term responders (P<0.001). Long-term responders did not significantly differ by age, isotype, previous autoSCT, dexametasone dose and chemotherapy lines. Long-term responders included 7 alloSCT patients compared to 0 alloSCT in no long-term responders group (P=0.01). Long-term responders had a better quality of response than no long-term responders (P<0.001): 45% PR or more versus 5%. In the multivariate regression model the quality of response was confirmed as the significant predictor of long-term response (P=0.04) and reduced relapse (P=0.01). *Conclusion*s. In conclusion, 40% of MM patients treated with lenalidomide and dexamethasone were long-term responders. All the allografted patients with follow-up >/=12 months were long-term responders, suggesting and immune-mediated activity of the drug. The quality of response was the best predictor of long-term response and better survival, indicating that also in the relapse setting the therapy should be aimed at the best tumor reduction.

0381

EFFECTIVENESS AND PATTERNS OF BORTEZOMIB USE IN A REAL-LIFE SETTING: THE VESUVE COHORT STUDY

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Background. Targeted therapies are a very important therapeutic progress in the treatment of multiple myeloma. Bortezomib, the first proteasome inhibitor, was registered in France in April 2004 as third line treatment and in April 2005 as second line treatment. To date, no evaluation of bortezomib in a real-life setting has been conducted in France *Aims.* The VESUVE cohort study was designed to describe patterns and evaluate effectiveness of bortezomib use in a real-life setting. *Methods.* VESUVE is a national multicentre cohort study, conducted in 60 French centres that included patients initiating bortezomib from May 2004 to April 2006, using nominative pharmacy dispensations and/or preparations. Among those identified, patients treated for multiple myeloma were followed for 36 months. For each patient, demographic data, clinical characteristics of multiple myeloma, and treatment data were collected from medical files using a standardized case report form. Response was assessed by an independent committee according to adapted International Myeloma Working Group criteria. The overall survival rate from the onset of bortezomib was assessed using the Kaplan-Meier method. *Results.* A total of 798 patients were followed: mean age was 65.6 years and 53.3% were men. Immunoglobulin myeloma was reported for 83.5% of patients (56.3% IgG, 25.1% IgA), light chain for 14.9% and non-secretory for 1.6%. More than one third of patients (34.1%) had a β2-microglobulin level higher than 3.5 mg/L. Cytogenetic exams were available for 340 patients. Among them, 35.0% had a deletion of chromosome 13. Bortezomib was administered as first line treatment in 0.5% of patients, as second line in 17.7%, as third line in 33.3%, as fourth line and more in 48.5%. The median number of bortezomib cycles was 4, and 6.3% of patients completed more than eight cycles. Baseline bortezomib dose was 1.3 mg/m² for 75.7% of patients, 42.9% received bortezomib alone, 43.0% in association with dexamethasone. Response was not assessed in 79 patients (single cycle) and in 126 (missing data). They were comparable for baseline prognostic factors with the 593 evaluated patients. For the latter, the overall best response rate was 58.4% (2.2% complete, 13.2% very good partial, 43.0% partial). Disease was stable for 35.4% of patients and progressive for 6.2%. The overall survival rate from the onset of bortezomib was 61.1% at 1 year [95%CI 57.6-64.4], 42.2% at 2 years [95%CI 38.7-45.7] and 31.1% at 3 years [95%CI 27.8-34.4]. The median overall survival was 19.2 months. *Conclusions*. This observational study shows that conditions of use in a real-life setting may differ from those of the summary of product characteristics in terms of concomitant treatment or number of cycles. Nevertheless, the effectiveness was close to the efficacy reported in clinical trials.

0382

THALIDOMIDE AND DEXAMETHASONE AS SALVAGE THERAPY AT FIRST RELAPSE IN PATIENTS WITH MULTIPLE MYELOMA: ANALYSIS OF LONG-TERM CLINICAL OUTCOMES

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Aim of the present analysis was to evaluate the long-term outcomes of a series of 100 patients who received thal-dex as salvage therapy at first relapse after prior ASCT or conventional chemotherapy. By study design, thal was started at the dose of 100 mg/daily for two weeks and then escalated to 200 mg/daily, provided that the initial tolerance was acceptable. Otherwise, thal was continued at the initial dose until progression. Dex was given at a monthly dose of 160 mg. The first 60 patients did not receive any thromboprophylaxis, while fixed low-dose warfarin (0.25 mg/day) was added to thal-dex in the subsequent 40 patients. Median age of the patients was 62 years. Median time from start of first-line therapy to thal-dex was 34 months. Up-front therapy for MM had included ASCT, either single (30%) or double (42%), while the remaining 28 patients had previously received conventional chemotherapy. 59% of the patients were treated with a fixed thal dose of 100 mg/daily. Overall, median duration of thal-dex therapy was 14 months. 65% of the patients stayed on treatment beyond the achievement of the best response or plateau phase; median duration of thal in these patients was 22 months (range 1-79). The most frequent adverse events were constipation (42%, grade III 8%), peripheral neuropathy (58%, grade III 5%), bradycardia (20%, grade III 0%) and skin rash (11%, grade III 1%). Venous thromboembolism was recorded in 7 patients (3 not receiving any thromboprophylaxis), at a median of 8 months (range 3-11) from the start of thal-dex therapy. The frequency of grade III neuropathy was significantly higher in patients receiving thal 200 mg/daily in comparison with those treated with 100 mg/daily (8.5% vs 1%, respectively, P=0.01). Discontinuation of thal due to toxicity was recorded in 8 patients after a median of 12 months. On an intention to treat basis, 46% of patients achieved at least a partial response at a median time of 3 months from the start of thal-dex treatment; the response rate was not significantly different between patients receiving thal 100 mg/daily and those treated with 200 mg/daily. The median duration of response (DOR) was 28 months, while the median time to next therapy was 15.5 months. With a median follow up of 25 months, median OS, TTP and PFS were 43, 22 and 21 months, respectively. TTP and PFS were significantly longer for patients responding to thal-dex therapy (TTP: 34 months vs 15 months for non-responders, P=0.005; PFS: 28 months vs 12 months for nonresponders, P=0.001, respectively). Median survival after relapse from thal-dex therapy was 26 months. In conclusion, low dose thal-dex was an effective treatment of first relapse in MM, yielding DOR, OS and EFS comparable to those reported with other novel agents when used in the same setting of patients. Low-dose thal-dex was generally well tolerated, as reflected by the long stay on treatment in the absence of progression (median: 25 months) and a low discontinuation rate (8%).

0383

POST-APPROVAL SAFETY STUDY (PASS) OF LENALIDOMIDE COMPARED WITH OTHER TREATMENTS IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA: FIRST REPORT ON 518 PATIENTS

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Aim and *Background.* Lenalidomide plus dexamethasone was EMEA approved 2007 for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy. Subsequently, an observational patient cohort study has been implemented to characterize the safety profile of lenalidomide in a normal clinical practice and to place the incidence of adverse events (AE) into context with those occurring in second line or later MM patients receiving other treat-

ments. *Methods.* Data has been collected prospectively from 518 MM patients in 117 institutions in 14 European countries. Patients had received at least one prior therapy and were commencing a new treatment in accordance with normal clinical practice with prescribed medication. No additional treatments or investigations outside of normal clinical practice were required. Data cut for this analysis was December 18th, 2009. *Results.* Of the 518 patients, 321 received lenalidomide plus dexamethasone, 105 bortezomib, 36 thalidomide, 28 other therapies and 28 had missing data. The median age of the total group was 70 years (range, 38-92), 56.9% were male. Most patients (75.4%) had a good performance status (ECOG 0-1) but 24.6% had an ECOG status of 2-4. The median number of previous treatment lines was 2 (1-6), 50.9% had two previous lines and 30.9% three or more. There were no important demographic or clinical differences in the baseline characteristics between the patient cohorts. Table 1 shows the NCI grade 3-4, AEs in the respective cohorts. 24.9% of patients in the lenalidomide cohort discontinued therapy. Patients in the lenalidomide cohort had a median Kaplan-Meier estimated treatment duration of 6.4 months. Discontinuation percentages and estimated median treatment duration for the bortezomib and thalidomide cohorts were 46.7% (3.6 months) and 41.7% (5.8 months), respectively. Primary reasons for discontinuation were adverse events (lenalidomide, 6.2%; bortezomib, 13.3%; thalidomide, 11.1%) and progression of disease (lenalidomide, 7.5%; bortezomib, 11.4%; thalidomide, 13.9%). *Conclusions.* In unselected groups of patients from normal clinical practice treated with lenalidomide, bortezomib, thalidomide or other therapies, lenalidomide demonstrates an acceptable safety profile. There are no major differences in the incidence of adverse events between lenalidomide, bortezomib and thalidomide treated patients. The overall discontinuation rate among lenalidomide-treated patients was roughly half that of patients treated with bortezomib or thalidomide, despite a longer treatment duration. Discontinuation of treatment due to adverse events or disease progression occurred less frequently in the lenalidomide cohort than in the thalidomide or bortezomib cohorts.

Events (NCI grades) (At least one event occurred)	Lenalidomide (N = 321)	Bortezomib (N = 105)	Thalidomide (N = 36)	Other Treatment (N = 28)
Event leading to death	5.0%	7.6%	5.6%	0%
Any grade 3–4 event	30.5%	33.3%	36.1%	14.3%
Drug-related grade 3–4 event	19.6%	17.1%	16.7%	7.1%
Drug-related serious event	10.6%	11.4%	11.1%	10.7%

Table 1. AEs according to NCI (v. 3) grading.

0384

A PHASE IB DOSE-ESCALATION STUDY OF ORAL PANOBINOSTAT (LBH589) AND IV BORTEZOMIB IN PATIENTS WITH RELAPSED OR RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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Background. Panobinostat (LBH589) is a potent pan-deacetylase inhibitor that has been shown *in vitro* to inhibit several HDAC isoenzymes including HDAC6, a key factor in both the formation of aggresomes and function of the Hsp90 chaperone protein. The combination of panobinostat and the proteasome inhibitor bortezomib has demonstrated synergistic cytotoxicity in multiple myeloma (MM) in both *in vitro* and *in vivo* studies which has been hypothesized to occur, in part, through inhibition of proteasome and aggresome function. *Aims.* The aim of this Phase IB dose-escalation study is to identify the maximum tolerated dose (MTD) of panobinostat and bortezomib when these are administered in combination in patients with relapsed or relapsed and refractory MM. *Methods.* Patients with relapsed or relapsed and refractory MM received panobinostat (p.o. thrice weekly) and bortezomib (i.v. Days 1, 4, 8, 11) on a 21-day cycle to establish the MTD of the combination. *Results.* As of Oct 9 2009, 38 patients were treated in 5 cohorts (see table). The median age of patients treated on the study was 62 years (range 46-78). Patients received a median of 2 prior therapies (range 1-7), including stem-cell transplant (n=30) and bortezomib (n=22; 13 bortezomib-refractory). No dose-limiting toxicities (DLTs) occurred in cohorts 1 and 3, 1 patient had DLT in cohort 2 (neutropenia), 4 had DLTs in cohort 4 (2 thrombocytopenia, 1 pneumonia/thrombocytopenia/neutropenia, 1 fatigue), and 1 had DLT in cohort 5 (thrombocytopenia/asthenia/dizziness). Hematologic adverse events (AEs): included Grade 3/4 thrombocytopenia (n=30), neutropenia (n=23), and anemia (n=6). Non-hematologic AEs included diarrhea (n=23), nausea (n=18), pyrexia (n=17), fatigue (n=16), and asthenia (n=13). There have been no treatment-related deaths. Responses (≥MR) were observed in 26/38 patients (68%) across all cohorts. Of note, responses were observed in 8/13 (62%) of bortezomib-refractory patients. Management of AEs, including thrombocytopenia, by dose reduction or interruption, allowed for longer treatment duration in cohort 3. Patients treated in cohort 3 also demonstrated the most favorable efficacy profile with 7/8 patients responding and no patients demonstrating progressive disease. Safety results supported the further enrolment of patients in a 6th cohort at the same dose level to confirm MTD. Altogether, these results led to the recommendation of the cohort 3 dose level for further evaluation in clinical trials, with a modified dose-schedule incorporating a week-long rest period. *Summary and Conclusions.* The combination of oral panobinostat and i.v. bortezomib has a predictable and manageable safety profile with promising activity in patients with relapsed or relapsed and refractory MM, including patients with bortezomib-refractory MM. Review of data of at least 12 evaluable patients treated at 20 mg panobinostat plus bortezomib 1.3 mg/m^2 is ongoing to confirm the MTD. This dose level, and modified schedule with panobinostat 2 weeks on and one week off will be used in phase II and III PANORAMA trials based on this combination in order to optimize therapy duration.

Cohort	1	2	3	4	5
Panobinostat dose	10 mg	20 mg	20 mg	30 mg	25 mg
Bortezomib dose	1.0 mg/m^2	1.0 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2
No. of patients: Total (BTZ-refractory)	**7 (4)**	**7 (5)**	**8 (2)**	**7 (0)**	**9 (2)**
CR		1 (0)	2 (0)	1 (0)	
VGPR	1 (0)				1 (0)
PR		3 (3)	3 (1)	4 (0)	6 (2)
MR	1 (1)		2 (1)	1 (0)	
SD*			1 (0)	1 (0)	1 (0)
PD	4 (2)	3 (2)			
NE	1 (1)				1 (0)

*SD: not meeting criteria for CR, VGPR, PR, MR, or PD.

Table 1.

0385

A PHASE I STUDY OF VORINOSTAT, LENALIDOMIDE, AND DEXAMETHASONE FOR RELAPSED AND REFRACTORY MULTPLE MYELOMA

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Background. Multiple myeloma (MM) is the second most common hematologic malignancy. Although novel treatment combinations have improved outcomes, new drug combinations are needed for this otherwise incurable disease. Vorinostat, an oral histone deacetylase inhibitor approved in the United States for the treatment of advanced cutaneous T-cell lymphoma, alters gene expression and protein activity, promoting MM cell death through multiple pathways. In preclinical studies, vorinostat was shown to synergistically enhance the anti-MM activity