)	40.7%	33.3%	0	9	2	16

Frequency of at Least Possibly Related Adverse Events, All Grades



Grade ≥ 2 hematologic and non-hematologic toxicities possibly probably or definitively associated with Everolimus.

	Frequency
Anemia	8 (24%)
Thrombocytopenia	5 (15%)
Neutropenia	5 (15%)
Hyperglycemia	2 (6%)
Oral ulcerations	7 (21%)
Pneumonitis	5 (15%)
Fatigue	4 (12%)
Rash	2 (6%)
Cellulitis	2 (6%)

CONCLUSIONS

- Everolimus is associated with rapid reductions of serum IgM levels in untreated WM patients.
- Both bone marrow and serum IgM reductions are seen following everolimus therapy in untreated WM patients, though common discordance of serum IgM to underlying bone marrow disease burden is common. Serial bone marrow assessments should be considered for more accurate response monitoring in WM patients receiving everolimus.
- With a median follow-up of 9 months (range 1-48 months), 6 patients continue on therapy without progression.
- Reasons for treatment discontinuation included non- response or disease progression (n=17), unacceptable toxicity (n=6, including 5 for pneumonitis and 1 for neutropenia), noncompliance (n=2), and loss of follow-up (n=2).