2. S042 Synopsis

Clinical Study Report Synopsis: Study H6Q-MC-S042

Title of Study: An Open-Label, Multicenter, Phase 2 Study of Single-Agent Enzastaurin HCl in Previously Treated Waldenstrom's Macroglobulinemia or Multiple Myeloma

Number of Investigator(s): This multicenter study included 7 principal investigator(s).

Study Center(s): This study was conducted at 5 study center(s) in 2 countries.

Publication(s) Based on the Study:
Ghobrial IM, Moreau P, Harris B, Poon T, Jourdan E, Maisonneuve H, Benhadji KA, Hossain AM, Nguyen TS, Wooldridge JE, Leblond V. A multicenter phase II study of single-agent enzastaurin in previously treated Waldenstrom Macroglobulinemia. *Clin Cancer Res*. 2012;18(18):5043-5050.

Length of Study:	**Phase of Development:** 2
Date of first patient enrolled: 15 July 2008 Date of last patient completed: 22 August 2012 Date of final database lock: 2 October 2012	

Objectives:

Primary Objective:

To determine whether further study of single-agent enzastaurin is warranted in patients with previously treated Waldenstrom's macroglobulinemia (WM) or multiple myeloma (MM), based on response rate (RR).

Secondary Objectives:

- To estimate the RR in patients with previously treated WM and MM.
- To estimate the time to progression (TTP) in patients with either WM or MM treated with enzastaurin.
- To assess the safety of enzastaurin in WM and MM.
- To explore the impact of adding dexamethasone to enzastaurin in MM patients with progressive disease (PD).
- To assess exploratory biomarkers relevant to enzastaurin and disease state, and assess their relationship with clinical outcome.

Study Design: Study H6Q-MC-S042 (S042) was an open-label, multicenter, Phase 2 study in WM and MM patients previously treated with single-agent enzastaurin. Patients with MM were enrolled, analyzed, and reported separately from those with WM. A Simon 2-stage design (Simon 1989) was employed for this study, and the decision to proceed from Stage 1 to Stage 2 was assessed independently for each cohort. Patient enrollment for each cohort continued while the RR of Stage 1 patients was being determined. However, the decision whether to proceed into Stage 2 only included the first 10 WM patients and the first 9 MM patients; it did not include any additional patients enrolled beyond those required in Stage 1. Simon advancement criteria was solely determined based on best response to treatment with single-agent enzastaurin. If the minimum number of responders (minor response [MinR; for WM] or minimal response [MR; for MM], partial response [PR], or complete response [CR]; ≥MR), 2 for WM or 1 for MM, was not achieved in the first 10 and 9 patients, respectively, the sponsor was to terminate the respective cohort. If the minimum number of responders was reached, then additional patients were to be enrolled (19 for WM and 8 for MM). Up to 21 additional patients (WM cohort expansion) were to be enrolled into the WM cohort if a total of 6 responders (≥MR) out of the first 29 WM patients was observed at Stage 2 to assess further efficacy and safety profiles for planning future studies.

Number of Patients:

Planned: As few as 19 patients (10 WM, 9 MM) or as many as 67 patients (50 WM, 17 MM)
Enrolled: WM = 42 patients; MM = 14 patients
Treated (at least 1 dose): WM = 42 patients; MM = 14 patients

Approval Date: 11-Jan-2013 GMT

Diagnosis and Main Criteria for Inclusion:
Patients were at least 18 years of age and must have WM or MM previously treated with at least 1 and no more than 5 prior therapies and have Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1, or 2. Patients with a serious heart condition, such as myocardial infarction within the last 6 months, unstable angina, or Class III or IV congestive heart failure as defined by the New York Heart Association; have electrocardiogram (ECG) abnormalities including baseline 12-lead ECG with corrected QT interval of >450 msec in males or >470 msec in females; personal or family history of congenital long QT syndrome, or QRS duration of >100 msec were excluded.

Study Drug, Dose, and Mode of Administration:
Enzastaurin 375 mg orally (po) 3 times daily (TID) on Day 1 as a loading dose, followed by 250 mg po twice daily (BID) thereafter.
Only for Patients with PD (Enzastaurin + Dexamethasone):
Enzastaurin 250 mg po BID on Day 2 onwards and subsequent cycles
Dexamethasone 20-40 mg po once daily (QD) on Days 1–4, 9–12, and 17–20 of a 28-day Cycle 1 and thereafter, continued for 4 cycles. After 4 cycles, dexamethasone 20-40 mg po QD on Days 1-4.

Comparator, Dose, and Mode of Administration:
None.

Duration of Treatment:
Treatment with enzastaurin continued until disease progression, toxicity, or discontinuation from study treatment as listed in the protocol.

Variables:
This study contained 2 parallel cohorts, consisting of WM and MM patients. All analyses were done separately for the 2 cohorts, unless otherwise stated.
Efficacy and safety analyses were conducted on multiple populations. An enrolled patient was defined as one who had signed informed consent and received at least 1 dose of study drug. The full analysis set (FAS) included all enrolled patients who had received at least 1 dose of study drug. The FAS for enzastaurin (FAS-Enz) included data from all patients in the FAS, but only for the time at which they were on single-agent enzastaurin therapy. The FAS for enzastaurin plus dexamethasone (FAS-Dex) included data from all patients in the FAS, but only after they discontinued single-agent enzastaurin therapy and were receiving both enzastaurin and dexamethasone.
The translational research (TR) analyses were conducted on the TR set. This set consisted of enrolled patients who were in the FAS and had at least 1 TR sample for the marker of interest.

Efficacy:
Primary Efficacy:
Primary efficacy analysis for WM was to compute objective RR according to the International Workshop on Waldenstrom's Macroglobulinemia (IWWM) criteria for the FAS-Enz population. Frequencies and percentages of all IWWM response criteria were reported. Best response, as derived from investigator-reported by-cycle IWWM response was used. The primary efficacy analysis for MM was to compute the objective RR according to the European Group for Blood and Bone Marrow Transplant (EBMT) criteria for the FAS-Enz population. Frequencies and percentages of all EBMT response categories were reported. Best response, as derived from investigator-reported by-cycle EBMT response was used.

Secondary Efficacy:

Secondary analyses on RR for WM:

- Objective RR as per the IWWM criteria, based on the FAS population.
- Objective RR as per the IWWM criteria, based on the FAS-Dex population

Secondary analysis on TTP for WM:

- For WM patients, TTP was calculated using the first progression from single-agent enzastaurin as the observed event. The analyses were done for all 3 patients populations (FAS, FAS-Enz, and FAS-Dex).

Secondary analyses on RR for MM:

- Objective RR as per the EBMT criteria, based on the FAS-Dex population
- Objective RR as per the EBMT criteria, based on the FAS population.

Secondary analyses on TTP for MM patients:

- The first analysis applied the TTP definition, using the first progression from single-agent enzastaurin as the observed event. This analysis was performed for EBMT and used the FAS-Enz population.
- The second analysis applied the TTP definition only for patients participating in the combination phase, and used the reported progression from enzastaurin plus dexamethasone as the only observed event (that is, ignoring the initial progression from enzastaurin therapy). This analysis was performed for EBMT using the FAS-Dex population.
- The third analysis was based on the FAS population.

Exploratory analyses investigated testing for trends among the cross-tabulation of best responses within response criteria, across therapies. Repeated endpoint analyses may have be undertaken to assess the robustness of the TTP results.

Safety:

The safety parameters included summaries of the incidence of adverse event (AEs) by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0, National Cancer Institute [NCI] 2006) that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality. The safety-related outcomes that were summarized included incidence of AEs, extent of exposure to study drug treatment, frequency of deaths and serious adverse events (SAEs), discontinuations due to AEs, treatment-emergent adverse events (TEAEs), frequency of hospitalizations and transfusions, and usage frequency of key concomitant medications.

Translational Research Analyses

The TR analyses were conducted on the TR population. Separate datasets were used to conduct the analysis for the TR. Immunohistochemistry (IHC) H-scores were determined for secondary biomarkers membrane pGSK3β, nuclear pGSK3β, cytoplasmic pGSK3β, nuclear pCREB, membrane PKCβ2, nuclear PKCβ2, cytoplasmic PKCβ2, cytoplasmic pS6, membrane PTEN, cytoplasmic PTEN, and nuclear PTEN. Also, plasma samples were analyzed for the expression levels of various analytes using human multi-analyte profile v 1.6 technology developed at Rules-Based Medicine (RBM; Austin, TX). Due to the small number of available IHC samples, the TR analyses focused on correlating each of the RBM marker expressions with TTP and RR.

Statistical Evaluation Methods:

For the MM cohort, efficacy and safety analyses were conducted on the FAS. This set included all enrolled patients who have received at least 1 dose of enzastaurin.

For the WM cohort, 2 populations were considered: the original planned cohort (29 patients), which included all enrolled patients up to Stage 2, and the expanded cohort (up to 50 patients), which included all enrolled patients up to the expansion phase. Efficacy analyses were conducted on both the original planned cohort (29 patients) and the expanded cohort (up to 50 patients). Safety and TR analyses were conducted either on the expanded cohort (up to 50 patients) if the study proceeded to the expansion phase or on the original planned cohort (29 patients) if the study did not proceed to the expansion phase. Patient characteristics and concomitant medication were summarized for both the original planned cohort (29 patients) and the expanded cohort (up to 50 patients).

Efficacy:

A responder was defined as any patient who exhibits a CR, PR, or MR. The best response was the best investigator-assessed response. Response and disease progression was confirmed when possible.

The duration of response was defined as the elapsed time from the date when the measurement criteria are first met for a CR, PR, or MR (whichever status was recorded first, before confirmation) until the date of first observation of objective disease progression. Duration of response was only calculated for confirmed responding patients.

Analysis of duration of response was as follows:

- For responding patients who died without objective PD (including death from study disease), duration of response was censored at the date of the last objective progression-free disease assessment.
- For responding patients not known to have died as of the data cut-off date and who did not have objective PD, duration of response was censored at the date of the last objective progression-free disease assessment.
- For responding patients who received subsequent systemic anticancer therapy (after discontinuation from the study chemotherapy) prior to objectively determined disease progression, duration of response was censored at the date of the last objective progression-free disease assessment prior to postdiscontinuation therapy.

Additionally, collected data were used to reconstruct the recently released international uniform response criteria (Durie et al. 2006) after the completion of the trial. This would facilitate comparison to results from other studies using the new response criteria.

Time to progression (TTP) was defined as the elapsed time from the date of study enrollment to the date of objectively determined PD. Analysis of TTP was as follows:

- For patients who died without documented objective PD (including death from study disease), TTP was censored at the date of the last objective progression-free disease assessment.
- For patients not known to have died as of the data cut-off date and who did not have objective PD, TTP was to be censored at the date of the last objective progression-free disease assessment.
- For patients who received subsequent systemic anticancer therapy (after discontinuation from study treatment) prior to objectively determined disease progression, TTP was to be censored at the date of the last objective progression-free disease assessment prior to postdiscontinuation therapy.
- For patients who are enrolled but have no further response or progression data, TTP was to be taken as censored after 1 day.

Safety:
All patients in the FAS were used for safety analysis.
Safety analyses included summaries of the incidence of laboratory and non-laboratory AEs by CTCAE group, term and maximum CTCAE grade (Version 3.0) that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality. The safety parameters related to AEs included:

- Incidence of TEAEs
- SAEs
- Discontinuations due to SAEs or non-serious AEs
- Deaths
- Hospitalizations that occur within the study treatment period or within 30 days of the last dose of study treatment
- Transfusions and use of concomitant medications.

Summary:

Protocol Violations

Protocol violations included protocol inclusion/exclusion criteria violations reported in 3 (7.1%) patients in the WM cohort and 14 (100%) patients in the MM cohort. None were considered serious to affect the interpretation of the study results.

Patient Disposition, Baseline Demographics, and Characteristics

A total of 42 WM patients were enrolled and received the study drug and were included in the FAS population. A total of 14 MM patients were enrolled and received the study drug and were included in the FAS population. There were no screen failures in either group.

In the WM cohort (FAS population), of the 42 patients, 35 were male and 7 were female. The mean (standard deviation [SD]) age was 64.57 (8.53) years. The primary basis for the diagnosis of WM was histopathological for 38 patients, cytological for 3 patients, and biochemical assay (with radiologic imaging) for 1 patient. The Durie-Salmon Stage for diagnosis was not applicable for WM patients. In the WM cohort, 39 patients had an ECOG PS of 0, and 3 patients had an ECOG PS of 1. The mean (SD) time since the initial diagnosis was 87.30 (59.92) months and the mean (SD) time since the last prior systemic therapy was 17.33 (22.37) months.

In the MM cohort, of the 14 patients, 8 were male and 6 were female. The mean (SD) age was 73.28 (7.51) years. The primary basis for the diagnosis of MM was histopathological for 1 patient, cytological for 5 patients, and biochemical assay (with radiologic imaging) for 8 patients. At the time of diagnosis, 1 patient had Durie-Salmon Stage I, 1 patient had Stage II, 11 patients had Stage III, and 1 patient had unknown stage. In total, 6 patients had an ECOG PS of 0, 5 patients had an ECOG PS of 1, and 2 patients had an ECOG PS of 2. The mean (SD) time since the initial diagnosis was 76.29 (45.19) months and the mean (SD) time since the last prior systemic therapy was 11.56 (14.20) months.

Baseline demographics and characteristics for the WM and MM patients are summarized in Table S042.2.1.

Table S042.2.1. Baseline Demographics, and Characteristics (WM and MM Patients)

	WM Patients	MM Patients
	Overall (N=42)	Overall (N=14)
Patients entered, N	42	14
Patients enrolled (FAS Population), N	42	14
Sex		
Male, n (%)	35 (83.3)	8 (57.1)
Female, n (%)	7 (16.7)	6 (42.9)
Age (years)		
Mean (SD)	64.57 (8.53)	73.28 (7.51)
Primary basis for diagnosis		
Histopathological, n (%)	38 (90.5)	1 (7.1)
Cytological, n (%)	3 (7.1)	5 (35.7)
Biochemical assay (with radiologic imaging), n (%)	1 (2.4)	8 (57.1)
Durie-Salmon stage at diagnosis, n (%)	---	
Stage I, n (%)	---	1 (7.1)
Stage II, n (%)	---	1 (7.1)
Stage III, n (%)	---	11 (78.6)
Unknown	---	1 (7.1)
ECOG PS at study baseline		
0, n (%)	39 (92.9)	6 (42.9)
1, n (%)	3 (7.1)	5 (35.7)
2, n (%)	--	2 (14.3)
Time since initial diagnosis (months)		
Mean (SD)	87.30 (59.92)	76.29 (45.19)
Time since last prior systemic therapy (months)		
Mean (SD)	17.33 (22.37)	11.56 (14.20)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; MM = multiple myeloma; N = number of patients in FAS; n = number of patients with in each category; PS = performance status; SD = standard deviation; WM = Waldenstrom's macroglobulinemia.

Sources: smdema11, smdema15, fqbdca11, fqbdca15, smbsca11, smbsca15.

All WM and MM patients were enrolled after at least 1 prior systemic therapy. Patients may have received more than 1 prior therapy. Systemic therapy included palliative therapy, adjuvant therapy, and curative therapy. The patient data on prior systemic therapy for the WM and MM patients are summarized in Table S042.2.2.

Table S042.2.2. Summary of Reported Prior Therapies and Transfusion (WM and MM Patients)

	WM Patients (N=42) N (%)	MM Patients (N=14) N (%)
Prior therapy		
Patients with prior surgery	0 (0.0)	0 (0.0)
Palliative	0 (0.0)	0 (0.0)
Curative	0 (0.0)	0 (0.0)
Patients with prior radiotherapy	0 (0.0)	4 (28.6)
Adjuvant/curative	0 (0.0)	3 (21.4)
Palliative	0 (0.0)	1 (7.1)
Patients with prior systemic therapy	42 (100.0)	14 (100.0)
Palliative	0 (0.0)	2 (14.3)
Adjuvant	0 (0.0)	1 (7.1)
Curative	42 (100.0)	12 (85.7)
Stem cell transplantation - autologous	0 (0.0)	0 (0.0)
Patients with prior systemic regimens	42 (100.0)	14 (100.0)
None	0 (0.0)	0 (0.0)
One regimen only	11 (26.2)	2 (14.3)
Two regimens only	17 (40.5)	3 (21.4)
Three or more regimens	14 (33.3)	9 (64.3)
Total number of patients with ≥1 transfusion[a]	7 (16.7)	7 (50.0)

Abbreviations: FAS = full analysis set; MM = multiple myeloma; N = number of patients in FAS; WM = Waldenstrom's macroglobulinemia.

Note: Patients may have been subject to more than 1 type of prior therapy. Prior therapies refer to therapies received before enrollment in the study (not including up to dexamethasone phase).

[a] Number of patients in FAS.

Sources: fqptxa11, fqptxa15, smtraa11, smtraa15.

Efficacy

All efficacy analyses were performed on the enrolled populations of 42 patients (WM cohort) and 14 patients (MM cohort) (FAS population).

Primary Analysis – Objective RR

A summary of the best response by IWWM (WM Patients) (FAS-WM) and EBMT (MM Patients) and is presented in Table S042.2.3.

In the WM cohort, the overall RR (CR+PR+MinR) was 38.1% (95% confidence interval [CI]: 23.4, 52.8). The objective RR (CR+PR) was 4.8% (95% CI: 0.0, 11.2). The overall RR (CR+PR+MinR) in the WM-FAS-Enz population and WM-FAS-Dex population was 33.3% (95% CI: 19.1, 47.6) and 28.6% (95% CI: 0.0, 62.0), respectively. No patients had a CR. Overall, 2 (4.8%) patients, both of whom were treated with enzastaurin alone, experienced PR; in both treatment populations, 14 (33.3%) patients each experienced MinR and stable disease, 3 (7.1%) patients experienced PD, and response was unknown in 9 (21.4%) patients.

In the MM cohort, the overall RR (CR+PR+MR) was 7.1% (95% CI: 0.0, 20.6). The overall RR (CR+PR+MR) in the MM-FAS-Dex population was 9.1% (95% CI: 0.0, 26.1). No patients had a CR or PR. Overall, 1 (7.1%) patient experienced MR, 4 (28.6%) patients experienced stable disease, 6 (42.9%) patients experienced PD, and response was unknown in 3 (21.4%) patients.

Table S042.2.3. Summary of Best Response by IWWM (WM Patients) and EBMT (MM Patients) (FAS WM)

	WM Patients			MM Patients		
	ENZ (N=42)[a]	ENZ+DEX (N=7)[b]	Overall (N=42)[c]	ENZ (N=12)[a]	ENZ+DEX (N=11)[b]	Overall (N=14)[c]
CR, n %	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR, n %	2 (4.8)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
MinR, n %	12 (28.6)	2 (28.6)	14 (33.3)	N/A	N/A	N/A
MR, n %	N/A	N/A	N/A	0 (0.0)	1 (9.1)	1 (7.1)
SD or no change, n %	16 (38.1)	0 (0.0)	14 (33.3)	5 (41.7)	1 (9.1)	4 (28.6)
PD, n %	2 (4.8)	2 (28.6)	3 (7.1)	2 (16.7)	3 (27.3)	6 (42.9)
Unknown, n %	10 (23.8)	3 (42.9)	9 (21.4)	5 (41.7)	6 (54.5)	3 (21.4)
Total evaluable, n %	42 (100.0)	7 (100.0)	42 (100.0)	12 (100.0)	11 (100.0)	14 (100.0)
Not evaluable, n %	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complete RR (CR), n %	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
(95% CI)[d]	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Objective RR (CR+PR), n %	2 (4.8)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
(95% CI)[d]	(0.0, 11.2)	(0.0, 0.0)	(0.0, 11.2)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Overall RR (CR+PR+MR), n %	14 (33.3)	2 (28.6)	16 (38.1)	0 (0.0)	1 (9.1)	1 (7.1)
(95% CI)[d]	(19.1, 47.6)	(0.0, 62.0)	(23.4, 52.8)	(0.0, 0.0)	(0.0, 26.1)	(0.0, 20.6)

Abbreviations: CI = confidence interval; CR = complete response; DEX = dexamethasone; EBMT = European Group for Blood and Bone Marrow Transplant; ENZ = enzastaurin; FAS = full analysis set; FAS-Dex = FAS for enzastaurin plus dexamethasone; FAS-Enz = FAS for enzastaurin; IWWM = International Workshop on Waldenstrom's Macroglobulinemia; MM = multiple myeloma; MinR = minor response; MR = minimal response; N = total number of subjects who received that treatment; n = number of patients with given response; N/A = not applicable; PD = progressive disease; PR = partial response; RR = response rate; SD = standard deviation; WM = Waldenstrom's macroglobulinemia.

[a] Number of patients in FAS-Enz.

[b] Number of patients in FAS-Dex.

[c] Number of patients in FAS.

[d] Confidence intervals for RRs are calculated by the normal approximation method for proportions (Leemis and Trivedi 1996).

Sources: fqresa11, fqresa15.

Duration of Overall Response

In the WM cohort (FAS population), 3 patients (18.8%) had measured events and 13 patients (81.3%) were censored. Median DoR is not estimable due to high censoring.

A summary of the Kaplan-Meier analysis of the duration of overall response by IWWM (CR, PR, or MinR) for the WM cohort FAS population is shown in Table S042.2.4.

In the MM cohort (FAS population), no patients had a measured event and 1 patient (100.0%) was censored.

Table S042.2.4. Summary of Kaplan-Meier Analysis of Duration of Response by IWWM (CR, PR, or MinR) (WM Patients)

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Kaplan-Meier Analysis of Duration of Overall Response by IWWM (MR, PR or CR) (WM Patient) Page 1 of 1
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Parameter	Overall (N=16)
Number (%) of Patients with Events	3 (18.8)
Number (%) of Patients Censored	13 (81.3)
Observed range (min, max)	(3.71, 38.37)
25th Percentile (95% CI)	19.32 (17.71, N/A)
Median (95% CI)	N/A (17.87, N/A)
75th Percentile (95% CI)	N/A
Rate of Duration of Response:	
3-month (95% CI)	1.00 (N/A, N/A)
Patients at risk	16
6-month (95% CI)	1.00 (N/A, N/A)
Patients at risk	13
9-month (95% CI)	1.00 (N/A, N/A)
Patients at risk	11
12-month (95% CI)	1.00 (N/A, N/A)
Patients at risk	9
18-month (95% CI)	0.76 (0.33, 0.94)
Patients at risk	6

Abbreviations: CI = confidence interval; CR = complete response; FAS = Full Analysis Set; IWWM=International Workshop on Waldenstrom's Macroglobulinemia; MR = minimal response; N = total number of subjects; PR = partial response; WM = Waldenstrom's Macroglobulinemia.

Time to Progression (TTP)

In the WM cohort (FAS population), 9 patients (21.4%) had a measured event and 33 patients (78.6%) were censored. The median TTP was 27.73 months (95% CI: 20.47, N/A). A summary of the Kaplan-Meier analysis of the TTP by IWWM for the WM cohort FAS population is shown in Table S042.2.5.

In the MM cohort (FAS population), 7 patients (50.0%) had a measured event and 7 patients (50.0%) were censored. The median TTP was 5.11 (95% CI: 2.86, N/A) months. A summary of the Kaplan-Meier analysis of the TTP by EMBT for the MM cohort FAS population is shown in Table S042.2.6.

Table S042.2.5. Summary of Kaplan-Meier Analysis of Time to Progression by IWWM (WM Patients)

Kaplan-Meier Analysis of Time to Progression by IWWM (WM Patient) Page 1 of 1
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Parameter	Overall (N=42)
Number (%) of Patients with Events	9 (21.4)
Number (%) of Patients Censored	33 (78.6)
Observed range (min, max)	(1.05, 40.51)
25th Percentile (95% CI)	18.89 (10.15, 27.73)
Median (95% CI)	27.73 (20.47, N/A)
75th Percentile (95% CI)	N/A
Rate of being progression-free for at least:	
3-month (95% CI)	0.95 (0.81, 0.99)
Patients at risk	35
6-month (95% CI)	0.92 (0.76, 0.97)
Patients at risk	27
9-month (95% CI)	0.92 (0.76, 0.97)
Patients at risk	18
12-month (95% CI)	0.86 (0.66, 0.95)
Patients at risk	13
18-month (95% CI)	0.79 (0.53, 0.92)
Patients at risk	11
21-month (95% CI)	0.65 (0.37, 0.83)
Patients at risk	9
24-month (95% CI)	0.58 (0.30, 0.78)
Patients at risk	8

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; N = total number of subjects; IWWM=International Workshop on Waldenstrom's Macroglobulinemia; WM = Waldenstrom's Macroglobulinemia.

[redacted]

Table S042.2.6. Summary of Kaplan-Meier Analysis of Time to Progression by EBMT (MM Patients)

Kaplan-Meier Analysis of Time to Progression by EBMT (MM Patients) Page 1 of 1
FAS-MM 13:27 16OCT2012
H6Q-MC-S042 PDPM

Parameter	Overall (N=14)
Number (%) of Patients with Events	7 (50.0)
Number (%) of Patients Censored	7 (50.0)
Observed range (min, max)	(0.13, 25.33)
25th Percentile (95% CI)	2.43 (1.94, 5.62)
Median (95% CI)	5.11 (2.86, N/A)
75th Percentile (95% CI)	N/A
Rate of being progression-free for at least:	
3-month (95% CI)	0.67 (0.34, 0.86)
Patients at risk	8
6-month (95% CI)	0.42 (0.15, 0.67)
Patients at risk	4
9-month (95% CI)	0.42 (0.15, 0.67)
Patients at risk	2
12-month (95% CI)	0.42 (0.15, 0.67)
Patients at risk	2
18-month (95% CI)	0.42 (0.15, 0.67)
Patients at risk	1
21-month (95% CI)	0.42 (0.15, 0.67)
Patients at risk	1
24-month (95% CI)	0.42 (0.15, 0.67)
Patients at risk	1

Abbreviations: CI = confidence interval; EBMT = European Group for Blood and Bone Marrow Transplant; FAS = Full Analysis Set; MM = Multiple Myeloma; N = total number of subjects.

[redacted]

Time to Progression (TTP) With and Without Confirmation by IWWM

In the WM cohort (FAS-Enz population), 25 patients (59.5%) had measured events and 17 patients (40.5%) were censored. Based on investigator-assessed PD (with and without confirmation), the median TTP was 12.88 (95% CI: 9.46, 20.47) months with a 12-month progression-free rate of 51% (95% CI: 32%, 67%) and a 24-month progression-free rate of 21% (95% CI: 8%, 39%).

A summary of the Kaplan-Meier analysis of the TTP with and without confirmation by IWWM is shown in Table S042.2.7.

Table S042.2.7. Summary of Kaplan-Meier Analysis of Time to Progression by IWWM (WM Patients)

Kaplan-Meier Analysis of Time to Progression With and Without Confirmation by IWWM (WM Patient) Page 1 of 1
FAS-WM-Enz 11:34 16OCT2012
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Parameter	(N=42)
Number (%) of Patients with Events	25 (59.5)
Number (%) of Patients Censored	17 (40.5)
Observed range (min, max)	(0.03, 40.18)
25th Percentile (95% CI)	6.24 (3.71, 10.91)
Median (95% CI)	12.88 (9.46, 20.47)
75th Percentile (95% CI)	22.14 (15.21, 40.18)
Rate of being progression-free for at least:	
3-month (95% CI)	0.90 (0.76, 0.96)
Patients at risk	35
6-month (95% CI)	0.77 (0.60, 0.87)
Patients at risk	25
9-month (95% CI)	0.67 (0.49, 0.80)
Patients at risk	17
12-month (95% CI)	0.51 (0.32, 0.67)
Patients at risk	12
18-month (95% CI)	0.38 (0.20, 0.56)
Patients at risk	9
21-month (95% CI)	0.30 (0.14, 0.48)
Patients at risk	7
24-month (95% CI)	0.21 (0.08, 0.39)
Patients at risk	5

Abbreviations: CI = confidence interval; CR = complete response; FAS = Full Analysis Set; IWWM=International Workshop on Waldenstrom's Macroglobulinemia; MR = minimal response; N = total number of subjects; PR = partial response; WM = Waldenstrom's Macroglobulinemia.

[redacted]

Safety

All safety analyses were performed on all patients who received at least 1 dose of study drug.

In the WM cohort, overall, 42 patients (100.0%) experienced at least 1 TEAE regardless of study drug causality, and 24 patients (57.1%) experienced a possibly study drug-related TEAE. Nine patients (21.4%) experienced SAEs regardless of study drug causality, and 2 patients (4.8%) experienced a possibly study drug-related SAE. One patient (2.4%) discontinued due to a possibly study drug-related SAE (septic shock). One patient (2.4%) discontinued due to a non-serious AE (anemia). One patient (2.4%) died while on therapy due to an AE (septic shock). One patient (2.4%) died due to study disease within 30 days of discontinuation. Four patients (9.5%) died due to study disease outside 30 days of discontinuation. An overview of AEs for the WM patients is presented in Table S042.2.8.

In the MM cohort, overall, 12 patients (85.7%) experienced at least 1 TEAE regardless of study drug causality, and 6 patients (42.9%) experienced possibly study drug-related TEAEs. Four patients (28.6%) experienced SAEs regardless of study drug causality, and 1 patient (7.1%) experienced a possibly study drug-related SAE (cardiac failure). One patient (7.1%) discontinued due to an SAE (cardiac failure). Two patients (14.3%) discontinued due to a nonserious AE (ECG QT prolonged, thrombocytopenia). Three patients (21.4%) died while on therapy, including 2 patients who died due to study disease and 1 patient who died due to an AE (cardiac failure) that was not study drug-related. One patient died within 30 days of discontinuation due to an AE (general physical health deterioration) that was not study drug-related. Also, 1 patient died due to an AE outside 30 days of discontinuation.

An overview of AEs for the MM patients is presented in Table S042.2.9.

Table S042.2.8. Overview of Adverse Events (WM Patients)

Overview of Adverse Events (WM Patient) Page 1 of 2
FAS-WM 12:26 16OCT2012
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	WM		
	ENZ (N=42) [2]	ENZ+DEX (N=7) [3]	Overall (N=42) [4]
Adverse Event [1]	n (%)	n (%)	n (%)
Patients with Treatment emergent adverse events (TEAE)	42(100.0)	7(100.0)	42(100.0)
Possibly Related to Study Drug	20 (47.6)	4 (57.1)	24 (57.1)
Patients with Serious adverse events (SAE)	7 (16.7)	4 (57.1)	9 (21.4)
Possibly Related to Study Drug	0 (0.0)	2 (28.6)	2 (4.8)
Patients with Serious, unexpected, reportable events (SUR)	0 (0.0)	0 (0.0)	0 (0.0)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
Patients with Discontinuation due to serious adverse events (SAE)	0 (0.0)	1 (14.3)	1 (2.4)
Possibly Related to Study Drug	0 (0.0)	1 (14.3)	1 (2.4)
Patients with Discontinuation due to non-serious adverse events	1 (2.4)	0 (0.0)	1 (2.4)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
Deaths on therapy	0 (0.0)	1 (14.3)	1 (2.4)
Possibly Related to Study Drug	0 (0.0)	1 (14.3)	1 (2.4)
Deaths within 30 days of discontinuation	1 (2.4)	0 (0.0)	1 (2.4)

Abbreviations: FAS = Full Analysis Set; N = total number of subjects who received that treatment; n = number of patients in specified category; WM = Waldenstrom's Macroglobulinemia.

[1] Patients may be counted in more than one category.
[2] N = Number of patients in FAS-Enz
[3] N = Number of patients in FAS-Dex
[4] N = Number of patients in FAS
MedDRA Version 15.0

Overview of Adverse Events (WM Patient) Page 2 of 2
FAS-WM 12:26 16OCT2012
H6Q-MC-S042 PDPM

Adverse Event [1]	WM ENZ (N=42) [2] n (%)	WM ENZ+DEX (N=7) [3] n (%)	WM Overall (N=42) [4] n (%)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: FAS = Full Analysis Set; N = total number of subjects who received that treatment; n = number of patients in specified category; WM = Waldenstrom's Macroglobulinemia.

[1] Patients may be counted in more than one category.
[2] N = Number of patients in FAS-Enz
[3] N = Number of patients in FAS-Dex
[4] N = Number of patients in FAS
MedDRA Version 15.0

[redacted]

Table S042.2.9. Overview of Adverse Events (MM Patients)

Overview of Adverse Events (MM Patient) Page 1 of 2
FAS-MM 12:26 16OCT2012
H6Q-MC-S042 PDPM

	MM		
	ENZ (N=12) [2]	ENZ+DEX (N=11) [3]	Overall (N=14) [4]
Adverse Event [1]	n (%)	n (%)	n (%)
Patients with Treatment emergent adverse events (TEAE)	11 (91.7)	9 (81.8)	12 (85.7)
Possibly Related to Study Drug	6 (50.0)	2 (18.2)	6 (42.9)
Patients with Serious adverse events (SAE)	1 (8.3)	4 (36.4)	4 (28.6)
Possibly Related to Study Drug	1 (8.3)	1 (9.1)	1 (7.1)
Patients with Serious, unexpected, reportable events (SUR)	0 (0.0)	0 (0.0)	0 (0.0)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
Patients with Discontinuation due to serious adverse events (SAE)	0 (0.0)	1 (9.1)	1 (7.1)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
Patients with Discontinuation due to non-serious adverse events	1 (8.3)	1 (9.1)	2 (14.3)
Possibly Related to Study Drug	1 (8.3)	0 (0.0)	1 (7.1)
Deaths on therapy	0 (0.0)	3 (27.3)	3 (21.4)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
Deaths within 30 days of discontinuation	0 (0.0)	1 (9.1)	1 (7.1)

Abbreviations: FAS = Full Analysis Set; MM = Multiple Myeloma; N = total number of subjects who received that treatment; n = number of patients in specified category.

[1] Patients may be counted in more than one category.
[2] N = Number of patients in FAS-Enz
[3] N = Number of patients in FAS-Dex
[4] N = Number of patients in FAS
MedDRA Version 15.0

Overview of Adverse Events (MM Patient) Page 2 of 2
FAS-MM 12:26 16OCT2012
H6Q-MC-S042 PDPM

	MM		
	ENZ (N=12) [2]	ENZ+DEX (N=11) [3]	Overall (N=14) [4]
Adverse Event [1]	n (%)	n (%)	n (%)
Possibly Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: FAS = Full Analysis Set; MM = Multiple Myeloma; N = total number of subjects who received that treatment; n = number of patients in specified category.

[1] Patients may be counted in more than one category.
[2] N = Number of patients in FAS-Enz
[3] N = Number of patients in FAS-Dex
[4] N = Number of patients in FAS
MedDRA Version 15.0

[redacted]

Translational Research Analysis

Sample Collection

A summary of sample collection for the FAS population is presented in Table S042.2.10.

Overall, in the WM cohort (FAS population), RBM data were reported for 28 patients; 17 patients had baseline RBM data available, 20 patients had post-baseline RBM data available, and 9 patients had both baseline and post-baseline RBM data. One patient had baseline IHC data available.

Overall, in the MM cohort (FAS population), RBM data were reported for 13 patients; 12 patients had baseline RBM data available, 6 patients had post-baseline RBM data available, and 5 patients had both baseline and post-baseline RBM data available. Three patients had baseline IHC data available.

Patient Demographics and Baseline Characteristics

A summary of patient demographics and baseline characteristics by cohort for the TR population is presented in Table S042.2.11.

Overall, in the WM cohort (TR population), of the 28 patients, 24 were male and 4 were female. A total of 27 patients (96.43%) were Caucasian. Overall, the mean (SD) age was 64.3 (9.2) years. Twenty-four patients (85.7%) received prior rituximab therapy. The number of prior systemic regimens received by patients was as follows: 1 regimen only, 3 patients (10.71%); 2 regimens only, 7 patients (25.0%); and 3 regimens only, 18 patients (64.29%).

Overall, in the MM cohort (TR population), of the 13 patients, 7 were male and 6 were female. All patients were Caucasian (100.0%). The mean (SD) age was 72.7 (7.5) years. All patients in the MM cohort received 3 or more prior systemic regimens. No patients in the MM cohort received prior rituximab therapy.

Table S042.2.10. Summary of Sample Collection (FAS Population)

PRODUCTION DATA - PRODUCTION MODE 1
Summary of Sample Collection
FAS Population
H6Q-MC-S042

Analysis Population	FAS Overall, WM cohort (N=42) n(%)	FAS Overall, MM cohort (N=14) n(%)
Patients with TR informed consent	28(66.7)	13(92.9)
Patients with reported IHC data	1(2.4)	3(21.4)
Patients with baseline IHC data (a)	1(2.4)	3(21.4)
Patients with treatment IHC data (b)	0(0.0)	0(0.0)
Patients with follow-up IHC data (c)	0(0.0)	0(0.0)
Patients with reported RBM data	28(66.7)	13(92.9)
Patients with baseline RBM data (a)	17(40.5)	12(85.7)
Patients with treatment RBM data (b)	4(9.5)	0(0.0)
Patients with follow-up RBM data (c)	17(40.5)	6(42.9)
Patients with both baseline and post-baseline RBM data	9(21.4)	5(35.7)

Abbreviations: IHC = immunohistochemistry; RBM = Rules-Based Medicine; TR = translational research; FAS = full analysis set; WM = Waldenstrom's macroglobulinemia; MM = Multiple Myeloma; n = number of patients in the category; N = number of enrolled patients within each cohort.
*a Patient with baseline (IHC or RBM) sample: the particular patient has sample collected before the enrollment date.
*b Patient with treatment (IHC or RBM) sample: the particular patient has sample collected between the enrollment date and discontinuation date.
*c Patient with followup (IHC or RBM) sample: the particular patient has sample collected after discontinuation date.
Post-baseline denotes treatment or followup. One patient in WM cohort has both treatment and follow-up RBM data, but no baseline RBM data.

Table S042.2.11. Summary of Patient Demographics and Baseline Characteristics by Cohort (TR Population)

PRODUCTION DATA - PRODUCTION MODE 1
Summary of Patient Demographics and Baseline Characteristics by Cohort
TR Population
H6Q-MC-S042

Analysis Populations	FAS Overall, WM cohort All(N = 28)	FAS Overall, MM cohort All(N = 13)
Sex [n (%)]		
No. of Patients	28	13
Male	24(85.71)	7(53.85)
Female	4(14.29)	6(46.15)
Origin [n (%)]		
No. of Patients	28	13
African	1(3.57)	0(0.00)
Caucasian	27(96.43)	13(100.00)
Age (years)		
No. of Patients	28	13
Mean (SD)	64.3(9.2)	72.7(7.5)
Median	65.0	76.2
Minimum	45.6	59.4
25th percentile	56.8	70.7
75th percentile	70.8	78.4
Maximum	82.3	81.0
Height at baseline (cm)		
No. of Patients	28	13
Mean (SD)	175.5(8.3)	162.5(10.7)
Median	175.0	162.0
Minimum	160.0	147.0
25th percentile	169.0	156.0
75th percentile	182.0	168.0
Maximum	192.0	187.0
Weight at baseline (kg)		
No. of Patients	28	13
Mean (SD)	84.1(14.9)	63.2(16.0)
Median	82.5	65.0
Minimum	62.0	45.0
25th percentile	72.5	50.0
75th percentile	94.5	80.0
Maximum	120.0	90.0

PRODUCTION DATA - PRODUCTION MODE 2
Summary of Patient Demographics and Baseline Characteristics by Cohort
TR Population
H6Q-MC-S042

Analysis Populations	FAS Overall, WM cohort All(N = 28)	FAS Overall, MM cohort All(N = 13)
Prior Rituximab Therapy [n (%)]		
No. of Patients	28	13
No	4(14.29)	13(100.00)
Yes	24(85.71)	0(0.00)
Number of Prior Systemic Regimens [n (%)]		
No. of Patients	28	13
One regimen only	3(10.71)	0(0.00)
Two regimens only	7(25.00)	0(0.00)
Three or more regimens	18(64.29)	13(100.00)

Abbreviations: TR = translational research; IHC = immunohistochemistry; RBM = Rules-Based Medicine; FAS = full analysis set; WM = Waldenstrom's macroglobulinemia; MM = Multiple Myeloma; BSA = Body Surface Area; SD = standard deviation; n = number of patients in the category; N = number of patients belonging to TR population for a particular cohort.

TR population consists of enrolled patients in FAS who have informed consent for TR research and have at least one reported IHC or RBM data or both.

[redacted]

Time to Progression ([TTP] TR Population)

A summary of the Kaplan Meier analysis for TTP by cohort (TR population) is presented in Table S042.2.12. In the WM cohort, 7 patients (25.0%) had measured events and 21 patients (75.0%) were censored. The overall median TTP was 21.16 months (95% CI: 12.88, -), with a 12-month progression-free rate of 0.79 (95% CI: 0.51, 0.92) and a 21-month progression-free rate of 0.52 (95% CI: 0.16, 0.79).

In the MM cohort, 6 patients (46.15%) had measured events and 7 patients (53.85%) were censored. The overall median TTP was 5.62 months (95% CI: 2.86, -) with a 3-month progression-free rate of 0.73 (95% CI: 0.37, 0.90), and 6-, 9-, 12-, 15-, and 18-month progression-free rates of 0.45 (95% CI: 0.17, 0.71).

Best RR (TR Population)

A summary of best response by cohort (TR population) is presented in Table S042.2.13.

In the WM cohort, the overall RR (CR+PR+MinR) was 42.9% (95% CI: 24.5, 61.2). The objective RR (CR+PR) was 7.1% (95% CI: 0.0, 16.7). No patients had a CR. Overall, 2 patients (7.1%) experienced a PR, 10 patients (35.7%) each experienced a MinR and stable disease, 2 patients (7.1%) experienced PD, and response was unknown in 4 patients (14.3%).

In the MM cohort, the overall RR (CR+PR+MR) was 7.7% (95% CI: 0.0, 22.2). No patients experienced a CR or PR. One patient (7.7%) experienced an MR, 4 patients (30.8%) experienced stable disease, 5 patients (38.5%) experienced PD, and response was unknown in 3 patients (23.1%).

Table S042.2.12. Summary of Kaplan Meier Analysis for Time to Progression by Cohort (TR Population)

Production Data Production Mode 19:50 Friday, May 13, 2011 1
Summary of Kaplan Meier analysis for Time to Progression by Cohort
TR Population
H6Q-MC-S042

Parameter	WM cohort (IWWM criteria) (N =28)	MM cohort (EBMT criteria) (N =13)
Number (%) of Patients with Events	7 (25.00)	6 (46.15)
Number (%) of Patients Censored	21 (75.00)	7 (53.85)
Observed range (min,max) (month)	(1.87, 21.82)	(0.13, 19.42)
25th percentile (95% CI) (month)	12.88 (9.76, 21.16)	2.86 (1.87, 5.62)
Median (95% CI) (month)	21.16 (12.88, .)	5.62 (2.86, .)
75th percentile (95% CI) (month)	.	.
Rate of being progression-free for at least:		
3-month (95% CI)	0.96 (0.76, 0.99)	0.73 (0.37, 0.90)
Patients at risk	24	8
6-month (95% CI)	0.92 (0.71, 0.98)	0.45 (0.17, 0.71)
Patients at risk	21	4
9-month (95% CI)	0.92 (0.71, 0.98)	0.45 (0.17, 0.71)
Patients at risk	14	2
12-month (95% CI)	0.79 (0.51, 0.92)	0.45 (0.17, 0.71)
Patients at risk	9	2
15-month (95% CI)	0.69 (0.38, 0.87)	0.45 (0.17, 0.71)
Patients at risk	7	1
18-month (95% CI)	0.69 (0.38, 0.87)	0.45 (0.17, 0.71)
Patients at risk	5	1
21-month (95% CI)	0.52 (0.16, 0.79)	
Patients at risk	3	0
24-month (95% CI)		
Patients at risk	0	0

Abbreviations: TR = translational research, IWWM = International Workshop on Waldenstrom's Macroglobulinemia, EBMT = European Group for Blood and Bone Marrow Transplant, FAS = full analysis set, WM = Waldenstrom's macroglobulinemia, MM = Multiple Myeloma, CI = confidence interval, min=Minimum, max=Maximum, N = number of patients belonging to TR population for a particular cohort.

Note: TR population consists of enrolled patients in FAS who have informed consent for TR research and have reported TR results.

[redacted]

Table S042.2.13. Summary of Best Response by Cohort (TR Population)

PRODUCTION DATA - PRODUCTION MODE 1
Summary of Best Response by Cohort
TR Population.
H6Q-MC-S042

Responses	WM cohort (IWWM criteria) (N = 28) n	WM cohort (IWWM criteria) (N = 28) %	MM cohort (EBMT criteria) (N = 13) n	MM cohort (EBMT criteria) (N = 13) %
Complete Response(CR)	0	0.0	0	0.0
Partial Response(PR)	2	7.1	0	0.0
Minor Response (MinR)	10	35.7	0	0.0
Minimal Response (MR)	0	0.0	1	7.7
Stable Disease or No Change (SD)	10	35.7	4	30.8
Progressive Disease (PD)	2	7.1	5	38.5
Unknown	4	14.3	3	23.1
Complete Response Rate (CR)	0	0.0	0	0.0
(95% CI)		(-)		(-)
Objective Response Rate (CR + PR)	2	7.1	0	0.0
(95% CI)		(0.0 - 16.7)		(-)
Overall Response Rate (CR + PR + MinR or MR)	12	42.9	1	7.7
(95% CI)		(24.5 - 61.2)		(0.0 - 22.2)

Abbreviations: TR = translational research; IWWM = International Workshop on Waldenstrom's Macroglobulinemia; EBMT = European Group for Blood and Bone Marrow Transplant; FAS = full analysis set; WM = Waldenstrom's macroglobulinemia; MM = Multiple Myeloma; CI = confidence interval; n = number of patients in the category; N = number of patients belonging to TR population for a particular cohort; CR = Complete Response; PR = Partial Response; MinR = Minor Response (WM cohort); MR = Minimal Response (MM cohort); SD = Stable Disease; PD = Progressive Disease.
Note: Confidence intervals for response rates are calculated by the normal approximation method for proportions (Leemis and Trivedi 1996).

RBM Analyte Expression Data (TR Population for WM Cohort)
In the WM cohort (TR population), 9 patients had both baseline and post-baseline RBM data. There was no difference between the 2 distribution means of baseline and post-baseline RBM analyte expression.

In the MM cohort (TR population), 12 patients had baseline RBM data, and 6 had post-baseline RBM data (1 with both baseline and post-baseline RBM data). There was no difference between the 2 distribution means of baseline and post-baseline RBM analyte expression.

Associations between clinical endpoints (TTP and overall RR) and RBM markers were evaluated for the TR population. Markers were assessed on an individual basis, that is, a given marker was analyzed separately. The analysis of overall RR used proportional odds logistic regression. Analyses of TTP used a Cox proportional hazards model.

Continuous RBM marker expressions were dichotomized into high and low expression groups and were treated as a continuous variable in the appropriate model in associating with the clinical endpoints (TTP and overall RR) for the WM cohort. Due to the small sample size in the MM cohort, only analyses associating the continuous marker expression with TTP were considered.

Cox Regression of TTP with Continuous RBM Marker Expression (TR Population for WM Cohort)
In the WM cohort, when unadjusting for multiple testing, there was an association between baseline prostate-specific antigen (PSA) (free) expression and TTP (unadjusted p=.045, false discovery rate [FDR]-adjusted p=.925) (Benjamini and Hochberg 1995). There was no association between continuous post-baseline PSA (free) expression and TTP (unadjusted p=.435, FDR-adjusted p=.984) (Table S042.2.14).

In the MM Cohort, there was no association between baseline or post-baseline RBM marker expression and TTP.

Logistic Regression of Overall RR with Continuous RBM Marker Expression (TR Population for WM Cohort)
When unadjusting for multiple testing, there was an association between baseline IL-15 expression and overall RR (unadjusted p=.048, FDR-adjusted p=.992). There was no association between post-baseline IL-15 expression and overall RR (unadjusted p=.124, FDR-adjusted p=.807) (Table S042.2.15).

Dichotomized cut-point for each marker in the WM cohort was determined using 1) the least detectable dose (LDD) for markers satisfying a pre-specified criterion (see footnote c in Table S042.2.16 and Table S042.2.17 for details on using the LDD as the cut-point), and 2) maximal chi square method scanning the central 50% of the marker values (Miller and Siegmund 1982) for markers not meeting the LDD criterion.

Cox Regression of TTP with Dichotomous RBM Marker Expression (TR Population for WM Cohort)
There was no association between baseline or post-baseline RBM marker expression class and TTP.

Logistic Regression of Overall RR with Dichotomous RBM Marker Expression (TR Population for WM Cohort)
There was an association between the class effect of dichotomized baseline and post-baseline IL-15 expression class (high vs. low expression group) and the overall RR (CR+PR+MinR) in a univariate logistic model; p=.018 at baseline (Table S042.2.16) and p=.037 post-baseline (Table S042.2.17). There was an association between the class effect of dichotomized post-baseline IL-5 expression and the overall RR; p=.341 at baseline (Table S042.2.16) and p=.037 at post-baseline (Table S042.2.17). The LDD was used as a threshold for markers satisfying a pre-specified criterion.

Table S042.2.14. Cox Regression Analysis of Time to Progression with Each Continuous RBM Marker for Baseline or Post-Baseline RBM Data WM Cohort (TR Population)

Production Data Production Mode 20:07 Friday, May 13, 2011 1
Cox Regression Analysis of Time to Progression (TTP) with each continuous RBM marker for WM Cohort.
TR Population. Baseline or Post-baseline RBM data
H6Q-MC-S042

	WM Cohort Baseline Expression (n=17)					WM Cohort Post-Baseline Expression (n=20)				
Marker	HR	(95% CI)		p-value (a)	FDR adj p-value (b)	HR	(95% CI)		p-value (a)	FDR adj p-value (b)
Prostate Specific Antigen, Free	0.31	(0.10,	0.98)	0.045	0.925	0.73	(0.34,	1.60)	0.435	0.984

Abbreviations: TR = translational research; WM = Waldenstrom's macroglobulinemia; MM = Multiple Myeloma; RBM = Rules-Based Medicine; TTP = time to progression; CI = confidence interval; HR = hazard ratio; n = number of patients with non-missing values for both the assessed marker and TTP.

a. The p-values are unadjusted from univariate Cox regression of time to progression on log-transformed RBM expression level.
b. The p-values are adjusted for multiple testing using the method of False Discovery Rate of Benjamini and Hochberg (1995).

Note: Values below detection limit for a particular marker are imputed as half of the minimum of the observed sample values for that marker.

Table S042.2.15. Cox Regression Analysis of Time to Progression with Each Continuous RBM Marker for Baseline or Post-Baseline RBM Data WM Cohort (TR Population)

Production Data Production Mode
Logistic Regression Analysis of Overall Response Rate (CR+PR+MinR) with each continuous RBM marker (WM Cohort)
TR Population. Baseline or Post-baseline RBM data
H6Q-MC-S042

	WM Cohort, Baseline Expression (n=17)					WM Cohort, Post-Baseline Expression (n=20)				
Marker	OR	(95% CI)		p-value (a)	FDR adj p-value (b)	OR	(95% CI)		p-value (a)	FDR adj p-value (b)
IL-15	13.39	(1.02,	176.24)	0.048	0.992	4.48	(0.66,	30.38)	0.124	0.807

Abbreviations: TR = translational research; FAS = full analysis set; WM = Waldenstrom's macroglobulinemia; RBM = Rules-Based Medicine; CR = Complete Response; PR = Partial Response; MinR = Minor Response; SD = Stable Disease; PD = Progressive Disease; CI = confidence interval; OR = odds ratio; n = number of patients with non-missing values for both the assessed marker and Overall Response Rate.

a. The p-values are from Logistic regression: Overall Response Rate = log (marker expression)
b. The p-values are adjusted for multiple testing using the method of False Discovery Rate of Benjamini and Hochberg (1995).

Note: Overall Response Rate is defined as binary response of CR or PR or MinR v.s. SD or PD or Unknown. Values below detection limit for a particular marker are imputed as half of the minimum of the observed sample values for that marker.

Table S042.2.16. Logistic Regression Analysis of Overall Response Rate Dichotomized by RBM Marker Expression at Baseline (WM Cohort) (TR Population)

	High Expression(a)		Low Expression(b)
Marker = IL-15			
Threshold(c)		-0.545	
Total number of patients, N	8		9
Patients with BOR of CR or PR or MinR, n (%)	6(75.00)		1(11.11)
Patients with BOR of SD or PD or Unknown, n (%)	2(25.00)		8(88.89)
Odds Ratio(d) (95% CI)		24.000(1.741-330.80)	
Wald chi square		5.637	
p-value(e)		.018	
Marker = IL-5			
Threshold(c)		1.386	
Total number of patients, N	3		14
Patients with BOR of CR or PR or MinR, n (%)	2(66.67)		5(35.71)
Patients with BOR of SD or PD or Unknown, n (%)	1(33.33)		9(64.29)
Odds Ratio(d) (95% CI)		3.600(0.257-50.330)	
Wald chi square		0.906	
p-value(e)		.341	

Abbreviations: TR = translational research; IWWM = International Workshop on Waldenstrom's Macroglobulinemia; FAS = full analysis set; WM = Waldenstrom's macroglobulinemia; RBM = Rules-Based Medicine; CR = Complete Response; PR = Partial Response; MinR = Minor Response; SD = Stable Disease; PD = Progressive Disease; OR = odds ratio, CI = confidence interval; LDD = least detectable dose.
a. Patients with High RBM Marker Expression.
b. Patients with Low RBM Marker Expression.
c. Point of the log-transformed RBM marker distribution that separates patients into high expression group (those with values above threshold) and low expression group (those with values equal or below threshold). For each marker, the log(LDD) is used as threshold for the markers satisfying the following criterion: if >= 3 samples have log-transformed expression <= log(LDD) and >= 3 samples have log-transformed expression > log(LDD), then use log(LDD) as threshold. The LDD is defined as mean plus 3 standard deviations of 20 standard diluent blank readings for a particular marker.
d. Odds Ratio comparing High to Low Expression Group.
e. p-value is not adjusted for multiple testing.
Note: Overall Response Rate is defined as a binary response of CR or PR or MinR v.s. SD or PD or Unknown.
The threshold for dichotomizing the RBM marker expression is in log scale. Values below detection limit for a particular marker are
arker.

[redacted]

Table S042.2.17. Logistic Regression Analysis of Overall Response Rate Dichotomized by RBM Marker Expression Post-baseline (WM Cohort) (TR Population)

	High Expression(a)		Low Expression(b)
Marker = IL-15			
Threshold(c)		-0.545	
Total number of patients, N	9		11
Patients with BOR of CR or PR or MinR, n (%)	6(66.67)		2(18.18)
Patients with BOR of SD or PD or Unknown, n (%)	3(33.33)		9(81.82)
Odds Ratio(d) (95% CI)		9.000(1.140-71.034)	
Wald chi square		4.345	
p-value(e)		.037	
Marker = IL-5			
Threshold(c)		1.386	
Total number of patients, N	9		11
Patients with BOR of CR or PR or MinR, n (%)	6(66.67)		2(18.18)
Patients with BOR of SD or PD or Unknown, n (%)	3(33.33)		9(81.82)
Odds Ratio(d) (95% CI)		9.000(1.140-71.034)	
Wald chi square		4.345	
p-value(e)		.037	

Abbreviations: TR = translational research; IWWM = International Workshop on Waldenstrom's Macroglobulinemia; FAS = full analysis set; WM = Waldenstrom's macroglobulinemia; RBM = Rules-Based Medicine; CR = Complete Response; PR = Partial Response; MinR = Minor Response; SD = Stable Disease; PD = Progressive Disease; OR = odds ratio, CI = confidence interval; LDD = least detectable dose.

a. Patients with High RBM Marker Expression.

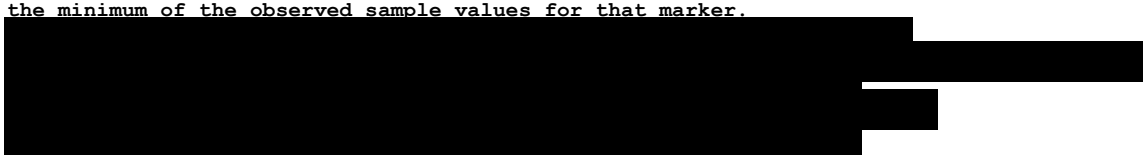
b. Patients with Low RBM Marker Expression.

c. Point of the log-transformed RBM marker distribution that separates patients into high expression group (those with values above threshold) and low expression group (those with values equal or below threshold). For each marker, the log(LDD) is used as threshold for the markers satisfying the following criterion: if >= 3 samples have log-transformed expression <= log(LDD) and >= 3 samples have log-transformed expression > log(LDD), then use log(LDD) as threshold. The LDD is defined as mean plus 3 standard deviations of 20 standard diluent blank readings for a particular marker.

d. Odds Ratio comparing High to Low Expression Group.

e. p-value is not adjusted for multiple testing.

Note: Overall Response Rate is defined as a binary response of CR or PR or MinR v.s. SD or PD or Unknown. The threshold for dichotomizing the RBM marker expression is in log scale. Values below detection limit for a particular marker are imputed as half of the minimum of the observed sample values for that marker.



Conclusions

Efficacy

The primary outcome measure was RR. Based on investigator-assessed best response:

- The overall RR (CR+PR+MinR) in the WM cohort was 38.1%.
- The overall RR (CR+PR+MinR) was 33.3% in the WM-FAS-Enz population and 28.6% in the WM-FAS-Dex population. Thus, based on ORR approximately 30%, it is sufficiently interesting to warrant further study in the larger WM patient population.
- The overall RR (CR+PR+MR) in the MM cohort was 7.1%.
- The overall RR (CR+PR+MR) in the MM-FAS-Dex population was 9.1%.

Safety

- Enzastaurin was safe and tolerable in previously treated WM and MM patients.

Translational Research Analysis

In the TR population:

- The overall median TTP was 21.16 months (95% CI: 12.88, -) in the WM cohort and 5.62 months (95% CI: 2.86, -) in the MM cohort.
- The overall RR (CR+PR+MR) was 42.9% (95% CI: 24.5, 61.2) in the WM cohort and 7.7% (95% CI: 0.0, 22.2) in the MM cohort.

In the WM cohort:

- When unadjusting for multiple testing, there was an association between continuous baseline PSA (free) expression and TTP (unadjusted p=.045). There was no association between continuous post-baseline PSA (free) expression and TTP (unadjusted p=.435).
- When unadjusting for multiple testing, there was an association between continuous baseline IL-15 expression and overall RR (unadjusted p=.048). There was an association between the class effect of dichotomized baseline and post-baseline IL-15 expression (high vs. low expression group) and the overall RR in a univariate logistic model (p=.018 at baseline and p=.037 post-baseline).
- There was an association between the class effect of dichotomized post-baseline IL-5 expression and the overall RR (p=.037 post-baseline).

In the MM cohort:

- There was no association between baseline or post-baseline RBM marker expression and TTP.

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