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

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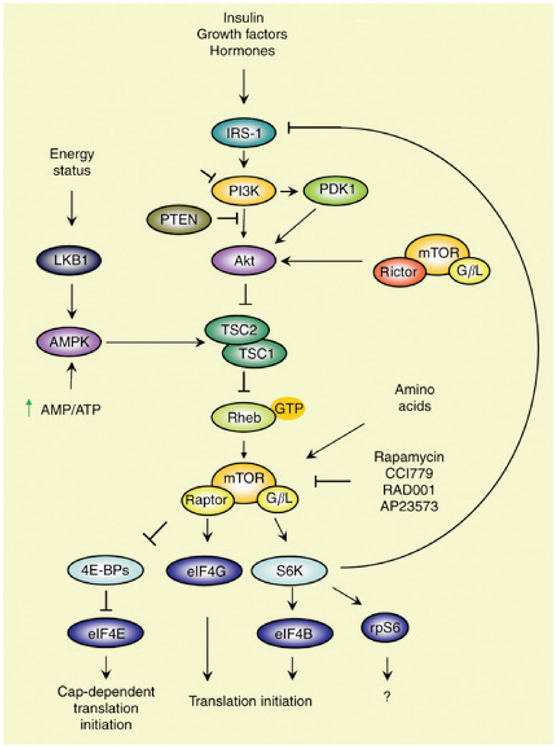
INTRODUCTION

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 6 and 12, and as required for response assessment.

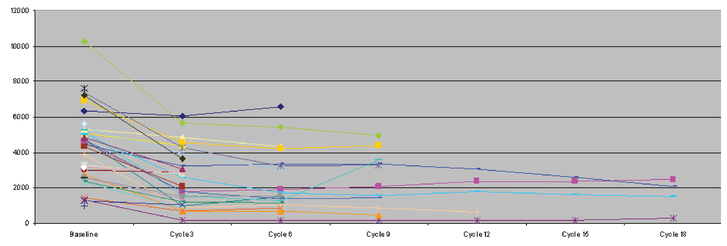
Baseline and Post-Everolimus Characteristics

Characteristics	Baseline Median (range)	Post-Everolimus Median (range)
Age	62 years (41-80 years)	n/a
Hematocrit*	31.3% (24.5-45.7%)	30.6% (20.2-35.8%)
Hemoglobin*	10.8 g/dL (7.8-15.7 g/dL)	10.4 g/dL (6.6-14.1 g/dL)
Serum IgM**	4,440 mg/dL (959-10,256 mg/dL)	1,925 mg/dL (146-7,280 mg/dL)
M-spike**	2.60 g/dL (0.31-5.31 g/dL)	1.50 g/dL (0.22-4.31 g/dL)
Beta 2 microglobulin	3.0 mg/L (1.6-6.7 mg/L)	n/a
Bone marrow involvement* (intertrabecular space)	70% (7.5-95%)	65% (10-95%)

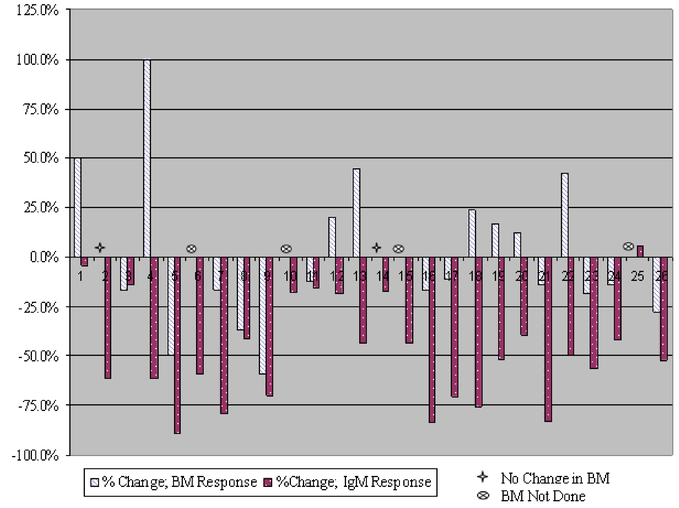
*p-value not statistically significant

**p-value<0.0001

Serum IgM Levels for All Participants (n=33)



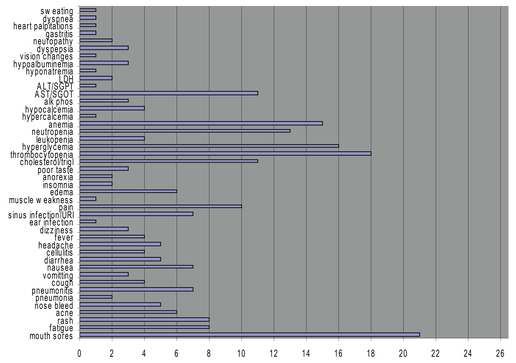
Bone Marrow Response vs. Serum IgM Response for Patients who Completed Cycle 6 (n=26)



IgM and Bone Marrow Responses to Everolimus Therapy

	Overall response rate	Major response rate	PR	MR	SD+PD
Serum IgM response (consensus criteria) (n=33)	**66.7%**	**42.4%**	**14**	**8**	**11**
Bone Marrow response (n=22)	**18.2%**	**9.0%**	**2**	**2**	**18**

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 observed in serum IgM levels in WM patients.
- Serum IgM discordance to underlying bone marrow disease burden is common, and serial bone marrow assessments are important for response monitoring in WM patients receiving Everolimus.
- With a median follow-up of 9 months (range 0-18 months), 15 patients remain on study.
- Reasons for study discontinuation included non-response or disease progression (n=11), unacceptable toxicity (n=6, including 5 for pneumonitis and 1 for neutropenia), and loss of follow-up (n=1).

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